Nos. 18-2133, -2134

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

MERCK SHARP & DOHME CORP.,

Appellant,

v.

WYETH LLC,

Appellee.

On Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board, in Nos. IPR2017-00378 and IPR2017-00380

OPENING BRIEF FOR APPELLANT MERCK SHARP & DOHME CORP.

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FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

MERCK SHARP & DOHME CORP. **v.** WYETH LLC

Case No. 2018-2133, -2134

CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ■ (appellant) ☐ (respondent) ☐ (appellee) ☐ (amicus) ☐ (name of party)

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Merck Sharp & Dohme Corp.	None	Merck & Co., Inc.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court **(and who have not or will not enter an appearance in this case)** are:

From Hogan Lovells US LLP: Arlene L. Chow and Ernest Yakob.

From MoloLamken LLP: Jeffrey A. Lamken, Michael G. Pattillo, Jr., Sara E. Margolis, and Benjamin T. Sirolly.

From Jones Day: Ryan B. McCrum and Jennifer L. Swize.

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

None.

12/18/2018
Date

/s/ Jeffrey A. Lamken
Signature of counsel

Please Note: All questions must be answered

Jeffrey A. Lamken
Printed name of counsel

cc: All counsel by ECF

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, Appellant Merck Sharp & Dohme Corp. notes that:

(a) there have been no other appeals in this case; and

(b) there are no other cases pending in this or any other court that will directly affect or be directly affected by this Court's decision in Nos. 18-2133, -2134.

INTRODUCTION

This should have been a textbook case of obviousness. In *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Supreme Court explained that "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious." *Id.* at 417. That precisely describes the sole patent claim on appeal.

Wyeth's '999 Patent claims a formulation that stabilizes certain vaccines—polysaccharide-protein conjugates—to prevent them from reacting with the silicone oil that is commonly used to lubricate vaccine storage containers. The problem is that the proteins in the conjugates unfold, and then clump or "aggregate," when they contact silicone oil. Independent claim 1 of the '999 Patent recites a generic formulation, with staple vaccine ingredients, that addresses silicone-induced protein aggregation. But that claimed solution was well known in the art before the patent's priority date. The Patent Trial and Appeal Board ("Board") thus found claim 1 (and multiple dependent claims) unpatentable as obvious—a determination Wyeth has not appealed.

Two dependent claims—claims 17 and 18—recite claim 1's same obvious formulation for stabilizing polysaccharide-protein conjugates. They differ from claim 1 only in that they identify the specific polysaccharide-protein conjugates to

be included in and stabilized by the formulation. Neither claim requires any particular level of immunogenicity (*i.e.*, immune response in the body). Nor do they differ from each other in the protein recited as a carrier; both recite the well-known CRM_{197} carrier protein. They instead differ from each other only in the polysaccharides—from particular bacterial strains or "serotypes"—that are attached to that carrier protein.

The Board found claim 17 obvious. Claim 17 recites the known stabilizing formulation with a conjugate composition that comprises polysaccharides corresponding to 7 particular bacterial serotypes. The Board found no reason to doubt that the obvious stabilizing formulation of claim 1, which works with some polysaccharide-protein conjugates, will work with others. The Board observed that it is the protein, not the polysaccharide, that is responsible for aggregation, and that it is the protein, not the polysaccharide, that the formulation prevents from reacting with silicone oil. The Board thus found that a skilled artisan would have been motivated to apply claim 1's known formulation to the particular polysaccharide-protein conjugates recited in claim 17 and would reasonably have expected success in doing so.

Claim 18 recites the same stabilizing formulation and the same carrier protein. It differs from claim 17 only in that it recites 6 additional polysaccharide serotypes, for a total of 13. Yet the Board reached the opposite result. Those con-

clusions cannot be reconciled. Just as a skilled artisan would have understood that the formulation would stabilize the polysaccharide-protein conjugates in claim 17, the artisan would have understood that the same formulation would stabilize the polysaccharide-protein conjugates in claim 18 in precisely the same way—rendering claim 18 obvious for the same reasons. *See KSR*, 550 U.S. at 417.

The Board reached the wrong result because it asked the wrong question. Under this Court's and the Supreme Court's decisions on obviousness, the Board was required to consider whether a skilled artisan would have recognized that the known stabilizing formulation of claim 1, which generally prevents silicone-oil-induced aggregation for polysaccharide-protein conjugate compositions (as in claim 17), would do the same for the polysaccharide-protein conjugate composition in claim 18. The Board instead asked a different question. It asked whether a skilled artisan would have been motivated to ***modify the known stabilizing formulation*** by adding the recited polysaccharide-protein conjugates of claim 18. That makes no sense. The formulation was known to be broadly effective in stabilizing polysaccharide-protein conjugates; a skilled artisan would not look to improve that stabilizing formulation by adding a particular conjugate composition. The Board's error in applying the wrong legal test, contrary to this Court's and Supreme Court precedents, itself requires reversal.

The Board also failed to offer the reasoned basis for its decision required by the Administrative Procedure Act. It stated that Merck had failed to show that a skilled artisan would have been "motivated . . . to modify [the prior-art stabilizing formulation] in a manner that yields the claimed invention with a reasonable expectation of successfully ***doing so***." Appx40 (emphasis added); *see* Appx39-44 (similar). But the Board never said what the "doing so" was—*i.e.*, what the artisan would not have expected to occur. There is no evaluation of evidence or analysis. It is thus unclear ***what*** the Board's rationale was, much less ***why*** the Board reached that conclusion. And every possible explanation runs headlong into the record; into science; or into disputes the Board never grappled with, much less identified an evidentiary basis for resolving. This Court's precedent is clear that far more was required of the Board—particularly in the face of overwhelming proof that claim 18 was obvious. Reversal is warranted.

JURISDICTIONAL STATEMENT

The Board asserted jurisdiction under 35 U.S.C. §§314, 318(a). Appx2; Appx52; Appx4200; Appx13239. The Board entered final written decisions on June 8, 2018. Appx1-50; Appx51-92. Merck timely appealed on July 6, 2018. Appx9220-9224; Appx18016-18020. This Court has jurisdiction under 28 U.S.C. §1295(a)(4)(A).

ISSUES PRESENTED

The '999 Patent is directed to formulations that "improve the stability of" vaccines "such as polysaccharide-protein conjugates." Appx290 (Abstract). Claim 18 recites (a) a well-known formulation for stabilizing polysaccharide-protein conjugate compositions against silicone-oil-induced protein aggregation with (b) a polysaccharide-protein conjugate composition that includes 13 polysaccharide serotypes conjugated to the CRM_{197} carrier protein. The issues presented are:

1. Whether, on the record before it, the Board erred in finding that Merck had not proved that claim 18 is unpatentable as obvious under 35 U.S.C. § 103.

2. Whether the Board applied the wrong legal test—contrary to *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), and *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064 (Fed. Cir. 2015)—in determining whether a skilled artisan would have been motivated to combine the known stabilizing formulation for polysaccharide-protein conjugates with the known elements of the particular polysaccharide-protein conjugate composition recited in claim 18.

3. Whether the Board's decision upholding claim 18 fails to meet the Administrative Procedure Act's requirement of reasoned decision-making, or is "arbitrary, capricious, an abuse of discretion, . . . not in accordance with law . . . [or] unsupported by substantial evidence," 5 U.S.C. § 706(2)(A), (E), because the

Board's rationale is not reasonably discernable, fails to grapple with the parties' arguments, and fails to address the evidence.

STATEMENT OF THE CASE

I. THE PRIOR ART AND THE '999 PATENT

A. Vaccine Formulation, Aggregation, and Stabilization

This case involves formulations for stabilizing vaccine compositions—specifically, compositions comprised of polysaccharide-protein conjugates—to prevent protein clumping or aggregation that otherwise occurs when such vaccines are stored in "siliconized" containers. While the stabilizing formulations are at the center of this controversy, we begin with the vaccines to be stabilized.

1. *Polysaccharide-Protein Conjugate Bacterial Vaccines*

Pneumococcal infections, caused by the *Streptococcus pneumoniae* (or pneumococcus) bacteria, are a "significant cause of morbidity, hospitalization and mortality worldwide." Appx987. Vaccines prevent such diseases by priming the immune system to recognize disease-causing organisms before exposure occurs. Appx686.

Polysaccharides. Many bacteria—including pneumococcus—are encapsulated by sugars or "polysaccharides." Appx686-687. The immune system targets the polysaccharides. As a result, vaccines against bacterial infections are often composed of these polysaccharides rather than the entire pathogen. Appx686-687.

Serotypes. Polysaccharide vaccines confer immunity only against the particular bacterial strains, or "serotypes," included in the vaccine. Appx687-688. The first polysaccharide vaccine against pneumococcal bacteria was licensed in 1977. Appx695. It was 14-valent—*i.e.*, it included polysaccharides from 14 pneumococcal serotypes. *Id.* Six years later, a 23-valent polysaccharide vaccine was commercialized. *Id.* Adding serotypes to a vaccine expands the scope of immunity. Appx693-694.

Carrier Proteins. While polysaccharide vaccines are effective for adults and older children, they are not effective at conferring immunity in young children. Appx687-688. For more than three decades, however, it has been known that the immune response in young children can be significantly improved if the polysaccharides in the vaccine are conjugated (or attached) to carrier proteins. Appx688-689. "CRM_{197}," a non-toxic mutant of diphtheria toxin, is a preferred carrier protein for polysaccharide-protein conjugate vaccines. *Id.* CRM_{197} was used as early as 1987. Appx1113-1119.

Conjugate Vaccines. Marketed by Wyeth since 2000, Prevnar® ("Prevenar" in Europe and elsewhere) is an example of a pneumococcal polysaccharide-protein conjugate vaccine composition. Appx695. Prevnar® contains 7 polysaccharide serotypes, each of which is individually conjugated to the CRM_{197} carrier protein. Appx695-696.

