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 7-9, 12-13, 15-16 and 21-22 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.

All challenged claims of the '999 Patent depend from sole independent claim 1, which is directed to a formulation of "polysaccharide-protein conjugates," well-known immunogenic components of vaccines. As recognized by the Examiner during prosecution, the claimed formulation recites staple vaccine components – buffer, salt, and aluminum adjuvant. The purported invention, as stressed by the Patent Owner: the formulation is housed in a standard container treated with silicone oil (*i.e.*, a "siliconized" container) and inhibits silicone-induced protein aggregation with standard formulation ingredients, *e.g.*, surfactant and/or aluminum salt adjuvant. Two co-pending Petitions based, *inter alia*, on the Chiron 2003, Smith 1988, Elan 2004, and Prevenar 2005 references - make clear that there is no invention in claim 1.[1] IPR2017-00378; IPR2017-00380.

[1] Chiron 2003 (Ex. 1011) discloses polysaccharide-protein conjugate formulations with all of Claim 1's ingredients, as well as surfactant. Smith 1988 (Ex. 1012)

Claim 1 recites buffer generally ("a pH **buffered** saline solution wherein the **buffer** has a pKa of about 3.5 to about 7.5") (emphasis added), whereas dependent claims 7-9, 12-13, 15-16 and 21-22 recite additional buffer details (*e.g.*, histidine buffer at pH 5.8 (claims 13 and 16) and 5 mM succinate buffer at pH 5.8 to 6.0 (claim 22)). The claimed buffer details merely reflect routine optimization of claim 1's old formulation; they would have been obvious choices. Indeed, the '999 Patent expressly states that buffer optimization "is within the skill of the art," and discloses nothing inventive as to buffer type, concentration or pH. Ex. 1001 at 16:12-15. Because all of the other formulation details of the challenged claims are explicitly disclosed in the prior art combinations of the co-pending Petitions (Chiron 2003/Smith 1988/Elan 2004 and Prevenar 2005/Chiron 2003), it follows that the challenged claims likewise would have been obvious over the same prior art combinations.

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establishes that lubrication of pharmaceutical containers was a necessity, with "essentially all" such treatments involving silicone oil. Elan 2004 (Ex. 1013) expressly teaches the addition of a surfactant to prevent protein aggregation induced by the silicone oil in standard syringes. And Patent Owner's own Prevenar polysaccharide-protein conjugate vaccine (disclosed in Prevenar 2005 (Ex. 1017)) was housed in pre-filled glass syringes, known to be siliconized; it included aluminum salt, and thus, inherently inhibited silicone-induced aggregation.

Additional prior art renders obvious claims 13 and 16, which recite formulations with histidine buffer at pH 5.8. Since that feature is not supported by the written description of the '999 Patent (or any of its parent applications), claims 13 and 16 are only entitled to the actual filing date of the '999 Patent (September 28, 2012) as their priority date. The combination of two polysaccharide-protein conjugate patent references, Merck 2011 (Ex. 1018) and the '787 Patent (an issued parent of the '999 Patent, sharing its disclosure) (Ex. 1004), renders those claims obvious; Merck 2011, notably, discloses every formulation ingredient of claims 13 and 16, including histidine buffer at pH 5.8.

As discussed in this Petition and the accompanying Declarations of Devendra Kalonia, Ph.D. (Ex. 1010) and Dennis L. Kasper, M.D. (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 has filed two additional Petitions for *inter partes* review of the '999 Patent on other grounds and/or addressing other patent claims. IPR2017-

00378 and IPR2017-00380. 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 7-9, 12-13, 15-16 and 21-22 of the '999 Patent, and respectfully submits that the claims are unpatentable based on the following grounds:

Ground 1. Claims 7-9, 12-13, 15-16 and 21-22 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 person of ordinary skill in the art ("POSITA").

Ground 2. Claims 7-9, 12-13, 15-16 and 21-22 are unpatentable as obvious under pre-AIA 35 U.S.C. § 103(a) over Prevenar 2005 (Ex. 1017) in view of Chiron 2003 (Ex. 1011) and the general knowledge of a POSITA.

Ground 3. Claims 13 and 16 are unpatentable as obvious under pre-AIA 35 U.S.C. § 103(a) over Merck 2011 (Ex. 1018) in view of the '787 Patent (Ex. 1004) and the general knowledge of a POSITA.

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

VI. BACKGROUND

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

1. Polysaccharides in Bacterial Vaccines

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

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. Studies performed in the 1980's and 1990's showed that conjugating polysaccharides to "carrier proteins" resulted in vaccines with

better immune responses 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*.

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[2]), 1051[3], 1053, 1058 (at 28, 38, 42), 1059, 1027 (at 5-6), 1028 (at 6)).

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

[2] 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 __").

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

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.

Vaccines are frequently multivalent, *i.e.*, they include polysaccharides from more than one serotype. *Id.*, ¶ 35. Patent Owner introduced a 7-valent polysaccharide-protein conjugate vaccine (Prevnar® a/k/a Prevenar in some countries) in 2000, which contained serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, conjugated to the CRM_{197} carrier protein. *Id.*, ¶¶ 41-42 (citing Ex. 1015[4] (at 3)). 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. 1010, ¶ 26 (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.*, ¶ 27.

[4] Ex. 1015 is a certified English translation of the original Spanish publication (Ex. 1014).

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*., ¶ 28. Beginning in the 1980's, the industry turned to single dose, pre-filled syringes for injection of the formulation into patients. *Id*., ¶ 29 (citing Ex. 1046 (at 9), ¶ 42 (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*., ¶¶ 30-32 (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*.; *see also id*. at ¶¶ 34, 42 (citing Exs. 1051, 1053, 1055, 1058 (at 7, 10, 15, 22, 26, 33, 37), 1060, 1056 (at 16, 28, 39, 40, 52, 62, 73, 83, 98, 100), 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) to improve processability and functionality.

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

Ex. 1010, ¶¶ 35-42. For decades, silicone oil has been the standard lubricant used in pharmaceutical containers. *Id.*, ¶ 38 (citing Ex. 1012 (at 5), 1064 (at 2), 1065 (at 7)). And, the '999 patent itself acknowledges the widespread use of silicone oil as a lubricant in pharmaceutical containers. *Id.*, ¶ 39 (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. *Id.*, ¶¶ 40-41 (quoting Ex. 1045 (at 46-47), Ex. 1047 (at 3)).