Wyeth, Merck, and others have since developed higher-valent (*i.e.*, expanded serotype) pneumococcal conjugate vaccines. By 2004, it was well known that Wyeth was developing a 13-valent version of Prevnar®. Appx696-697. By 2006 (the priority date for the patent at issue here), at least five other polysaccharide-protein conjugate vaccines against various bacteria, utilizing CRM_{197} as the carrier protein, had been commercialized. Appx691-692; *see* pp. 11, 12-13, *infra*.

2. *The Problem of—and Known Solution for—Aggregation of Protein-Based Vaccines Stored in Siliconized Containers*

Because proteins are broken down in the gastrointestinal tract, protein-based pharmaceuticals—including polysaccharide-protein conjugate vaccines—cannot be delivered orally. Appx792. They are typically delivered by injection. *Id.* Such injectables are housed in glass vials sealed with a rubber stopper, or in single-dose, pre-filled syringes. Appx792-793. Many components of those containers (*e.g.*, syringe barrels, plunger tips, and vial stoppers) are lubricated with silicone oil to facilitate smoother movement. Appx796-800; Appx932-933. Silicone oil has been the standard lubricant since the 1950s due to its "'stability, hydrophobicity, lubricity, and low toxicity.'" Appx797-798 (quoting Appx933 (Smith 1988)).

Aggregation. Silicone oil, however, can cause protein-based vaccines to "aggregate" or clump. Appx802-804. This clumping occurs because of an interaction—called "adsorption"—between the silicone oil and certain regions of the protein. Proteins include both hydrophilic (water-loving) and hydrophobic

(water-hating) regions. Appx801. A protein in solution typically folds so that its hydrophilic regions are exposed, but its hydrophobic regions are "buried in the core of the protein," away from the solution. *Id.*

Silicone oil, however, is hydrophobic. Contact with silicone oil thus "may cause [a] protein to unfold in such a way that the protein's own hydrophobic regions can bind to the silicone oil." Appx802-803. This may expose additional hydrophobic regions of the protein, which in turn bind to exposed hydrophobic regions of other proteins, causing aggregation. *Id.* Thus, in a polysaccharide-protein conjugate vaccine, it is "the protein component" that "drives aggregation (as opposed to the polysaccharide in the conjugate)." Appx804-805. Polysaccharides are hydrophilic and "are not inclined to aggregate." *Id.*

Aggregation in polysaccharide-protein conjugate vaccines is undesirable. The clumping can cause "clouding or haziness" in the product, which may in turn "cause a patient or consumer to lose confidence" in the vaccine. Appx301, 1:35-36. Clumping may also put at risk "uniformity of dose content of the active ingredient." *Id.*, 1:38-41.

B. Relevant Prior Art

The '999 Patent purports to claim "novel formulations which inhibit precipitation of immunogenic compositions" when "stored in container[s]" lubricated with silicone oil. Appx301, 1:22-24, 10:10. It discloses a generic formulation with

staple vaccine ingredients that addresses the problem of silicone-induced aggregation. That solution, however, was well-known by the time of the patent's 2006 priority date. At that time, it was known that surfactants—simple detergents, like soap—could be used to minimize protein aggregation caused by silicone oil. Appx805 (citing Appx1831; Appx1374). Many surfactants had "already been approved for use internationally in medicinal products," Appx1847, and were actually used in "many licensed protein-based formulations," including polysaccharide-protein conjugate (and other) vaccines, Appx805-806. The prior art thus was robust.

1. *Chiron (International PCT Application No. WO 03/009869)*

Published in February 2003, Chiron discloses a formulation "[t]o improve the stability of vaccines." Appx898 (Abstract). Chiron's stabilizing formulation includes (1) an antigen, (2) an aluminum salt, and (3) histidine (a buffer), often in the form of a saline solution. *Id.*; Appx900, 2:1; Appx912-913, 14:3-15:6. It also includes a surfactant, such as the "Tween 80" product, "to minimise adsorption of antigens to containers." Appx904, 6:14-15. Tween is the commercial name of a surfactant often used in protein-based vaccine formulations. *See* Appx805-806.

Chiron's formulation stabilizes a range of bacterial vaccines. Appx900-901, 2:8-3:19. But Chiron explains that it is preferably directed to the "prevention and/or treatment of bacterial meningitis," including that caused by pneumococcus.

Appx904, 6:32-35. Chiron specifies that the antigen used in its formulation "is preferably . . . a saccharide antigen," including from *Streptococcus pneumoniae*. Appx900, 2:5-15.

Chiron also discloses that, "[w]here a saccharide or carbohydrate antigen is used," that antigen "is preferably conjugated to a carrier protein in order to enhance immunogenicity." Appx901, 3:20-21. Chiron lists multiple proteins that could be used, but explains that the "CRM_{197} diphtheria toxoid is particularly preferred." *Id.*, 3:21-23. Chiron suggests using its formulation to stabilize a wide range of conjugate compositions with different polysaccharides, including the Wyeth 7- and 9-valent pneumococcal CRM_{197} conjugate compositions that had been reported as of that date. *Id.*, 2:5-3:30; *id.*, 2:15 (citing Appx10937 (Rubin 2000)).

2. *Smith ("Siliconization of Parenteral Drug Packaging Components")*

Smith, a 1988 article published in the Journal of Parenteral Science and Technology, explains that nearly all pharmaceutical containers are lubricated with silicone oil. Appx932-933. "Silicone fluid," it observes, "is commonly applied to plastic syringe barrels and glass cartridges used as plunger barrels to facilitate easy movement of the plunger." Appx932.

3. *Elan (International PCT Application No. WO 2004/071439)*

Elan is an international PCT application published in 2004. It discloses that silicone oil can cause protein aggregation, and that such aggregation can be resolved by the addition of a surfactant (polysorbate 80—which is included in the Chiron formulation). Appx960-961.

4. *Peña ("Present and Future of the Pneumonia Vaccination")*

Published in February 2004 by Wyeth itself, Peña discusses the state of pneumonia-vaccine art. Peña discloses that, at the time, there were "two available vaccines to prevent invasive pneumococcal illness in Spain: 23-valent polysaccharides (VNP-23V) and 7-valent conjugated (VNC-7V)." Appx987. Peña explains that the 23-valent pneumococcal polysaccharide vaccine "is not immunogenic in those less than two years of age." Appx988. Wyeth had therefore developed a 7-valent polysaccharide-protein conjugate vaccine. *Id.*; *see* pp. 7-8, *supra*. That 7-valent vaccine contains polysaccharides of seven serotypes of pneumococcal bacteria (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), each conjugated to the CRM_{197} carrier protein. Appx988.

Peña also explains that protein "conjugated vaccines for 9, 11 and 13 serotypes" were "in a very advanced study phase." Appx987. The 9-valent vaccine "incorporate[s]" serotypes 1 and 5 into the 7-valent conjugate vaccine; the 11-valent vaccine further adds serotypes 3 and 7F; and the 13-valent vaccine further

adds serotypes 6A and 19A. Appx993. Thus, the 13-valent vaccine includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. *Id.* Adding these serotypes, Peña states, confers additional resistance by broadening "the spectrum of ages and countries" covered. *Id.* Those pneumococcal serotypes were well-known as the top vaccine candidates by 2002. *See, e.g.*, Appx1219 (Hausdorff 2002).

Peña discloses that Wyeth's 9-valent conjugate vaccine exclusively uses the CRM_{197} carrier protein. *See* Appx995 (citing paper entitled "Safety and immunogenicity of a nonavalent pneumococcal vaccine conjugated to CRM_{197}"). Multiple other sources disclose that Wyeth's 9- and 11-valent vaccines used CRM_{197} as the sole carrier protein. *See* Appx1223 (Obaro 2002) ("[e]ach polysaccharide or oligosaccharide" in Wyeth's 9-valent protein-conjugated vaccine "was coupled independently to CRM_{197}"); Appx1232 (Overturf 2002) (in Wyeth's "11-valent vaccine," the "polysaccharides [were] conjugated to CRM_{197}"); Appx1243 (O'Brien 2004) (same).

5. *Prevenar (Summary of Product Characteristics for Prevenar)*

Published in 2005 on the website of the European Medicines Agency, Prevenar sets forth the characteristics of Wyeth's 7-valent pneumococcal polysaccharide-protein conjugate vaccine. Prevenar discloses that each of the 7 sero-

types of the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) is individually conjugated to the CRM_{197} carrier protein. Appx1024.

C. The '999 Patent

Wyeth has obtained myriad patents worldwide covering its polysaccharide-protein conjugate vaccines, from its 7-valent version to and including patents for its 13-valent conjugate composition. *See, e.g.*, U.S. Patent Nos. 5,360,897, 5,785,937, 8,808,708, 8,895,024, 9,399,060; European Patent No. 1868645; Japanese Patent Nos. 4472770, 5173920, 5730261.

The Wyeth patent at issue here, however—the '999 Patent—is not directed to a novel conjugate vaccine. It purports to cover formulations that "***improve the stability*** of immunogenic compositions ***such as*** polysaccharide-protein conjugates." Appx290 (Abstract) (emphasis added). "More particularly," the Abstract states, "the invention described [in the patent] addresses a need in the art for formulations which stabilize and inhibit particulate formation (e.g., aggregation, precipitation) of immunogenic compositions" that are "stored in container[s]" with silicone oil. *Id.*; *see also* Appx301, 1:22-24 (Field of the Invention) ("the invention relates to novel formulations which inhibit precipitation of immunogenic compositions"); *id.*, 2:53-55 (Summary of the Invention) ("The present invention broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions.").

The patent explains that stability "is a necessary and highly desirable goal" because it allows vaccine compositions to "appear fresh, elegant and professional," increasing patient confidence. Appx301, 1:28-36. But, the patent explains, silicone oil reduces stability—it "induces protein secondary and tertiary conformational changes," causing proteins to aggregate. *Id.*, 2:17-20. Because silicone oil "is a necessary component" for many pharmaceutical preparations, there is an "ongoing need" for formulations that inhibit the protein aggregation it can cause. *Id.*, 2:31-49.

The patent purports to disclose a solution to the aggregation problem: It states that "formulating an immunogenic composition with a surfactant such as Tween^{TM} 80 significantly enhances the stability and inhibits precipitation of an immunogenic composition." Appx305, 10:36-39. The patent describes the results of "stability stud[ies]" of formulations involving the "addition of a surfactant" to "immunogenic composition[s]," including "a thirteen-valent pneumococcal conjugate." *Id.*, 10:35-11:5. The patent indicates that the disclosed thirteen-valent polysaccharide-protein conjugate compositions are "prepared by standard techniques known to those skilled in the art." Appx309, 17:19-20. The conjugation of each polysaccharide "to a carrier protein (e.g., CRM_{197})," it explains, is achieved by "conventional means." *Id.*, 17:37-45.

Independent claim 1 of the '999 Patent recites "[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.

Appx316, 31:7-12 (line breaks added). Dependent claims 2 and 14 recite particular surfactants within claim 1's formulation. *Id.*, 31:13-17, 51-58.

Dependent claim 17 recites the formulation of claim 1, but specifies that the polysaccharide-protein conjugate composition to be stabilized comprises 7 *S. pneumoniae* polysaccharide serotypes—4, 6B, 9V, 14, 18C, 19F, and 23F—each conjugated to a CRM_{197} carrier protein. Appx316, 32:11-22. Those are the same 7 serotypes, and the same carrier protein, in Wyeth's commercialized Prevnar® vaccine. *Compare* pp. 13-14, *supra*.

Dependent claim 18 is the only claim at issue in this appeal. It recites the formulation of claim 1, but specifies that the polysaccharide-protein conjugate composition to be stabilized comprises 13 *S. pneumoniae* polysaccharide serotypes—4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, and 19A—each attached to a CRM_{197} carrier protein. Appx316, 32:23-44. Those are the same 13 poly-

saccharide serotypes, and the same carrier protein, identified in Peña. *See* pp. 12-13, *supra*.

II. PROCEDURAL HISTORY

On December 1, 2016, Merck filed two petitions for *inter partes* review.[1] In the first petition (the "378 Proceeding"), Merck challenged claims 1-6, 10, 11, 14, and 17-20 of the '999 Patent as obvious in view of combinations of Chiron, Smith, Elan, and Peña. In the second petition (the "380 Proceeding"), Merck urged that the same claims of the '999 Patent were obvious in view of combinations of Chiron, Prevenar, and Peña.[2]

A. The Board Institutes Review

The Board instituted review of all challenged claims. The Board found that Merck had shown "that there is a reasonable likelihood that it would prevail in showing the unpatentability" of each claim "over the combined references." Appx4216.

The institution decision first addressed claim construction. Wyeth had argued that the term "polysaccharide-protein conjugate" requires a particular level

[1] Merck filed a third petition for *inter partes* review of certain claims of the '999 Patent. While that petition is not relevant here, the Board found the challenged claims to be unpatentable as obvious.

[2] The 378 Proceeding and the 380 Proceeding presented similar issues in many respects. For simplicity's sake, we cite only to the Board's decisions in the 378 Proceeding, except where citation to the 380 Proceeding is necessary to address specific issues.

of immunogenicity—*i.e.*, immune response in the body. Appx4204-4205. The Board rejected reading that limitation into the claims. Wyeth had not established that the claims require the "formulation to provide any particular 'level of immunogenicity' or effectiveness as a vaccine composition." Appx4207. Instead, the claims focus on another "property of the formulation"—its ***stability*** through "inhibition of aggregation/precipitation induced by the siliconized container means." Appx4206-4207.

With respect to the claim at issue in this appeal—dependent claim 18—the Board found that Merck had established a "reasonable likelihood of . . . showing that claim 18 would have been obvious." Appx4222. The Board rejected Wyeth's argument that it would not have been obvious to conjugate each of the 13 poly-saccharide serotypes of claim 18 to CRM_{197}. Appx4222-4223. The Board found that using a single carrier protein was a "known" approach. Appx4222. Wyeth argued that a skilled artisan "would not have had a reasonable expectation of successfully using a common carrier to prepare a 13-valent conjugate vaccine" because others in the industry had used multiple carrier proteins with higher-valent vaccines. Appx4228. The Board rejected that, too: None of the references Wyeth cited suggest that multiple carriers were selected "out of a necessity." *Id.* The Board further found that those references would not have "discouraged a person of skill in the art from using a common carrier in Chiron's formulation." *Id.*

The Board also found—contrary to Wyeth's contention—that the prior art directed skilled artisans to CRM_{197}. The Board explained that Wyeth itself acknowledged that "the single carrier protein approach was known." Appx4222. Moreover, it found "reasonable" Merck's explanation that a skilled artisan would have known that each of the polysaccharide conjugates identified in Peña "included the same CRM_{197} carrier." Appx4227. And the Board agreed with Merck that a skilled artisan likely would have known that the claimed ***formulation*** "would have inhibited aggregation induced by a siliconized container" when CRM_{197} was used as the carrier protein for those conjugates. *Id.*

B. The Board's Final Written Decisions

The Board issued its final written decisions on June 8, 2018. Appx1-50; Appx51-92. The Board concluded that Merck proved all challenged claims unpatentable, except for claim 18.

The Board began by describing the purported invention: It explained that the '999 Patent's basic formulation includes (1) a polysaccharide-protein conjugate, (2) a buffered saline solution, (3) an aluminum salt, and (4) a surfactant. Appx3. The formulation is housed in a container lubricated with silicone oil. Appx4. The invention's purpose, the Board explained, is to stabilize polysaccharide-protein conjugate vaccines by inhibiting protein aggregation caused by silicone oil. *Id.*; *see also* Appx11 ("[T]he claims are directed to a formulation

comprising a polysaccharide-protein conjugate . . . wherein the formulation inhibits aggregation induced by the siliconized container means.").

The Board then rejected a new claim-construction argument urged by Wyeth. Appx4291-4295. Wyeth argued that the term "polysaccharide-protein conjugate" requires that the conjugate be "antigenic" (which Wyeth characterized as a prerequisite for immunogenicity). Appx7-9. The Board refused to read that limitation into the claims. As in its institution decision, the Board stated that, "[a]lthough . . . the claimed invention is directed toward an immunogenic composition, we also note that the claims do not recite any specific level of immunogenicity for the composition." Appx10.

The Board then examined whether the '999 Patent's claims were obvious.

1. *Independent Claim 1*

In the 378 Proceeding, the Board analyzed the obviousness of independent claim 1 over Chiron, Smith, and Elan. Wyeth never denied that Chiron teaches a formulation comprising ***all*** the ingredients recited by claim 1. Appx21. The parties' dispute instead focused on whether the prior art teaches: (1) placing Chiron's formulation into a siliconized container means, and (2) that Chiron's formulation inhibits protein aggregation. *Id.* The Board answered "yes" to both questions.

The Board first agreed that a skilled artisan "would have used a siliconized container to store Chiron's formulation." Appx27. It "would have been reasonable to expect," the Board stated, "that Chiron prepared the formulation . . . with a goal of ultimately commercializing the formulation and distributing it in siliconized containers, consistent with industry standards." Appx28-29.

The Board further found "it was well-known in the pharmaceutical industry" that silicone oil causes protein aggregation. Appx33. A skilled artisan, moreover, would have reasonably expected that silicone-induced aggregation would be successfully inhibited by addition of a surfactant. Appx34. Elan confirmed that the surfactant in Chiron's formulation "resolved protein precipitation, i.e., aggregation, induced by the siliconized container." *Id.* Thus, according to the Board, a skilled artisan "would have appreciated that Chiron's formulation inhibits aggregation induced by a siliconized container means." Appx32.

The Board thus concluded that claim 1 was obvious. Appx34-35. Given that Wyeth presented no separate argument on dependent claims 2-6, 10, 11, 14, 19, and 20, the Board concluded that they were obvious and unpatentable for the same reasons. Appx35.

In the 380 Proceeding, the Board reached the same conclusion, although it analyzed the obviousness of claim 1 over Chiron and Prevenar. Appx68. While the Board's analysis differed from that of the 378 Proceeding in respects not

relevant here, the Board again concluded that independent claim 1 was obvious, as were dependent claims 2-6, 10, 11, 14, 17, 19, and 20, for which Wyeth had presented no separate argument. Appx77.

2. *Dependent Claim 17*

In the 378 Proceeding, the Board separately analyzed claim 17 over Chiron, Smith, and Elan.[3] Claim 17 applies the formulation of claim 1 to a composition comprising 7 specified *S. pneumoniae* polysaccharide serotypes, each attached to a CRM_{197} carrier protein. Appx316, 32:11-22.

The Board concluded that "a person of ordinary skill in the art would have found it obvious to prepare Chiron's formulation in a manner that meets each limitation of claim 17." Appx37. The Board pointed out that Chiron "expressly discloses that its formulation may be prepared using a saccharide antigen from *S. pneumoniae*," and cites a reference "disclosing a vaccine comprising the same seven valent polysaccharide-protein conjugate recited in the claim." *Id.*

The Board rejected Wyeth's argument that the specific polysaccharides recited in claim 17 might alter the conjugate's behavior in the presence of silicone oil, preventing or reducing the required inhibition of silicone-induced aggregation. Appx36-37. The "protein component"—not the polysaccharide component—"is

[3] Wyeth presented no separate argument regarding claim 17 in the 380 Proceeding. Accordingly, in that proceeding, the analysis of claim 17 was merged with the analysis of the independent claim.

responsible for [silicone-induced] aggregation." Appx38. As a result, the identity of the polysaccharides "would not have affected a surfactant's inhibition of silicone-induced protein aggregation." *Id.* The Board thus was "not persuaded that any such modified response would cause a person of skill in the art to no longer reasonably expect the [surfactant] component of the formulation [to] inhibit any aggregation induced by a siliconized container means." Appx37-38. For essentially "the same reasons," the Board found claim 17 obvious over Merck's alternate combination of Chiron, Smith, Elan, and Peña. Appx43.