6. Aggregation of Proteins

Proteins include hydrophilic and hydrophobic regions. Ex. 1010, ¶ 44. 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.*, ¶ 45. 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.*

7. Silicone-Induced Aggregation

The extreme hydrophobicity of silicone oil makes it a desired lubricant. Ex. 1010, ¶ 47. 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.*, ¶ 48 (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.*, ¶ 49. In the "Background of the Invention" section, the '999 Patent describes aggregation and precipitation caused by silicone oil. *Id.* (citing Ex. 1001 at 2:17-31). 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. 1010, ¶ 51. 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. 1010, ¶ 52. 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 32)). 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*., ¶ 53 (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 vaccine, Vaxem Hib. *Id*. (citing Exs. 1051, 1053). A formulator would have had every incentive to rely on this regulatory-approved solution to a known problem again. *Id*., ¶ 54 (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. 1010, ¶ 55. 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. 1010, ¶ 58. 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 Ex. 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.

To that end, the inventors purported to be the first to recognize that surfactants inhibit silicone-induced aggregation. Ex. 1001 at 10:35-39. The '999 Patent also suggests that adsorption of antigens onto aluminum phosphate adjuvant inhibits silicone-induced aggregation. *See, e.g., id*. at 1001; 29:14-26.

In addition to surfactant and aluminum salt, the '999 Patent discloses and claims other common formulation ingredients without characterizing them as inventive or contributing to inhibition of silicone-induced aggregation. Ex. 1010, ¶ 73 (citing Ex. 1001 at (6:10 - 7:10)). For example, the '999 Patent does not allege anything inventive as to buffer (type, concentration and pH). *Id*., ¶ 74. 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. Ex. 1010, ¶ 74. The inventors studied the:

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

Ex. 1001 at 23:17-23. The formulations were stable in both succinate and phosphate buffer: "It was observed in this study, that the SCP/Tween™ 80 formulations (in either buffer) were completely stable at 25° C. and 37° C. for the entire stability study (i.e., up to eight weeks and six weeks, respectively)." *Id*. at 23:25-29.[6]

C. Prosecution History of the '999 Patent

The '999 Patent is the last in a family of three non-provisional applications (Exs. 1002, 1005, 1003), all claiming priority back to Provisional Application No. 60/795,261, filed April 26, 2006 (Ex. 1006). The '999 Patent was filed on

[6] 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. 1010, ¶ 75. 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*.

September 28, 2012 with a preliminary amendment that, *inter alia*, added new claims 41-55. Ex. 1002 at 101-106. The buffer of new claims 47 and 50 (issuing as claims 13 and 16) was "histidine at pH 5.8." *Id*. at 104. Patent Owner vaguely cited two full pages of the specification ("page 7, line 20, to page 9, 23") as support for all of the new claims collectively. *Id*. at 106. Patent Owner did not cite specific support for "histidine at pH 5.8," and as detailed *infra*, there is no written description of this limitation (let alone its combination with the other claimed elements).

Sole independent claim 24 of the preliminary amendment (corresponding to claim 1 of the '999 Patent) 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.

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

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

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

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

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

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

D. Chiron 2003

Grounds 1 and 2 of this Petition relies on Chiron's International Patent Publication No. WO 03/009869 ("Chiron 2003"). Ex. 1011. Because Chiron 2003 was published on February 6, 2003, more than one year prior to the earliest possible priority date of the '999 Patent (April 26, 2006), it is prior art under pre-AIA § 102(b). Chiron 2003 is directed to aluminum-adjuvanted vaccine formulations (just like the '999 Patent) with histidine buffer providing 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, 14:3 - 15:9 (Examples 7-9).

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." Ex. 1011 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, Ground 1 of 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,[7] 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.

[7] 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.

F. Elan 2004

Ground 1 of 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. Prevenar 2005

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

Prevenar 2005 is part of the EMEA's European Public Assessment Report ("EPAR") for Prevenar, and was publicly accessible via a link on the EMEA's webpage devoted to the Prevenar EPAR.[8,9] Because Prevenar 2005 was published

[8] Archived copies of the contemporaneous Prevenar EPAR webpage are also accessible via the Internet Archive. Ex. 1016 at 4-8 Although the frame linking to the Prevenar 2005 SPC (Ex. 1016 at 7) was archived January 24, 2005 (one day prior to the date that the Prevenar 2005 SPC was archived), the Prevenar SPC did not change during that time. Ex. 1077 (printout of the EU Community Register

as of January 25, 2005, which is more than one year before the earliest possible priority date of the '999 Patent (April 26, 2006), Prevenar 2005 is prior art under pre-AIA § 102(b).

Prevenar 2005 discloses both the composition and container of Patent Owner's Prevenar vaccine, which was licensed in the European Union on February 2, 2001. An approved form of the vaccine was a "0.5 ml suspension for injection in pre-filled syringe (Type I glass)." Ex. 1017 at 14 (§ 6.5). Such pre-filled syringes were known to be siliconized. Ex. 1010, ¶ 128. As explained *supra* at Section VI.A.5, no suitable alternatives existed at the time for lubricating glass syringe barrels to allow for smooth plunger movement. Notably, in Prevenar 2005, the components in contact with the glass barrel interior or formulation - *i.e.*, the plunger stopper and the tip cap - were made of standard butyl rubber, which reinforces that the glass barrel interiors were lubricated with silicone oil. *Id.* (citing Ex. 1076 at 7).

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entry for Prevenar, establishing that no Prevenar marketing decisions were rendered between January 24, 2005 and January 25, 2005).

[9] Moreover, it had been expressly reported in the literature prior to April 26, 2006 that the EMEA SPCs - including specifically the Prevenar SPC - were publicly accessible via the EMEA's website. *See* Ex. 1074.

Prevenar 2005 includes every formulation ingredient of the single independent claim 1 of the '999 Patent, other than a buffer. Ex. 1010, ¶ 129. Prevenar 2005 features 7 pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C 19F and 23F), each "[c]onjugated to the CRM_{197} carrier protein"; these are the same polysaccharide-protein conjugates recited in dependent claim 17 of the '999 Patent. Ex. 1017 at 9 (§ 2). The polysaccharide-protein conjugates of Prevenar 2005 were "adsorbed on aluminium phosphate (0.5 mg)." *Id*. And the excipients included "[s]odium chloride." *Id*. at 14 (§ 6.1).