3. *Dependent Claim 18*

Finally, the Board analyzed claim 18. That claim is identical to claim 17, except that the vaccine composition recites 6 additional polysaccharide serotypes (for a total of 13), all conjugated to the same CRM_{197} carrier protein. *See* Appx316, 32:23-44. The Board, however, concluded that Merck had failed to prove claim 18 obvious.

The 378 Proceeding. In the 378 proceeding, the Board first considered the obviousness of claim 18 over Chiron, Smith, and Elan. Merck had urged that "[t]he application of the [stabilizing] formulation of claim 1 to the [13-serotype] conjugates of claim 18 would have been obvious for the same reasons" as claim 17. Appx272. Merck argued that, because the formulation acts on the protein—not the polysaccharide—it would have been obvious that Chiron's formulation

"would still inhibit silicone-induced aggregation" of the "claimed pneumococcal polysaccharide-protein conjugates," whether applied to the 7 conjugates of claim 17, or the 13 conjugates of claim 18. Appx270.

The Board did not address whether it would have been obvious for a skilled artisan to seek to stabilize the recited 13 conjugates against silicone-induced aggregation using Chiron's formulation. Instead, the Board asked a different question: It asked whether Merck had "established by a preponderance of the evidence that a person of skill in the art would [have] found it obvious to ***modify Chiron's formulation*** to comprise the thirteen valent conjugate recited in claim 18." Appx39 (emphasis added). It concluded that Merck had not.

The Board acknowledged that Merck had "provide[d] evidence that the thirteen pneumococcal serotypes recited in claim 18 were known in the art." Appx39. But it stated the Merck had "not provided a reason that a person of skill in the art would have modified ***Chiron's formulation*** to comprise a thirteen valent conjugate." *Id.* (emphasis added). In particular, Merck had "not demonstrated that ***Chiron*** teaches or suggests incorporating a thirteen valent conjugate into its formulation." *Id.* (emphasis added). The Board stated, without elaboration, that none of the other references, "or the knowledge [of] one having skill in the art[,] would have motivated the artisan to modify Chiron in a manner that yields the

claimed invention with a reasonable expectation of successfully doing so." Appx40.

The Board next considered Merck's challenge to claim 18 over Chiron, Smith, Elan, and Peña. Again, the Board concluded that Merck had "not provided a reason that a person of skill in the art would have modified Chiron's formulation to comprise a thirteen valent conjugate." Appx44. The Board acknowledged that Peña expressly discloses "a 13-valent pneumococcal conjugate vaccine with the same serotypes recited by claim 18." Appx44. Merck, moreover, had presented evidence that a skilled artisan would have known of 7-, 9-, and 11-valent conjugate vaccines where CRM_{197} was the sole carrier protein. Appx43. But the Board stated it was "unable to assess whether" Peña itself "involved a formulation comprising each of the thirteen known serotypes conjugated to a CRM_{197} polypeptide, as required by the claim." Appx44. "As a result," the Board asserted, there was not "sufficient evidence . . . to determine whether a skilled artisan who endeavored to modify Chiron's formulation to yield a 13-valent pneumococcal conjugate vaccine with the same serotypes as in Peña would have had a reasonable expectation of successfully doing so." *Id.* The Board did not elaborate on what it meant by "successfully doing so." It left unaddressed whether it meant that an artisan would not have expected that Chiron would stabilize the 13-valent conjugate composition; whether it meant that a skilled artisan would not have believed she

was capable of successfully conjugating the 13 polysaccharide serotypes to CRM_{197}; or whether it meant something else entirely.

The Board did not expressly address ***Wyeth's*** primary argument on non-obviousness either. Wyeth contended that a skilled artisan would not have had a reasonable expectation of successfully obtaining an ***immunogenic*** 13-valent CRM_{197} conjugate composition. Appx4329-4336. Wyeth argued that the artisan would have had "significant concerns" that conjugating all 13 serotypes to CRM_{197} would cause "immune interference." Appx4333. Conjugating too many serotypes to one carrier, it suggested, might result in "carrier induced epitope suppression," or "CIES." Appx4333-4334. According to Wyeth, concerns about CIES would have prevented an artisan from having a "reasonable expectation of success in using CRM_{197} as the sole carrier for a 13-valent vaccine." Appx4336.

Merck explained that CIES was irrelevant to the '999 Patent, because the patent's claims do not require any particular level of immunogenicity. Appx274. Merck also presented evidence that artisans would have found purported concerns of CIES to be minimal. Wyeth's own expert, Dr. Fattom, admitted that "CIES is not something that will prevent you from developing any vaccine with any valency. It's a risk management and risk evaluation." Appx7159-7160, 77:25-78:21. Merck had also established—and Wyeth's expert had confirmed—that the patent itself contained no hint that the invention represented a breakthrough in

overcoming CIES. *See* Appx303, 6:49-7:3; Appx310-311, 19:24-21:47; Appx312-315, 23:36-29:32. Instead, the '999 Patent describes the preparation of the mentioned conjugates as "known" and "conventional." Appx309, 17:19-20, 45.

The 380 Proceeding. The Board considered claim 18's obviousness over Chiron and Prevenar. Appx81. Prevenar discloses a vaccine in which 7 of the serotypes recited in claim 18 (4, 6B, 9V, 14, 18C, 19F, and 23F) are individually conjugated to the CRM_{197} carrier protein. Appx1024. The Board framed the question as whether, having combined Chiron's stabilizing formulation with Prevenar's 7-valent polysaccharide-protein conjugate composition, "a person of skill in the art would [have] found it obvious to further modify Prevenar's formulation to comprise the thirteen valent conjugate recited in claim 18." Appx83.

The Board again acknowledged that the 13 "pneumococcal serotypes recited in claim 18 were known in the art." Appx83. But, without further elaboration, it concluded there was no reason the prior art would have "motivated" a skilled artisan to include the 13 serotypes conjugated to CRM_{197} "with a reasonable expectation of successfully doing so." *Id.*

Finally, the Board considered the combination of Chiron, Prevenar, and Peña. As in the 378 Proceeding, it acknowledged that Peña discloses a pneumococcal conjugate vaccine with the 13 serotypes recited in claim 18. Appx86. Because Peña did not expressly disclose whether it "involved a formulation com-

prising each of the thirteen known serotypes conjugated to a CRM_{197} polypeptide, as required by the claim," the Board ruled that there was not "sufficient evidence . . . to determine whether a skilled artisan who endeavored to further modify Prevenar's formulation to yield a 13-valent pneumococcal conjugate vaccine with the same serotypes as in Peña would have had a reasonable expectation of successfully doing so." *Id.* The Board again did not elaborate on ***what*** result the artisan would not anticipate as successful or ***why*** success might be doubted. Nor did it address the '999 Patent's statement that any conjugation was conducted using well-known, standardized techniques. Appx310, 19:39-41.

SUMMARY OF ARGUMENT

I. Claim 18 is obvious, and the Board erred in ruling otherwise. The claim recites a formulation that stabilizes polysaccharide-protein conjugate vaccines against silicone-oil-induced aggregation, together with 13 particular polysaccharide-protein conjugates to be combined with, and stabilized by, the formulation. Every element of claim 18 was known in the prior art. In holding claim 1 obvious—as well as claims 2-6, 10, 11, 14, 17, 19, and 20—the Board found that the recited stabilizing formulation was obvious, as was its use with various polysaccharide-protein conjugates. And there is nothing non-obvious about the particular polysaccharide-protein conjugates recited in claim 18. The polysac-

charide serotypes were all well-known, as was conjugating such polysaccharides to the CRM_{197} carrier protein.

A skilled artisan would self-evidently have been motivated to combine claim 18's recited conjugates with the stabilizing formulation, and would have had a reasonable expectation of success. A skilled artisan would have understood the need to stabilize the conjugates against silicone-oil-induced protein aggregation. And as the Board found in connection with claim 17, a skilled artisan would also have understood that the stabilizing formulation would broadly stabilize any polysaccharide-protein conjugate composition, regardless of the identity of the polysaccharide serotypes. The protein, not the polysaccharides, is responsible for aggregation; the formulation prevents the proteins, not polysaccharides, from interacting with silicone oil. A skilled artisan thus would have had every reason to use the known formulation to stabilize the recited conjugates.

II. The Board also committed legal error by applying the wrong test in evaluating motivation to combine. Under *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), and this Court's decision in *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064 (Fed. Cir. 2015), the Board was required to ask whether a skilled artisan would have understood, from the prior art's teachings, that Chiron's formulation could usefully be ***applied*** to stabilize the 13 conjugates recited in claim 18. The answer to that question is yes: The formulation prevents the aggregation caused by

protein interacting with silicone oil; that formulation was expected to work regardless of the polysaccharides. But the Board instead framed the issue differently. It asked whether a skilled artisan would have been motivated to modify Chiron, which taught the recited stabilizing formulation, by adding the particular 13 polysaccharide-protein conjugates recited in claim 18. That improperly focuses on whether there was a reason to ***change*** Chiron's effective, general stabilization formula—not on whether Chiron's formulation will solve the same problem in the same way for a similar composition. The Board adopted precisely the approach *Belden* rejects.

III. The Board's decision separately fails the Administrative Procedure Act's requirements of reasoned decision-making. The Board concluded that Merck had failed to show that a skilled artisan would have been "motivated . . . to modify" the prior-art stabilizing formulation "in a manner that yields the claimed invention with a reasonable expectation of successfully doing so." Appx40. But the Board never explained what the "doing so" was—what the artisan would not have expected to succeed at doing. The Board did not back up its conclusory statement with further analysis. Nor did it identify the relevant evidence. So it is unclear what the Board's rationale was, much less why the Board reached that conclusion.

The Board might have meant that a skilled artisan would not have expected that Chiron's formulation would stabilize the recited 13 conjugates against

silicone-induced aggregation. But that runs headlong into the Board's other findings and the '999 Patent itself. Or, the Board may have been expressing doubt on the artisan's motivation to make, or expectation of success in making, a 13-valent conjugate composition within the scope of the claim, independent of the stabilizing formulation. But the patent says the techniques were standard.

Regardless, the Board never explicitly said what it meant. It made no findings to adequately support its rationale—whatever that rationale was. Nor did the Board address the parties' competing contentions and evidence. The Board's failure to provide a reasoned decision itself requires reversal.

STANDARD OF REVIEW

"Whether a claimed invention would have been obvious is a question of law, based on factual determinations . . . ." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015). This Court "review[s] the Board's compliance with the governing legal standards de novo and its underlying factual determinations for substantial evidence." *Id.*

This Court's review of the Board's judgment, however, "is rooted not just in the law of obviousness but in basic principles of administrative law." *Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 992 (Fed. Cir. 2017). Under the Administrative Procedure Act, this Court "review[s] the Board's IPR decisions to ensure that they are not 'arbitrary, capricious, an abuse of discretion, . . . otherwise

not in accordance with law . . . [or] unsupported by substantial evidence.'" *Id.* (alterations in original) (quoting 5 U.S.C. § 706(2)(A), (E)). The Board's decision fails that standard if, among other things, it has not "provide[d] a reasoned basis" for its conclusions. *Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 905 (Fed. Cir. 2018) (citing *S.E.C. v. Chenery Corp.*, 318 U.S. 80, 94 (1943)).

ARGUMENT

The Board's decision upholding claim 18 of the '999 Patent cannot be sustained. *First*, the record before the Board shows that the claim is plainly obvious. *Second*, the Board committed legal error in evaluating obviousness, framing the motivation-to-combine inquiry in a fashion that *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), and *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064 (Fed. Cir. 2015), both foreclose. *Third*, the Board failed to articulate a discernable rationale for finding claim 18 non-obvious, failed to grapple with the arguments before it, and failed to support its decision with sufficient evidentiary findings. As a result, the decision cannot be reconciled with the Administrative Procedure Act's requirements of reasoned decision-making. Reversal is warranted.

I. CLAIM 18 OF THE '999 PATENT WAS OBVIOUS BECAUSE IT APPLIES A KNOWN STABILIZATION FORMULATION FOR A KNOWN PURPOSE

An invention is not eligible for a patent if it is "obvious," *i.e.*, "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious . . . to a person having

ordinary skill in the art" at the time the patent application was filed. 35 U.S.C. § 103. Obviousness is "an expansive and flexible" inquiry. *KSR*, 550 U.S. at 415.

Where the invention combines prior-art elements, this Court often asks whether a skilled artisan "would have been motivated to combine the prior art to achieve the claimed invention and whether there would have been a reasonable expectation of success in doing so." *In re Warsaw Orthopedic, Inc.*, 832 F.3d 1327, 1333 (Fed. Cir. 2016). That motivation can be found in prior-art references, "the background knowledge, creativity, and common sense of the person of ordinary skill," "the 'interrelated teachings of multiple patents,'" or "'any need or problem known in the field of endeavor at the time of invention and addressed by the patent.'" *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1329 (Fed. Cir. 2009).

Claim 18 of the '999 Patent is plainly obvious. It recites a generic formulation for stabilizing polysaccharide-protein conjugates against silicone-oil-induced aggregation. And it combines that formulation with—so as to stabilize—a composition comprising 13 specific polysaccharide-protein conjugates. But all the elements of both the stabilizing formulation and the conjugate composition were known in the art. A skilled artisan, moreover, would have had a clear and strong motivation to combine the two to stabilize the conjugate composition against silicone-oil-induced protein aggregation—and every reason to expect success. As

the Board found, the protein—not the polysaccharide—is responsible for aggregation; the formulation prevents the protein from interacting with silicone oil. What works with a protein conjugate is expected to work regardless of the polysaccharides.

The Board thus found ***all*** the other challenged claims obvious. The Board found that a skilled artisan would have been motivated to use Chiron's formulation to stabilize the generic polysaccharide-protein conjugate recited in claim 1. Claims 2-6, 10, 11, 14, 19, and 20 were obvious for the same reasons. The Board likewise found that the artisan would have been motivated to use Chiron's formulation to stabilize the specific composition recited in claim 17, which comprises 7 particular polysaccharide serotypes conjugated to CRM_{197}. The Board rejected any argument that the identity of the particular polysaccharides might reduce effectiveness: Because the "protein component," not the polysaccharide, "is responsible for [silicone-induced] aggregation," the identity of the polysaccharides "would not have affected a surfactant's inhibition of silicone-induced protein aggregation." Appx38. By the same logic, a skilled artisan would have been motivated to use Chiron's formulation to stabilize the polysaccharide-protein conjugate composition recited in claim 18, which differs from claim 17's composition only in that it includes 6 additional polysaccharide serotypes. The Board erred in holding otherwise.

A. All Elements of Claim 18 Were Known in the Art

There can be little dispute that every element of claim 18 was known in the prior art in view of Chiron, Smith, Elan, and Peña.[4]

1. Dependent claim 18 recites "[t]he formulation of claim 1." Appx316, 32:24. Claim 1 in turn recites 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." *Id.*, 31:7-10. That formulation "is comprised in a siliconized container means," and "inhibits aggregation induced by the siliconized container means." *Id.*, 31:10-12. The '999 Patent repeatedly touts that formulation as the "present invention," which supposedly yields the "unexpected and surprising results" of "enhanc[ing] the stability and inhibit[ing] precipitation of an immunogenic composition." Appx305, 10:35-39; *see* Appx290 (Abstract) (claimed formulations "improve the stability of immunogenic compositions such as polysaccharide-protein conjugates").

The Board, however, found that every limitation of claim 1 was already known in the art. Wyeth did not deny "that Chiron teaches a formulation comprising the ingredients recited in independent claim 1." Appx21. The Board agreed with Merck that a skilled artisan "would have used a siliconized container to store Chiron's formulation." Appx27. As disclosed in Smith, such use was "consistent

[4] In the 380 Proceeding, the prior art references Prevenar, Chiron, and Peña disclose every element of claim 18.

with industry standards at the time." Appx28-29. And finally, the Board explained that, in light of Elan, a skilled artisan "would have appreciated that Chiron's formulation inhibits aggregation induced by a siliconized container means." Appx30-32.

The use of surfactants and the other identified materials to inhibit silicone-induced aggregation thus was obvious for polysaccharide-protein conjugates. Chiron in particular discloses such materials. Appx898 (Abstract); Appx904, 6:14-15; *see* pp. 10-11, *supra*. It specifies their use to stabilize "saccharide antigen[s]" from *Streptococcus pneumoniae*. Appx900, 2:15. It expresses a "prefer[ence]" that the polysaccharide be "conjugated to a carrier protein in order to enhance immunogenicity." Appx901, 3:20-21. And it declares that, among carrier proteins, "CRM_{197} . . . is particularly preferred." *Id.*, 3:22-23.[5]

2. All claim 18 adds is that it specifies particular polysaccharide-protein conjugates to be combined with, and stabilized by, claim 1's generic formulation. The conjugates include 13 *S. pneumoniae* polysaccharide serotypes—4, 6B, 9V,

[5] In the 380 Proceeding, the Board found that every element of claim 1's formulation was known in the art. Prevenar teaches every claimed ingredient but one. Wyeth "d[id] not dispute that the only difference between the ingredients recited in claim 1 and Prevenar's formulation is that Prevenar does [not] include a histidine buffer." Appx72. The only missing element—a histidine buffer—is disclosed in Chiron. Appx74-75. Chiron teaches that a histidine buffer "enhances . . . stability," so the artisan would have "had a reason" to add it to the Prevenar vaccine. *Id.* The Board thus found claim 1's formulation obvious. Appx76-77.

14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, and 19A—each attached to a CRM_{197} carrier protein. Appx316, 32:24-45.

The patent never suggests that anything about claim 18's particular polysaccharide-protein conjugate composition is inventive. That is not surprising. As the Board explained, the claims do not require the "formulation to provide any particular 'level of immunogenicity' or effectiveness as a vaccine composition." Appx4207. Instead, the specification merely identifies that polysaccharide-protein conjugate composition as one example that a skilled artisan would want to stabilize against silicone-oil-induced aggregation: It discloses the results of "stability stud[ies]" when claim 1's formulation was applied to that composition. *See* Appx305-306, 10:15-11:45.

The recited composition, in fact, is merely an obvious and logical choice for use with the purportedly novel stabilizing formulation. All the elements of that composition would have been known to a skilled artisan. The Board agreed that the "thirteen pneumococcal serotypes recited in claim 18 were known in the art." Appx39. Peña (and other references in evidence before the Board) identifies those 13 serotypes as the top candidates for a conjugate vaccine. *See* Appx992; Appx1219 (identifying "PCV-11"—that is, serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, "plus 6A and 19A, [which] comprise all major serotypes in each age group studied"). Peña explains that Wyeth (among others) was already

working with a vaccine with those particular 13 serotypes. Appx993 ("In this respect, work is being conducted to incorporate new serotypes to the 7-valent conjugate vaccine, with the 9-valent (which incorporates the serotypes 1 and 5), 11-valent (adding 3 and 7F) and 13-valent (6A and 19a) vaccines in various stages of research.").[6]

The Board acknowledged that using the CRM_{197} protein as a carrier for saccharides of pneumococcal serotypes—whichever serotypes might be chosen—was widely known. Appx41. Chiron teaches that the "CRM_{197} diphtheria toxoid is particularly preferred" when conjugating pneumococcal polysaccharides. Appx901, 3:23-24. Chiron and Peña confirm that CRM_{197} is an effective carrier protein for multi-valent conjugate compositions. As the Board observed, Chiron cites a reference to Wyeth's pneumococcal conjugate vaccine with 7 of the 13 serotypes recited in claim 18, each conjugated to CRM_{197}. *See* Appx37. Wyeth's Peña discloses those same 7 serotypes of pneumococcal bacteria, each conjugated to the CRM_{197} carrier protein. *See* Appx988. Peña further discloses that "[t]here are other conjugated vaccines for 9, 11 and 13 serotypes"—including the 13 serotypes recited in claim 18. Appx987. "[A]lthough they ha[d] not yet been marketed" as of 2004, they were "in a very advanced study phase." *Id.* Still other sources confirm that Wyeth's 9- and 11-valent vaccines used CRM_{197} as the sole carrier

[6] Peña explains that, by adding serotypes, Wyeth "could broaden the spectrum of ages and countries" covered by the vaccine. Appx993.

protein. *See* p. 13, *supra* (discussing Appx1223 (Obaro 2002), Appx1232 (Overturf 2002), and Appx1243 (O'Brien 2004)).