Prevenar 2005 indicates that particulates should not be visible in the pre-filled syringe: "The vaccine should be well shaken to obtain a homogeneous white suspension and be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise." *Id*. (§ 6.6). An absence of particulates means that there is no visible protein aggregation, including that induced by silicone oil. Ex. 1010, ¶ 130.

H. Merck 2011

Ground 3 of this Petition relies on International Patent Publication No. WO 2011/100151 A1 ("Merck 2011"). Ex. 1018. As discussed below, because claims 13 and 16 of the '999 Patent recite a formulation with histidine pH 5.8 that is not described in the specification of the '999 Patent (or its parent applications), Ex. 1010, ¶ 223, those claims are only entitled to a priority date of September 28, 2012

(the actual filing date of the '999 Patent). Because Merck 2011 was published on August 18, 2011, more than one year before the filing date of the '999 Patent (September 28, 2012), it is pre-AIA §102(b) prior art with respect to claims 13 and 16 of the '999 Patent.

Merck 2011 discloses polysaccharide-protein conjugate formulations, including (1) aluminum phosphate, (2) sodium chloride, and (3) histidine buffer at pH 5.8. Merck teaches "a multivalent polysaccharide-protein conjugate mixture consisting of capsular polysaccharides from 15 different serotypes of *S. pneumoniae* conjugated to a carrier protein," and that "the adjuvant is aluminum phosphate." Ex. 1018 at 2:21-24; 3:1-2. Merck 2011 also discloses that "[i]n a preferred embodiment, the vaccine composition is formulated in L-histidine buffer with sodium chloride." *Id*. at 15:16-17. Example 3 makes clear that embodiment includes histidine buffer at pH 5.8. *Id*. at 18:23-29. Merck 2011 further discloses that "[t]he composition of the invention can be formulated as . . . pre-filled syringes." *Id*. at 13:1-2.

I. The '787 Patent

Ground 3 of this Petition further relies on the '787 Patent (U.S. Patent No. 7,935,787), which is in the same family as the '999 Patent. Ex. 1004. The specification of the '787 Patent is identical to that of the '999 Patent, and shares the same teachings at the '999 Patent, *e.g.*, that surfactants and aluminum adjuvant

inhibit silicone-induced aggregation. But the '787 Patent issued on May 3, 2011 (more than one year before the actual filing date of the '999 Patent), and is pre-AIA §102(b) prior art with respect to claims 13 and 16 of the '999 Patent.

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. 1010, ¶ 82. 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.[10] The terms – "polysaccharide" and "container means" – are explicitly defined in the

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

specification of the '999 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 15 and 16. The '999 Patent specifically defines the term "polysaccharide" broadly. Ex. 1001 at 16:32-38. As defined in the '999 Patent, 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." Ex. 1001 at 17:19-37.

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. 1010, ¶ 91.

B. "container means"

The term "container means" appears in independent claim 1. The specification of the '999 Patent specifically defines "container means." Ex. 1001 at 13:40-56. That 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. 1010, ¶ 95.

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. 1010, ¶ 97. This construction is consistent with the plain language of the claim, the specification (which expressly teaches that the invention includes the use of surfactants to inhibit silicone-induced aggregation), and the prosecution history (where Patent Owner uniformly referred

to the invention as inhibition of silicone-induced aggregation by the "formulation," not an individual ingredient). *Id*., ¶¶ 98-102.

IX. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Claims 7-9, 12-13, 15-16 and 21-22 Would Have Been Obvious over Chiron 2003 in View of Smith 1988, Elan 2004 and the General Knowledge of a POSITA

The challenged claims recite nothing more than obvious details of the vaccine components recited in sole independent claim 1, *i.e*., buffer, saline, aluminum salt and polysaccharides. At their narrowest, the challenged claims recite the following limitations (not necessarily in combination with each other):

- either histidine buffer at pH 5.8 (claims 13 and 16), or 5 mM succinate buffer at pH 5.8 to 6.0 (claim 22);
- sodium chloride salt (claims 9, 12-13, 15-16);
- aluminum phosphate adjuvant (claims 12-13, 15-16); and
- pneumococcal polysaccharides (claims 15-16).

As detailed below, the only claim limitations not expressly disclosed in the combination of Chiron 2003, Smith 1988 and Elan 2004 are (1) a pH of 5.8 for the histidine buffer, and (2) 5 mM succinate buffer at pH 5.8 to 6.0. But, as a matter of routine optimization, a POSITA would have considered a pH of 5.8 to maximize adsorption of acidic antigens (such as the claimed pneumococcal polysaccharides) to aluminum phosphate. Likewise, a POSITA would have treated succinate as an

acceptable substitute for histidine; the choice of the 5 mM buffer concentration and a pH in the range of pH 5.8 to 6.0 are already expressly taught by Chiron 2003.

1. Claim 1

The co-pending Petition in IPR2017-00378, based on the same prior art combination, addresses the obviousness of sole independent claim 1. Because each challenged claim in this Petition depends from that claim, the obviousness of claim 1 is addressed here.

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. 1010, ¶ 136. 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, 5:15, 11:30 - 12:15 and 14:3-17:4 (Examples 2 and 7-9).

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. 1010, ¶ 1038. 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. 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. "Oligosaccharides" are shortened versions of bacterial polysaccharides, and as

[11] "Aluminium" is an alternate name for "aluminum," used primarily in Europe. There is no difference between "aluminium" and "aluminum." Ex. 1010, ¶ 139.

discussed above, oligosaccharides and saccharides fall within the '999 Patent's express definition of "polysaccharide." Ex. 1007, ¶¶ 50-52; Ex. 1010, ¶ 141.

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. 1010, ¶ 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. 1010, ¶¶ 144-147 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. 1010, ¶ 144. 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*., ¶ 145 (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*., ¶ 146. 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*., ¶ 147 (citing Exs. 1051, 1053, 155).

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. 1010, ¶ 148. 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 Sections 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. 1010, ¶ 149. 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. 1010, ¶ 151. 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. 1010, ¶ 153. 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*., ¶ 154. 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. 1010, ¶ 144.

2. Claim 7

a. "The formulation of claim 1, wherein the pH buffered saline solution has a pH of 5.5 to 7.5."

The entire preferred pH range of Chiron 2003 (pH "between 6 and 7," which "may be maintained by the use of a buffer") is within the range of pH 5.5-7.5 recited in claim 7 of the '999 Patent. Ex. 1011 at 6:7-8; *see also id*. at 15:6 (pH 7.14±0.05), 14:6-9 (pH 7.2±0.05).

3. Claim 8

a. "The formulation [of] claim 1, wherein the buffer is phosphate, succinate, histidine or citrate.

Chiron 2003 is directed at formulations in which "histidine preferably acts as a buffer." Ex. 1011 at 5:15; *see also id*. at 11:30 - 12:15 and 14:3 - 17:4 (Examples 2 and 7-9).

4. Claim 9

a. "The formulation of claim 1, wherein the salt in the pH buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof."

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).

5. Claim 12

a. "The formulation of claim 1, wherein the buffer is histidine,"

Chiron 2003 is directed at formulations in which "histidine preferably acts as a buffer." Ex. 1011 at 5:15. This claim requires aluminum phosphate, and Chiron 2003 discloses that histidine is "a useful additive for improving the adsorption of antigens to aluminium hydroxyphosphate."[12] *Id.* at 12:14-15. Additionally, Chiron 2003 discloses that "[t]he use of histidine in combination with an aluminium phosphate (particularly a hydroxyphosphate) is particularly advantageous for acidic antigens." *Id.* at 5:3-4; *see also id.* at claim 9. CRM_{197}, as well as the

[12] It was 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. 1010, ¶ 56.

majority of bacterial polysaccharides, including, pneumococcal and meningococcal polysaccharides, are acidic antigens. *Id*. at 12:2-3; Ex. 1007, ¶ 55.

b. "the salt in the pH buffered saline solution is sodium chloride"

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).

c. "and the aluminum salt is aluminum phosphate."

Chiron 2003 discloses a preference for aluminum phosphate over aluminum hydroxide with respect to conjugate vaccine formulations, because of concerns that aluminum hydroxide would hydrolyze polysaccharide antigens, decreasing vaccine immunogenicity. Ex. 1007, ¶ 54; Ex. 1011 at 1:22-24, 11:31 - 12:5. 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).

6. Claim 13

a. "The formulation of claim 1, wherein the buffer is histidine at pH 5.8, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate."

The only difference between claims 12 and 13 is that claim 13 requires the histidine buffer be "at pH 5.8." The effective buffering range of histidine is

approximately pH 5.0-7.0, and the choice of a specific pH within that range would have been a matter of routine optimization. Ex. 1010, ¶ 161. Significantly, the '999 Patent does not provide any written description for histidine buffer at pH of 5.8, let alone suggest that it is crucial to the invention or provides unexpectedly beneficial results. *Id.*; *see ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012) (finding invalidity over prior art where "there is no allegation of criticality or any evidence demonstrating any difference across the range [*i.e.*, the broader range of the prior art]").

Chiron 2003 discloses a **preferred** pH range of 6 to 7, but does not exclude a pH of 5.8. Ex. 1010, ¶ 162. To the contrary, a POSITA would have been motivated to choose histidine buffer with a pH below 6 to increase adsorption of acidic antigens (such as CRM_{197} and most bacterial polysaccharides) to aluminum phosphate adjuvant. *Id.*, ¶ 163. As noted by Chiron 2003, "CRM_{197} is acidic and thus does not completely adsorb to negatively charged aluminium phosphates." Ex. 1011 at 12:2-3. As pH is decreased, the net charge of each of the acidic antigens and aluminum phosphate adjuvant becomes less negative, reducing repulsive forces and promoting adsorption. Ex. 1010, ¶ 163. Moreover, as Chiron 2003 also notes, "[h]istidine, however, is positively charged and it was thought that this might be able to mask the negative charge." Ex. 1011 at 12:3-4. As pH is decreased, the net charge of histidine is more positive, further promoting

adsorption. Ex. 1010, ¶ 163. And, there is no reason to believe that a slightly lower or higher pH than pH 6 to 7 would have frustrated the purposes of Chiron 2003. *Id*., ¶ 162. By way of example, Chiron 2003 discloses histidine buffers with a pH's of around 7.15 and 7.2 – both outside Chiron's preferred range of 6 to 7. Ex. 1011 at 14:3-15:6.

7. Claim 15

a. "The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, the buffer is histidine, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate."

Claim 15 simply adds a "pneumococcal polysaccharides" limitation to claim 12 (reciting histidine buffer, sodium chloride and aluminum phosphate). As discussed above, Chiron 2003 discloses the formulation of claim 12. It would have been obvious to use pneumococcal polysaccharide-protein conjugates in that formulation, and that such formulations would still inhibit silicone-induced aggregation. Ex. 1010, ¶ 164. 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. 1010, ¶ 165. 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.

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. 1010, ¶ 166. And there was a known solution (surfactants) for solving that known *protein* aggregation problem.

8. Claim 16

a. "The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, the buffer is histidine at pH 5.8, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate."

Claim 16 simply adds a "pneumococcal polysaccharides" limitation to claim 13 (reciting histidine buffer at pH 5.8, sodium chloride and aluminum phosphate). As discussed above, Chiron 2003 discloses the formulation of claim 13. It would have been obvious to use pneumococcal polysaccharide-protein conjugates in that formulation, and that such formulations would still inhibit silicone-induced aggregation. Ex. 1010, ¶ 167. 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. 1010, ¶ 168. 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. 1010, ¶ 169. And there was a known solution (surfactants) for solving that known *protein* aggregation problem.

9. Claim 21

a. "The formulation of claim 8, wherein the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0."