The '999 Patent itself confirms that, by the time the provisional application was filed in 2006, creating the recited conjugates was routine. It explains that the conjugate's "polysaccharides were prepared by standard techniques known to those skilled in the art." Appx310, 19:29-30. And it explains that conjugation of the 13 polysaccharides to CRM_{197} was "achieved by conventional means." Appx310, 19:40-41.

B. Combining the Stabilizing Formulation with the Recited Polysaccharide-Protein Conjugate Composition Was Obvious

Given that the elements of claim 18 were known in the prior art, the only remaining inquiry is whether a skilled artisan "would have been motivated to combine" the recited stabilizing formulation with the recited polysaccharide-protein conjugate composition to stabilize it, "and whether there would have been a reasonable expectation of success in doing so." *Warsaw*, 832 F.3d at 1333.

The answer is "yes." An artisan with a composition comprising the 13 polysaccharide-protein conjugates recited in claim 18 "would have used a silicon-ized container" to store it, "consistent with industry standards"—just as the Board found for the composition of claim 17. Appx27, Appx28-29. The '999 Patent acknowledges that silicone oil is a "necessary component of plastic syringes" used to house vaccines, as it "lubricate[s] the rubber plunger and facilitate[s] transfer of

the plunger down the syringe barrel." Appx301, 2:31-34; *see* Appx932 (Smith). So did the Board. "The evidence reveals," the Board found, the "use of silicone oil as a lubricant was ubiquitous by that time." Appx24-25.

Motivation to combine can arise from "any need or problem known in the field of endeavor at the time of invention and addressed by the patent." *Perfect Web Techs.*, 587 F.3d at 1329. Here, the problem of protein aggregation from storing protein-based vaccine compositions in silicone-oil-lined containers was widely recognized: "[I]t was well-known in the pharmaceutical industry that silicone oil lubricant in contact with pharmaceutical formulations, including vaccines, could lead to protein aggregation." Appx33. The solution was also known: As the Board explained, Elan confirms that the surfactant in Chiron's formulation "resolved protein precipitation, i.e., aggregation, induced by the siliconized container." Appx34. The Board thus found that, in light of those teachings, a skilled artisan "would have appreciated that Chiron's formulation"—which includes all the elements of the formulation recited in claim 1, from which claim 18 depends—"inhibits aggregation induced by a siliconized container means." Appx32.

That makes motivation to combine a foregone conclusion. When storing the polysaccharide-protein conjugate composition of claim 18 in a siliconized container, a skilled artisan would have resolved the known problem of silicone-induced aggregation by using the well-known solution of stabilizers such as

surfactants. Any artisan would thus have been "motivated to combine" the polysaccharide-protein conjugate vaccine with the known formulation of Chiron to stabilize it against the known problem of silicone-oil-induced protein aggregation. *Warsaw*, 832 F.3d at 1333. Indeed, claim 1 was obvious because skilled artisans would have been motivated to combine the known stabilizing formulation with the claim's generic "polysaccharide protein conjugates" to stabilize them. Appx34. Claim 17 was obvious because skilled artisans would have been motivated to use ***the same*** known formulation to stabilize that claim's composition comprising 7 specific polysaccharide-protein conjugates. Appx37-38. And claim 18 was obvious for the same reason. A skilled artisan would have been motivated to use ***the same*** stabilizing formulation to achieve the same result for claim 18's composition comprising 13 polysaccharide-protein conjugates.

The artisan likewise would have had "a reasonable expectation of success in doing so," *Warsaw*, 832 F.3d at 1333, as Chiron's formulation would have been expected to inhibit silicone-induced aggregation regardless of the identity of the particular polysaccharide serotypes. As the Board explained in its analysis of claim 17, Merck's expert had "explained persuasively" that a person of ordinary skill in the art would have understood that any differences in the "polysaccharide molecules would not have affected" the formulation's ability to "inhibit[] . . . silicone-induced protein aggregation." Appx38. It is "the protein component"—

not the polysaccharide component—that "is responsible for such aggregation." *Id.* For that very reason, there is no plausible reason for treating claim 18 any differently than claim 17—or claim 1—which the Board found obvious.

Claim 18 fits squarely within the textbook case of motivation to combine the Supreme Court identified in *KSR*. The Supreme Court explained that, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. Here, Chiron teaches "a technique [that] has been used to improve one device": It discloses a formulation that inhibits silicone-oil-induced protein aggregation in myriad polysaccharide-protein conjugate compositions. *Id.* A skilled artisan thus would have recognized that Chiron could "improve similar devices": It would stabilize the particular 13 polysaccharide-protein conjugates recited in claim 18—"in the same way." *Id.* Wyeth has never suggested that merely combining the claimed conjugates with the stabilizing formulation in a siliconized container is "beyond [the artisan's] skill." *Id.* "[U]sing the [stabilizing] technique" of the recited formulation with the recited conjugates thus "is obvious." *Id.*

II. THE BOARD'S RATIONALE FOR UPHOLDING CLAIM 18 IS LEGALLY UNSUSTAINABLE BECAUSE IT APPLIES AN ERRONEOUS MOTIVATION-TO-COMBINE FRAMEWORK

The Board's decision upholding claim 18 cannot be sustained for a second reason: It applied the wrong legal test. In particular, it committed a major error of obviousness law. Appx40. The Supreme Court's decision in *KSR*, and this Court's decision in *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064 (Fed. Cir. 2015), foreclose the motivation-to-combine framework employed by the Board below.

A. The Board Departed from the Straightforward Motivation-To-Combine Framework Required by *KSR* and *Belden*

In *KSR*, the Supreme Court established a clear framework for evaluating motivation to combine. Motivation to combine, it explained, asks whether an artisan "would recognize" that "a technique [that] has been used to improve one device" "would improve similar devices in the same way." *KSR*, 550 U.S. at 417. Consistent with that, Merck had urged that the relevant question here was whether "[t]he ***application*** of the [stabilizing] formulation of claim 1 to the [13-serotype] conjugates of claim 18 would have been obvious" to a skilled artisan. Appx272 (emphasis added).

The Board, however, reframed the issue as whether a skilled artisan "would have ***modified Chiron's formulation*** to comprise a thirteen valent conjugate."

Appx39 (emphasis added).[7] This Court has held, however, that such an approach does not "withstand[] scrutiny through the lens of governing law." *Belden*, 805 F.3d at 1076. It improperly focuses on whether there was a reason to ***change*** Chiron's effective, general stabilization formula. But the proper question is whether an artisan would have understood that Chiron's formulation could usefully be ***applied*** to stabilize the 13 recited polysaccharide-protein conjugates against silicone-oil-induced protein aggregation. *Id.*; *see also KSR*, 550 U.S. at 417. For that reason alone, reversal is warranted. *See E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 999 (Fed. Cir. 2018).

B. This Court's *Belden* Decision Makes the Board's Error Clear

Belden makes the Board's error particularly clear.

1. *Belden* concerned an obviousness challenge, on *inter partes* review, to a patent for a method of making cables for telecommunications. 805 F.3d at 1067. The independent claim recited an improved technique for making such cables—a method of aligning transmission wires around a core in a way that prevented an unwanted "twisting motion of the core" relative to the transmission wires during manufacture. *Id.* at 1068. The relevant dependent claims specified a type of trans-

[7] Similarly, in the 380 Proceeding, the Board asked whether the artisan "would [have] found it obvious to further modify Prevenar's formulation [*i.e.*, after having already combined it with Chiron] to comprise the thirteen valent conjugate recited in claim 18." Appx83.

mission wire to which the technique could be applied—"twisted pairs of insulated conductors." *Id.* (emphasis omitted).

Two pieces of prior art, in combination, disclosed the elements of the dependent claims. *Belden*, 805 F.3d at 1075. The first reference, JP '910, disclosed the same method of aligning transmission wires around a core, to prevent twisting of the core, as recited in the independent claim. *Id.* at 1073. The transmission wires in prior-art JP '910, however, were "bare metal conductors," rather than the twisted pairs of insulated conductors recited in the dependent claims. *Id.* at 1076. Another reference, CA '046, disclosed transmission wires that were "insulated twisted pairs" of conductors. *Id.* at 1075. But that reference did not address the alignment problem. The "dispute concern[ed] motivation to combine" the two references—the alignment teachings with twisted pairs of insulated conductors. *Id.*

The Board framed the issue as "whether a skilled artisan would ***substitute*** the twisted pairs of CA '046 into the [alignment] method of JP '910." *Belden*, 805 F.3d at 1075 (emphasis added). It concluded that, because JP '910 discloses only bare-metal conductors, "one of ordinary skill, tasked to produce the conventional twisted cable of CA '046, would ***not*** have been motivated by the teachings of JP '910 simply to substitute twisted pairs of insulated conductors for the bare metal conductors in the method of JP '910." *Id.* at 1076.