Although the buffer of Chiron 2003 is preferably histidine buffer, a POSITA would have found it obvious to use other well-known buffers (such as the claimed

succinate buffer) during routine optimization. Ex. 1010, ¶ 170. Indeed, the data in Figure 1 of the '999 Patent demonstrates that other buffers perform similarly to succinate buffer in the context of surfactant inhibiting silicone-induced aggregation. *Id*. Since succinate has an effective buffering range (approximately pH 4.6 to 6.6) that overlaps in large part with both the buffering range for histidine (approximately pH 5.0 to 7.0) and the physiologically acceptable pH range (approximately pH 5.5 to 7.5), a POSITA would have treated succinate as an acceptable substitute for histidine. *Id*.

The choice of the specific buffer concentration and pH range is also a matter of routine optimization. *Id*., ¶ 171. The claimed concentration range is a common one for buffers. *Id*.; *see also* Ex. 1011 at 5:11-12 (histidine buffer at 2-10 mM). The claimed pH range (5.8-6.0) is especially obvious, not only because it is close to the pKa of succinate (around 5.64), but also because Chiron 2003 discloses a pH of 6.0 as part of its preferred range (6 to 7). Ex. 1010, ¶ 171.

10. Claim 22

a. "The formulation of claim 21, wherein the succinate buffer is at a final concentration of 5 mM."

Claim 22 depends from claim 21 and only adds that the succinate buffer is at a final concentration of 5 mM. The succinate buffer concentration of claim 22 would have been obvious for the same reasons provided with respect to claim 21. Ex. 1010, ¶ 172. The choice of specific buffer concentration is a matter of routine

optimization and 5 mM is a standard one for buffers. *Id*.; *see also* Ex. 1011 at 5:12-13 ("most preferably, [concentration of histidine buffer] is about 5mM").

B. Claims 7-9, 12-13, 15-16 and 21-22 Would Have Been Obvious over Prevenar 2005 in View of Chiron 2003 and the General Knowledge of a POSITA

Ground 2 likewise makes clear that the challenged claims recite nothing more than obvious details of the vaccine components recited in sole independent claim 1, *i.e*., buffer, saline, aluminum salt and polysaccharides. At their narrowest, the challenged claims recite the following limitations (not necessarily in combination with each other):

- either histidine buffer at pH 5.8 (claims 13 and 16), or 5 mM succinate buffer at pH 5.8 to 6.0 (claim 22);
- sodium chloride salt (claims 9, 12-13, 15-16);
- aluminum phosphate adjuvant (claims 12-13, 15-16); and
- pneumococcal polysaccharides (claims 15-16).

As detailed below, the only claim limitations not expressly disclosed in the combination of Prevenar 2005 and Chiron 2003 are (1) a pH of 5.8 for the histidine buffer, and (2) 5 mM succinate buffer at pH 5.8 to 6.0. But, as a matter of routine optimization, a POSITA would have considered a pH of 5.8 to maximize adsorption of acidic antigens (such as the claimed pneumococcal polysaccharides) to aluminum phosphate. Likewise, a POSITA would have treated succinate as an

acceptable substitute for histidine; the choice of the 5 mM buffer concentration and a pH in the range of pH 5.8 to 6.0 are already expressly taught by Chiron 2003.

1. Claim 1

The co-pending Petition in IPR2017-00380, based on the same prior art combination, addresses the obviousness of sole independent claim 1. Because each challenged claim in this Petition depends from that claim, the obviousness of claim 1 is addressed here.

a. "A formulation comprising"

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

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

A "saline solution" includes a salt, usually sodium chloride. Ex. 1010, ¶ 175. Prevenar 2005 discloses use of "[s]odium chloride." Ex. 1017 at 16 (§ 6.1). Chiron 2003 discloses that "[t]he composition may also comprise a sodium salt e.g.

sodium phosphate or sodium chloride." Ex. 1011 at 5:28; *see, e.g., id.* at 14:3 - 17:4 (Examples 7-9).

Buffer (used to resist change in pH) is a standard component of many protein-based pharmaceuticals, including polysaccharide-protein conjugate vaccines (*e.g.*, Vaxem Hib and ProHIBiT). Ex. 1010, ¶¶ 58, 179; Exs. 1051, 1053, 1061 (at __). Acknowledging this, Chiron 2003 teaches a preference for histidine buffer. *Id.* at 1:6-7, 5:15, 5:6-7, 11:30 - 12:15 and 14:3 - 17:4 (Examples 2 and 7-9).

It would have been obvious to use the histidine buffer of Chiron 2003 for the aluminum phosphate-adjuvanted polysaccharide-protein conjugates of Prevenar 2005. Ex. 1010, ¶ 178. Chiron 2003 teaches that histidine improves the stability of aluminum-adjuvanted vaccines:

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

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

> The histidine preferably acts as a buffer. Histidine buffers are well known to the skilled person. Accordingly, the histidine may be ionised within the composition of the invention. **The composition preferably has enhanced pH stability and/or reduced antigen hydrolysis when compared to an equivalent composition** in which histidine buffer system is either replaced with a sodium phosphate buffer system or **in which no buffer system is included.** Reduced hydrolysis may be a consequence of enhanced pH stability.

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

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

Given that histidine buffer is recited in dependent claim 8 of the '999 Patent, it is inherently within the scope of this claim limitation. Ex. 1010, ¶ 182. The histidine buffer disclosed in Chiron 2003 is an amino acid, and the pKa with respect to the side group proton is approximately 6.0. *Id*. (citing Ex. 1045 at 22).

d. "(ii) an aluminum salt"

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

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

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

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

An approved formulation of Prevenar 2005 is provided in a "pre-filled syringe (Type I glass)," which was known to be siliconized. Ex. 1010, ¶ 187 (citing Ex. 1017 at 16, Ex. 1076 at 7).

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

The aluminum phosphate-adjuvanted formulation of Prevenar 2005 (as modified further in view of Chiron 2003) inherently inhibits silicone-induced aggregation in siliconized containers.[13] Ex. 1010, ¶ 188. As recognized during prosecution, inhibition of silicone-induced aggregation is an inherent property of the old formulation of claim 1. *See supra* at Section VI.C. Patent Owner also stressed in the specification of the '999 Patent and during prosecution that adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation. *See supra* at Sections VI.B-C. Both Prevenar 2005 and Chiron 2003 teach adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant. Each Prevenar 2005 conjugate is "adsorbed on aluminium phosphate (0.5 mg)." Ex. 1017 at 11. For Chiron 2003, "[a]ntigen is preferably adsorbed to the aluminium salt." Ex. 1011 at 4:5.

Patent Owner may stress that the data of the '999 Patent (associating aluminum phosphate adjuvant with silicone-induced aggregation) was obtained for

[13] Even if Patent Owner was the first to appreciate this inherent property, it is well-established that reciting the inherent property in a claim does not confer patentability to otherwise old subject matter. *See, e.g.*, *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009); *In re Spada*, 911 F.2d 705, 708-09 (Fed. Cir. 1990).

formulations with succinate buffer, whereas the combination of Prevenar 2005 and Chiron 2003 yields a formulation with a different buffer - histidine. Such an argument is squarely contradicted by the numerous dependent claims (8, 12, 13, 15, 16) that specifically recite histidine buffer. Ex. 1010, ¶ 192.

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

It would have been obvious to combine Prevenar 2005 and Chiron 2003 to arrive at the claimed formulation, and a POSITA would have had a reasonable expectation of success in doing so. Ex. 1010, ¶ 193. Because inhibition of silicone-induced aggregation is an inherent property of the claimed formulation, claim 1 would have been obvious.

Prevenar 2005 teaches a formulation containing pneumococcal polysaccharide-CRM_{197} conjugates adsorbed to aluminum phosphate salt, and sodium chloride, in pre-filled glass syringes (known to be siliconized). Ex. 1017 at 11, 16. As discussed *supra*, the Prevenar 2005 formulation inherently inhibits silicone-induced aggregation. The only limitation missing from Prevenar 2005 is buffer, but as discussed *supra*, Chiron 2003 provides explicit motivation to add histidine buffer to the Prevenar 2005 formulation. Ex. 1010, ¶ 194.

A POSITA would also have had a reasonable expectation of success in incorporating the histidine buffer of Chiron 2003 in the Prevenar 2005 formulation.

Id., ¶ 195. Buffer was a common component of vaccines, and Chiron 2003 teaches that histidine buffer confers pH- and antigen-stability to a pneumococcal conjugate formulation with aluminum phosphate adjuvant (as in Prevenar 2005). *Id*. Based on Chiron 2003, a POSITA would have successfully optimized the Prevenar 2005 formulation with buffer to arrive at claim 1. *Id*.

2. Claim 7

a. "The formulation of claim 1, wherein the pH buffered saline solution has a pH of 5.5 to 7.5."

The entire preferred pH range of Chiron 2003 (pH "between 6 and 7," which "may be maintained by the use of a buffer") is within the range of pH 5.5-7.5 recited in claim 7 of the '999 Patent. Ex. 1011 at 6:7-8; *see also id*. at 15:6 (pH 7.14±0.05), 14:6-9 (pH 7.2±0.05).

3. Claim 8

a. "The formulation [of] claim 1, wherein the buffer is phosphate, succinate, histidine or citrate.

As explained with respect to claim 1, it would have been obvious to modify Prevenar 2005 in view of Chiron 2003 to include histidine buffer. Ex. 1010, ¶ 200.

4. Claim 9

a. "The formulation of claim 1, wherein the salt in the pH buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof."

Prevenar 2005 discloses "[s]odium chloride" as an excipient. Ex. 1017 at 14 (§ 6.1). Likewise, 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).

5. Claim 12

a. "The formulation of claim 1, wherein the buffer is histidine,"

As explained with respect to claim 1, it would have been obvious to modify Prevenar 2005 in view of Chiron 2003 to include histidine buffer. Ex. 1010, ¶ 203. As discussed *infra*, the additional limitations recited in the claim (sodium chloride and aluminum phosphate) do not affect the obviousness analysis, as both Prevenar 2005 and Chiron 2003 disclose each of those ingredients. *Id*., ¶ 204.

b. "the salt in the pH buffered saline solution is sodium chloride"

Prevenar 2005 discloses "[s]odium chloride." Ex. 1017 at 14 (§ 6.1). Likewise, 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).

c. "and the aluminum salt is aluminum phosphate."

Prevenar 2005 incorporates "aluminium phosphate (0.5 mg)." Ex. 1017 at 9. Likewise, 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).

6. Claim 13

a. "The formulation of claim 1, wherein the buffer is histidine at pH 5.8, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate."

The only difference between claims 12 and 13 is that claim 13 requires the histidine buffer be "at pH 5.8." The effective buffering range of histidine is approximately pH 5.0-7.0, and the choice of a specific pH within that range would have been a matter of routine optimization. Ex. 1010, ¶ 209. Significantly, the '999 Patent does not provide any written description for histidine buffer at pH of 5.8, let alone suggest that it is crucial to the invention or provides unexpectedly beneficial results. *Id.*, ¶ 210; *see ClearValue,* 668 F.3d at 1345 (finding invalidity over prior art where "there is no allegation of criticality or any evidence demonstrating any difference across the range [*i.e.*, the broader range of the prior art]").

Chiron 2003 discloses a **preferred** pH range of 6 to 7, but does not exclude a pH of 5.8. Ex. 1010, ¶ 211. To the contrary, a POSITA would have been motivated to choose histidine buffer with a pH below 6 to increase adsorption of acidic antigens (such as CRM_{197} and most bacterial polysaccharides) to aluminum phosphate adjuvant. *Id.*, ¶ 213. As noted by Chiron 2003, "CRM_{197} is acidic and thus does not completely adsorb to negatively charged aluminium phosphates." Ex. 1011 at 12:2-3. As pH is decreased, the net charge of each of the acidic antigens and aluminum phosphate adjuvant becomes less negative, reducing repulsive forces and promoting adsorption. Ex. 1010, ¶ 213. Moreover, as Chiron 2003 also notes, "[h]istidine, however, is positively charged and it was thought that this might be able to mask the negative charge." Ex. 1011 at 12:3-4. As pH is decreased, the net charge of histidine is more positive, further promoting adsorption. Ex. 1010, ¶ 213. And, there is no reason to believe that a slightly lower or higher pH than pH 6 to 7 would have frustrated the purposes of Chiron 2003. *Id.*, ¶ 211. By way of example, Chiron 2003 discloses histidine buffers with a pH's of around 7.15 and 7.2 – both outside Chiron's preferred range of 6 to 7. Ex. 1011 at 14:3-15:6.