This Court reversed, finding "legal error[ ]." *Belden*, 805 F.3d at 1075. The first prior art reference "plainly disclose[d] the need to align the conducting wires with the core and how to do so." *Id.* at 1076. It was obvious to apply that same solution to insulated wires in the second reference as well. The "alignment problem and solution," the Court observed, "do not depend on whether the wires are insulated." *Id.* "The Board's disregard of the insulation-independent alignment teaching of JP '910," it continued, "violates the principle that a reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect." *Id.* (emphases and alterations omitted).

The issue was not whether an artisan would have been motivated to ***modify the technique*** in JP '910 by ***substituting the twisted pairs*** of insulated conductors of CA '046 for the bare metal one. Rather, "the proper question" was "whether JP '910 taught a solution to the problem of aligning cable components that a skilled artisan would have been motivated to use in making CA '046's [insulated-conductive] cables." *Belden,* 805 F.3d at 1077. When the question was properly framed, the evidence was "one-sided"—the motivation to combine was clear. *Id.*

2. The Board committed precisely the same mistake here as in *Belden*. Here, as there, the independent claim recites a known solution to address a known problem. *See* pp. 40-42, *supra*. The prior art "plainly discloses the need" to

stabilize polysaccharide-protein conjugates against silicone-oil-induced protein aggregation "and how to do so." *Belden,* 805 F.3d at 1076. That is as true for the particular polysaccharide-protein conjugates in dependent claim 18 as it is for the generic polysaccharide-protein conjugate in independent claim 1 or the specific polysaccharide-protein conjugates in dependent claim 17. "The [protein aggregation] problem and solution do not depend on" the particular polysaccharides employed. *Id.* Because (as the Board found with respect to claim 17) the "protein component," not the polysaccharide component, "is responsible for [silicone-induced] aggregation," a skilled artisan would have understood that the identity of the polysaccharides recited in claim 18 "would not have affected a surfactant's inhibition of silicone-induced protein aggregation." Appx38.

Here, as in *Belden*, the Board incorrectly framed the motivation-to-combine inquiry. It repeatedly framed the issue as whether a skilled artisan would have been motivated to ***modify*** the prior-art improvement technique by adding a particular known item that technique could improve. It thus asked whether a skilled artisan would "have modified Chiron's formulation to comprise a thirteen valent conjugate."[8] Appx39; *see also* Appx44 (similar). But that is the same wrong inquiry this Court rejected in *Belden*—"whether a skilled artisan would substitute

[8] The Board repeated that error in the 380 Proceeding, asking whether a "person of skill in the art would [have] found it obvious to further modify Prevenar's formulation to comprise the thirteen valent conjugate." Appx83; Appx86 (similar).

the twisted pairs of CA '046 into the method of JP '910." 805 F.3d at 1075. That improperly focuses on whether an artisan would have modified "the particular ***invention*** [Chiron] is describing." *Id.* at 1076. The proper inquiry is whether a skilled artisan would have been motivated to employ the "[polysaccharide]-independent [stabilization] teaching[s]" Chiron discloses. *Id.* It makes little sense to ask whether a skilled artisan would have sought to improve Chiron's generic stabilizing formulation merely by choosing one of the innumerable polysaccharide-protein conjugate compositions that could be stabilized by it.

Under *Belden*, the Board was required to consider Chiron "for everything that it ***teaches*** by way of technology." 805 F.3d at 1076. As a result, the proper question was whether Chiron "taught a solution to the problem of [silicone-oil-induced aggregation] that a skilled artisan would have been motivated to use" when storing the conjugate composition of claim 18 in a siliconized container. *Id.* at 1077; *see KSR*, 550 U.S. at 417 (addressing whether an artisan "would recognize" that "a technique [that] has been used to improve one device" "would improve similar devices in the same way"). And as in *Belden*, when the "proper question" is asked, "the record is one-sided"—the motivation to combine is clear. 805 F.3d at 1077; *see* pp. 39-42, *supra*. Simply put, claim 18 is nothing more "than the predictable use of" a prior-art stabilizing formulation, "according to [its] established function[ ]," to achieve a predictable result. *KSR*, 550 U.S. at 417.

Because the Board asked the wrong question, its decision "rests on legal errors." *Belden*, 805 F.3d at 1075. And those legal errors plainly affected its conclusions, as the discrepancy between the Board's analysis of claim 17 and claim 18 proves. In claim 17, the Board properly considered the prior art's teaching that Chiron's ability to stabilize a polysaccharide-protein conjugate did not depend on the identity of the polysaccharides. It thus found that a skilled artisan would have been motivated to combine Chiron with the particular polysaccharide-protein conjugates recited in that claim. But it failed to consider that same teaching with respect to claim 18, and somehow reached the conclusion that a skilled artisan would not have been motivated to combine Chiron with a composition that differs only in the identity of polysaccharides. That makes no sense. The decision should be reversed.

III. THE BOARD'S DECISION UPHOLDING CLAIM 18 FAILS THE REQUIREMENTS OF REASONED DECISIONMAKING

Reversal is warranted for a third reason. The Board did not merely hold non-obvious that which was obvious. Nor did it merely apply an incorrect legal standard for obviousness. It also failed in its duty under the Administrative Procedure Act to ***explain*** its rationale for upholding claim 18, and to ***support*** that decision with evidentiary findings.

This Court's review "is rooted not just in the law of obviousness but in basic principles of administrative law." *Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d

987, 992 (Fed. Cir. 2017). This Court thus "review[s] the Board's IPR decisions to ensure that they are not 'arbitrary, capricious, an abuse of discretion, . . . otherwise not in accordance with law . . . [or] unsupported by substantial evidence.'" *Id.* (alterations in original) (quoting 5 U.S.C. § 706(2)(A), (E)). The Board's decision here fails that standard. Despite its length, the decision does not "provide a reasoned basis" for upholding claim 18. *Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 905 (Fed. Cir. 2018) (citing *S.E.C. v. Chenery Corp.*, 318 U.S. 80, 94 (1943)).

In upholding claim 18, the Board stated several times that a person of ordinary skill would not have been "motivated . . . to modify Chiron in a manner that yields the claimed invention with a reasonable expectation of successfully doing so." Appx40; *see* Appx39-44. But the Board never explained ***what*** the artisan would not have expected to be successful—and it is far from clear what the Board meant. The Board ***might*** have meant that a skilled artisan would not have expected that Chiron's formulation would stabilize the recited 13 conjugates against silicone-induced aggregation. *But see* pp. 51-53, *infra*. The Board ***may*** have been expressing doubt on the artisan's motivation to make, or reasonable expectation of success in making, a 13-valent conjugate composition within the scope of the claim, independent of the stabilizing formulation. *But see* pp. 56-61, *infra*. Or the Board ***might*** have credited (*sub silentio*) Wyeth's argument that an artisan would

not have had a reasonable expectation of successfully obtaining an ***immunogenic*** 13-valent CRM_{197} conjugate composition. *But see* pp. 61-65, *infra*.

But that is all speculation. The Board never explicitly said what it meant. The "need for specificity pervades" this Court's review of a PTAB decision "on motivation to combine" and the attendant question of the artisan's reasonable likelihood of success. *In re NuVasive, Inc.*, 842 F.3d 1376, 1381-82 (Fed. Cir. 2016). The Board provided no specificity. It did not support its vague conclusion with even enough discussion for the reader to be certain ***what*** its rationale was. The Board likewise failed to "make the necessary findings" to provide "an adequate evidentiary basis" to support its rationale—whatever it was. *Id.* at 1382 (quotation marks omitted). Mere "conclusory statements" on the issue of "motivation to combine" and reasonable likelihood of success are "insufficient." *Id.* at 1383.

Regardless, each and every conceivable rationale on this record cannot stand. Each would be "arbitrary," inconsistent, "capricious," or "unsupported by substantial evidence" in its own right. *Pers. Web Techs.*, 848 F.3d at 992 (quotation marks omitted).

A. The Board's Express Findings Foreclose the Theory That Skilled Artisans Would Have Had No Reasonable Expectation That Chiron's Formulation Would Stabilize the 13 Polysaccharide-Protein Conjugates of Claim 18

The Board faulted Merck for not establishing that a skilled artisan would have been "motivated . . . to modify Chiron in a manner that yields the claimed

invention [*i.e.*, by including the 13 recited polysaccharide-protein conjugates] with a reasonable expectation ***of successfully doing so***." Appx39-40 (emphasis added). If the Board meant that skilled artisans would not have reasonably expected Chiron's formulation to stabilize a composition with the 13 claimed conjugates, the Board failed to "explain and support" that rationale. *Pers. Web Techs.*, 848 F.3d at 993. And any such conclusion would defy the evidence and the Board's own findings with respect to claim 17.

Claim 17 applies the stabilizing formulation of claim 1 to a composition comprising seven specific *S. pneumoniae* polysaccharide serotypes, each conjugated to a CRM_{197} carrier protein. Appx316, 32:12-23. The Board found that obvious. Appx36-38. It rejected Wyeth's argument that skilled artisans would have expected that including those 7 serotypes in claim 1's composition would "alter its behavior in the presence of silicone oil," rendering the claimed inhibition of silicone-induced aggregation unpredictable. Appx36-37. The Board explained that the "protein component"—rather than the polysaccharide component—"is responsible for [silicone-induced] aggregation." *Id.* As a result, the identity of the polysaccharides recited in claim 17 "would not have affected a surfactant's inhibition of silicone-induced protein aggregation." Appx38. Because the protein, not the polysaccharides, is what drives silicone-induced aggregation, the Board rejected the notion that fears of "such modified response would cause a person of

skill in the art to no longer reasonably expect the [surfactant] component of the formulation would inhibit any aggregation induced by a siliconized container means." Appx37-38.

Claim 18 differs from claim 17 only in that it adds six additional polysaccharide serotypes (for a total of 13), each likewise conjugated to a CRM_{197} carrier protein. *See* Appx316, 32:24-45. Thus, the Board's findings with respect to claim 17 apply equally: Because the "protein component is responsible for [silicone-induced] aggregation," a skilled artisan would have understood that including additional polysaccharide-protein conjugates in claim 18 "would not have affected a surfactant's inhibition of silicone-induced protein aggregation." Appx38.