7. Claim 15

a. "The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, the buffer is histidine, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate."

Claim 15 simply adds a "pneumococcal polysaccharides" limitation to claim 12 (reciting histidine buffer, sodium chloride and aluminum phosphate). The combination of Prevenar 2005 and Chiron 2003 yields the claimed formulation. Ex. 1010, ¶ 214. In brief, Prevenar 2005 discloses:

- 7 pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), each "[c]onjugated to the CRM_{197} carrier protein" (Ex. 1017 at 9);
- "[s]odium chloride" (*id*. at 14 (§ 6.1)); and
- "aluminium phosphate (0.5 mg)" (*id*. at 9).

The only limitation not disclosed by Prevenar 2005 is histidine buffer. As explained with respect to claim 1, it would have been obvious to modify Prevenar 2005 in view of Chiron 2003 to include histidine buffer. Ex. 1010, ¶ 215.

8. Claim 16

a. "The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, the buffer is histidine at pH 5.8, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate."

Claim 16 simply adds a "pneumococcal polysaccharides" limitation to claim 13 (reciting histidine buffer at pH 5.8, sodium chloride and aluminum phosphate). The combination of Prevenar 2005 and Chiron 2003 yields the claimed formulation. Ex. 1010, ¶ 216. In brief, Prevenar 2005 discloses:

- 7 pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), each "[c]onjugated to the CRM_{197} carrier protein" (Ex. 1017 at 9);
- "[s]odium chloride" (*id*. at 14 (§ 6.1)); and
- "aluminium phosphate (0.5 mg)" (*id*. at 9).

The only limitation not disclosed by Prevenar 2005 is histidine buffer at pH 5.8. As explained with respect to claim 1, it would have been obvious to modify Prevenar 2005 in view of Chiron 2003 to include histidine buffer. Ex. 1010, ¶ 217. And, as explained with respect to claim 13, the choice of pH 5.8 would have been a matter of routine optimization. *Id*.

9. Claim 21

a. "The formulation of claim 8, wherein the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0."

A POSITA would have found it obvious to use the claimed succinate buffer, at the claimed concentration and pH ranges, for Prevenar 2005. Ex. 1010, ¶ 218. As discussed with respect to claim 1, a POSITA would have been motivated to use (with a reasonable expectation of success) the histidine buffer of Chiron 2003 for the aluminum-adjuvanted polysaccharide-protein conjugates of Prevenar 2005. *Id.*, ¶ 219. A POSITA would have found it obvious to use other well-known buffers (such as the claimed succinate buffer) during routine optimization. *Id.* Since succinate has an effective buffering range (approximately pH 4.6 to 6.6) that overlaps in large part with both the buffering range for histidine (approximately pH 5.0 to 7.0) and the physiologically acceptable pH range (approximately pH 5.5 to 7.5), a POSITA would have treated succinate as an acceptable substitute for histidine. *Id.*

The choice of the specific buffer concentration and pH range is also a matter of routine optimization. *Id.*, ¶ 220. The claimed concentration range is a common one for buffers. *Id.*; *see also* Ex. 1011 at 5:11-12 (histidine buffer at 2-10 mM). The claimed pH range (5.8-6.0) is especially obvious, not only because it is close

to the pKa of succinate (around 5.64), but also because Chiron 2003 discloses a pH of 6.0 as part of its preferred range (6.0-7.0). Ex. 1010, ¶ 220.

10. Claim 22

a. "The formulation of claim 21, wherein the succinate buffer is at a final concentration of 5 mM."

Claim 22 depends from claim 21 and only adds that the succinate buffer is at a final concentration of 5 mM. The succinate buffer concentration of claim 22 would have been obvious for the same reasons provided with respect to claim 21. Ex. 1010, ¶ 221. The choice of specific buffer concentration is a matter of routine optimization and 5 mM is a standard one for buffers. *Id*.; *see also* Ex. 1011 at 5:12-13 ("most preferably, [concentration of histidine buffer] is about 5mM").

C. Claims 13 and 16 Would Have Been Obvious over Merck 2011 in View of the '787 Patent and the General Knowledge of a POSITA

Claims 13 and 16 of the '999 Patent each depend from claim 1, and each limits the buffer, salt (of the saline solution), and aluminum salt of claim 1 to histidine buffer at pH 5.8, sodium chloride, and aluminum phosphate, respectively.[14] But the specification of the '999 Patent, and its parent applications, provide no written description of histidine buffer at pH 5.8 (let alone in combination with the other claim elements), as required by pre-AIA 35 U.S.C.

[14] Claim 16 further requires that the conjugates of claim 1 include one or more pneumococcal polysaccharides.

§ 112, ¶ 1; claims 13 and 16 are only entitled a priority date of September 28, 2012 (the actual filing date of the '999 Patent). *Thermo Fischer Scientific Inc. v. 454 Life Sciences Corp.*, IPR2016-00316, Paper 12 (PTAB July 6, 2016) at 24-26 (finding that a claim was not entitled to a priority date earlier than its actual filing date because the written description requirement was not satisfied). Given the later priority date, claims 13 and 16 would have been obvious over Merck 2011 in view of the '787 Patent and the general knowledge of a POSITA. Example 3 of Merck 2011 discloses the pneumococcal polysaccharide-protein conjugate formulations of claims 13 and 16, including histidine buffer at pH 5.8 and aluminum phosphate adjuvant. The '787 Patent (sharing the disclosure of the '999 Patent) teaches the provision of pneumococcal polysaccharide-protein conjugate formulations in siliconized pre-filled syringes, and that adsorption to aluminum phosphate inhibits silicone-induced aggregation. Given that both references are directed to aluminum-adjuvanted pneumococcal conjugate vaccines in pre-filled syringes, a POSITA would have been motivated to combine the two with a reasonable expectation of success.

1. Claims 13 and 16 Are Only Entitled to a Priority Date of September 28, 2012

Claims 13 and 16 – each of which requires histidine buffer at pH 5.8 – are only entitled to a priority date of September 28, 2012 (the actual filing date of the '999 Patent). The law is clear that an overly broad disclosure in a specification is

insufficient to satisfy the written description requirement of pre-AIA § 112, ¶ 1.[15] Because the specifications of the '999 Patent family do not describe histidine buffer at pH 5.8 (let alone in combination with the other elements of claims 1, 13 and 16), Ex. 1010, ¶ 223, they do not satisfy the written description requirement of pre-AIA § 112, ¶ 1. The specifications only disclose that, in some embodiments, the pH of the formulation is anywhere between pH 5.5 and pH 7.5, and that, "in other embodiments," histidine buffer is one of several possibilities. *Id*. (citing Exs. 1001 (at 5:57-60), 1005 (at 52), 1003 (at 19), 1006 (at 11)). The only time pH 5.8 is disclosed is in connection with succinate buffer, not histidine buffer. *Id*. (citing Exs. 1001 (at 5:60-62), 1005 (at 52), 1003 (at 19), 1006 (at 11)). The above

[15] *See, e.g., Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1346 (Fed. Cir. 2013) ("In contrast to the claims—which narrowly recite specific alpha-amylase variants that result from mutating a particular parent enzyme at a single amino acid position to yield distinctive functional properties—the supporting disclosure of the 2000 application provides only generalized guidance listing several variables that might, in some combination, lead to a useful result."); *In re Wako Pure Chemical Indus. Ltd.*, 4 Fed. Appx. 853, 857 (Fed. Cir. 2001) (priority document only described substituents containing 1-10 carbons, and "nothing in the disclosure leads one skilled in the art to select moieties having the specific 3–8 range of carbon atoms recited in the . . . claims.").

disclosure "fail[s] to provide sufficient 'blaze marks' to guide a reader through the forest of disclosed possibilities." *Novozymes*, 723 F.3d at 1346.

2. Claim 13

a. "The formulation of claim 1,"

The formulation of claim 1 requires: "(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." Example 3 of Merck 2011 teaches a "Formulation of a 15-valent Pneumococcal Conjugate Vaccine" with "sodium chloride and L-histidine, pH 5.8, containing buffer" and "aluminum phosphate." Ex. 1018 at 18:23-29. Claim 1 of the '999 Patent further requires that the formulation is in a siliconized container and inhibits silicone-induced aggregation. The '787 Patent teaches the provision of pneumococcal polysaccharide-protein conjugate formulations in siliconized pre-filled syringes, and that adsorption to aluminum phosphate inhibits silicone-induced aggregation. Ex. 1004 at Example 4 (27:35-30:43).

b. "wherein the buffer is histidine at pH 5.8,"

The aluminum-adjuvanted formulation of Example 3 of Merck 2011 includes "L-histidine, pH 5.8, containing buffer." Ex. 1018 at 18:23-29.

c. "the salt in the pH buffered saline solution is sodium chloride"

The aluminum-adjuvanted formulation of Example 3 of Merck 2011 includes "sodium chloride." Ex. 1018 at 18:23-29.

d. "and the aluminum salt is aluminum phosphate."

The aluminum-adjuvanted formulation of Example 3 of Merck 2011 includes "aluminum phosphate." Ex. 1018 at 18:23-29.

e. A POSITA Would Have Been Motivated to Apply (with a Reasonable Expectation of Success) the Teachings of the '787 Patent to Merck 2011

Since both Merck 2011 and the '787 Patent are directed to aluminum-adjuvanted pneumococcal conjugate vaccines in pre-filled syringes, a POSITA would have been motivated to combine their teachings. Ex. 1010, ¶ 231. Given the '787 Patent's shared disclosure with the '999 Patent, a POSITA also would have had a reasonable expectation of success as to inhibition of protein aggregation upon applying the teachings of the '787 Patent to Merck 2011. *Id.*, ¶ 232.

3. Claim 16

a. "The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, the buffer is histidine at pH 5.8, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate."

Claim 16 simply combines the limitations of claim 3 (reciting pneumococcal polysaccharides) and claim 13 (reciting histidine buffer at pH 5.8, sodium chloride

and aluminum phosphate). Example 3 of Merck 2011 teaches an aluminum-adjuvanted formulation for a "15-valent Pneumococcal Conjugate Vaccine." Ex. 1018 at 18:23-29. Thus, this claim would have been obvious for the same reasons provided above with respect to claim 13. Ex. 1010, ¶ 234.

D. Secondary Considerations

To the extent Patent Owner argues that secondary considerations support a finding of non-obviousness, Petitioner reserves the right to respond in Petitioner's Reply; such alleged secondary considerations will not overcome the strong evidence of obviousness based on prior art.

As an initial matter, with respect to at least claims 12-13 and 15-16, Patent Owner's Prevnar 13® does not include histidine buffer and is not a commercial embodiment. Ex. 1057. Moreover, 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. Even with respect to buffer, only a single dependent claim (22) recites a particular buffer concentration, but that claim does not recite any specific type or amount of conjugate(s), saline solution or aluminum salt. The challenged claims are also silent with respect to the amounts of the two claimed formulation

ingredients that purportedly inhibit silicone-induced aggregation, surfactant and aluminum salt.

X. CONCLUSION

Petitioner respectfully submits that it has established a reasonable likelihood that it will prevail as to the obviousness of claims 7-9, 12-13, 15-16 and 21-22 of the '999 Patent. Petitioner respectfully requests that this Petition be granted, *inter partes* review be instituted, and claims 7-9, 12-13, 15-16 and 21-22 of the '999 Patent be found unpatentable and canceled.

Respectfully submitted,

Dated: December 2, 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.

7. The formulation of claim 1, wherein the pH buffered saline solution has a pH of 5.5 to 7.5.

8. The formulation claim 1, wherein the buffer is phosphate, succinate, histidine or citrate.

9. The formulation of claim 1, wherein the salt in the pH buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof.

12. The formulation of claim 1, wherein the buffer is histidine, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate.

13. The formulation of claim 1, wherein the buffer is histidine at pH 5.8, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate.

15. The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, the buffer is histidine, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate.

16. The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, the buffer is histidine at pH 5.8, the salt in the pH buffered saline solution is sodium chloride and the aluminum salt is aluminum phosphate.

21. The formulation of claim 8, wherein the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0.

22. The formulation of claim 21, wherein the succinate buffer is at a final concentration of 5 mM.

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, 13,985 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,562,999, along with all exhibits and other supporting documents, was served on December 2, 2016, by FedEx overnight delivery (Saturday 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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