The Board made no findings to suggest that a skilled artisan would somehow have expected the 13 conjugates of claim 18 to respond any differently in the stabilizing formulation than the 7 conjugates of claim 17. To the extent that was the Board's rationale, it is "unsupported by substantial evidence." *Pers. Web Techs.*, 848 F.3d at 992; *see also Belden*, 805 F.3d at 1073. And the "internal[] inconsisten[cy]" between such a finding and the Board's finding on the same issue with respect to claim 17 renders any such theory "arbitrary and capricious." *Nat. Res. Def. Council v. U.S. Nuclear Regulatory Comm'n*, 879 F.3d 1202, 1214 (D.C. Cir. 2018).

B. Any Suggestion That Skilled Artisans Would Have Lacked Motivation or Ability To Make a Composition Comprising the Recited 13 Conjugates Fails As Well

It is possible that the Board meant a skilled artisan would have had no motivation to make, or expectation of success in making, ***the polysaccharide-protein conjugate composition*** recited in claim 18—wholly apart from whether she would have combined it with Chiron's stabilizing formulation. That, too, would fail, for myriad reasons.

As a preliminary matter, that rationale would make no sense. The '999 Patent does not purport to disclose inventive vaccines or polysaccharide-protein conjugate compositions themselves. The patent's title is "Formulations Which ***Stabilize*** and Inhibit Precipitation of Immunogenic Compositions." Appx290 (emphasis added). The Abstract states that "the invention described [in the patent] addresses a need in the art for formulations which stabilize and inhibit particulate formation (e.g., aggregation, precipitation) of immunogenic compositions" that are "stored in container[s]" with silicone oil. *Id.* The Field of the Invention and Summary of the Invention likewise confirm that the purported invention relates to the stabilizing formulation. Appx301, 1:22-24 (Field of the Invention) ("the invention relates to novel formulations which inhibit precipitation of immunogenic compositions"); *id.*, 2:53-55 (Summary of the Invention) ("The present invention broadly

relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions.").

Nowhere does the patent suggest that the disclosed 13-valent polysaccharide-protein conjugate composition captured by claim 18 was unknown in the art, or that it could not be made using standard conjugation methods. The specification simply cites that composition as ***an example*** of a conjugate composition that ***could be stabilized*** using the '999 Patent's supposedly inventive formulation. *See* pp. 15-16, *supra*. It would be strange for a conjugate composition that is nowhere touted as inventive to be what renders the claim non-obvious.

Wyeth, moreover, has obtained many patents covering its polysaccharide-protein conjugate vaccines (with earlier priority dates, and earlier expiration dates). *See* p. 14, *supra*. The '999 Patent is not one of them. As the Board elsewhere acknowledged, "[a]lthough . . . the claimed invention is directed toward an immunogenic composition," its focus is on ***stabilizing*** such compositions against silicone-induced aggregation. Appx10. The claims, as the Board recognized, do not require the "formulation to provide any particular 'level of immunogenicity' or effectiveness as a vaccine composition." Appx4207. For that reason, too, it would make little sense for the recited conjugate composition to somehow make the claim non-obvious.

In any event, if the Board upheld claim 18 based on the conclusion that a skilled artisan would have had no motivation to make, or no expectation of successfully making, a 13-valent conjugate composition within the scope of the claim, "[t]he Board did not sufficiently explain and support [that] conclusion[]." *Pers. Web Techs.*, 848 F.3d at 993. And it failed to address, much less resolve, critical disputes over such issues. *See NuVasive*, 842 F.3d at 1382 ("precedent dictates that the PTAB must make a finding of a motivation to combine when it is disputed").

1. *Any Conclusion That a Skilled Artisan Would Not Have Been Motivated To Conjugate the 13 Recited Polysaccharides to the CRM_{197} Protein, or Would Not Have Expected the Conjugation To Be Successful, Is Unexplained and Unsupported*

Any suggestion that those skilled in the art would have lacked motivation to create, or expectation of success in creating, the recited "thirteen valent conjugate" itself, Appx44, has no "reasoned basis" in the Board's decision, *Paice*, 881 F.3d at 905.

The Board acknowledged, as it must, that Wyeth's own Peña reference discloses "a 13-valent pneumococcal conjugate vaccine with the same serotypes recited by claim 18." Appx44. Peña explains that those 13 serotypes are among the 23 commonly known pneumococcal serotypes. Appx988. The Board acknowledged (at Appx39) that "Petitioner's declarant" had "provide[d] evidence that the thirteen pneumococcal serotypes recited in claim 18 were known in the art" as early as

2002—years before the '999 Patent's 2006 priority date. *See* Appx1219 (identifying "PCV-11"—that is, serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, "plus 6A and 19A"—as "compris[ing] all major serotypes in each age group studied"). The Board thus did not deny that a skilled artisan would have been motivated to include those specific serotypes in a polysaccharide-protein conjugate composition.

The Board nonetheless stated that it was "unable to assess" whether the 13-valent pneumococcal conjugate composition disclosed in Peña was "***conjugated to a CRM$_{197}$ polypeptide***, as required by the claim." Appx44 (emphasis added). "As a result," it asserted, there was not "sufficient evidence for us to determine whether a skilled artisan who endeavored to modify Chiron's formulation to yield a 13-valent pneumococcal conjugate vaccine with the same serotypes as in Peña would have had a reasonable expectation of successfully doing so." *Id.*

But there was ample evidence on that issue. The Board just failed to address it. Peña states that in Wyeth's "7-valent pneumococcal conjugate vaccine"—which includes 7 of the 13 serotypes recited in claim 18—the polysaccharides are "conjugated individually with a protein . . . CRM 197." Appx988. Peña further discloses that "work is being conducted to incorporate new serotypes to the 7-valent conjugate vaccine" that uses CRM$_{197}$. Appx993. Consistent with that disclosure, Peña cites a study describing a 9-valent pneumococcal conjugate

vaccine—containing 9 of the 13 serotypes recited in claim 18—in which the polysaccharides are conjugated to CRM_{197}. *See* Appx995 (citing paper entitled "Safety and immunogenicity of a nonavalent pneumococcal vaccine conjugated to CRM_{197}"). Nowhere does Peña suggest that any other carrier protein had been considered or used for the 13-valent composition. When Wyeth's Peña reference then describes the "pneumococcal conjugate" with the same 13 polysaccharide serotypes as claim 18, Appx44; Appx992, the obvious—indeed, only—conclusion is that, like ***all*** the other examples, the polysaccharides were conjugated to CRM_{197}. In its Institution Decision, the Board found Merck's explanation that a skilled artisan would have known that each of the polysaccharide-protein conjugates identified in Peña "included the same CRM_{197} carrier" to be "reasonable." Appx4223. It provided no explanation for reversing course in the Final Written Decision. The Board certainly never explained why a skilled artisan would have thought the protein was anything ***other*** than the single CRM_{197} carrier protein.

Even if Peña alone does not expressly disclose that the 13 polysaccharides are each conjugated to CRM_{197} as recited in claim 18, a skilled artisan would have been motivated to select CRM_{197} as the carrier protein—and would have had a reasonable expectation of success—based on the "interrelated teachings" of the prior art. *Perfect Web Techs.*, 587 F.3d at 1329. Chiron expressly teaches that the "CRM_{197} diphtheria toxoid ***is particularly preferred***" when conjugating pneumo-

coccal polysaccharides. Appx901, 3:22-23 (emphasis added). As early as 1987, CRM_{197} had been used as a carrier for polysaccharide-protein conjugate vaccines. Appx1113-1119. And by the time the '999 Patent was filed, many of the commercialized polysaccharide-protein conjugate vaccines used CRM_{197} as the single carrier protein. Appx691-692 (Kasper Decl.). Why would a skilled artisan turn away from Chiron's "particularly preferred" protein? *See* Appx901, 3:22-23. The Board does not say (if that is what it meant).

There was a rich history of using CRM_{197} as the single carrier protein, including with high-valent conjugates. In addition to Peña (Appx988), Chiron (Appx901, 3:20-24 (citing Appx1894)) and Prevenar (Appx1024) disclose 7-valent vaccines where the polysaccharides are conjugated to CRM_{197}. In addition to Peña, other prior-art publications disclose that Wyeth's 9- and 11-valent vaccines used only CRM_{197}. *See* Appx1223 (Obaro 2002) (noting that "[e]ach polysaccharide or oligosaccharide" in Wyeth's 9-valent vaccine used in the study "was coupled independently to CRM_{197}"); Appx1232 (Overturf 2002) (in Wyeth's 11-valent vaccine, "polysaccharides [were] conjugated to CRM_{197}"); Appx1243 (O'Brien 2004) (same).

Finally, it was known that ***Wyeth itself*** had a ***13-valent conjugate*** composition that used CRM_{197} as a single-carrier protein. As Merck's expert, Dr. Kasper, explained, "when Wyeth applied for a facility license to produce the 13-valent

conjugate vaccine in around 2003, the Ireland EPA noted that CRM_{197} would be ***the only carrier protein*** for the 7-, 9- and ***13-valent*** versions of the vaccine." Appx697-698 (Kasper Decl.) (emphasis added).

Thus, when the art before the Board is "considered for everything it teaches," *Belden*, 805 F.3d at 1076 (emphasis omitted), it is clear that a skilled artisan would have been motivated to conjugate the 13 recited polysaccharides to CRM_{197}, and would have expected to succeed. While the Board faulted Merck for invoking "hindsight reasoning," Appx40, the evidence shows that using CRM_{197} was actually among the most "predictable"—and actually used—"variation[s]" in the field. *KSR*, 550 U.S. at 417.

The '999 Patent itself refutes any suggestion—never advanced by Wyeth below—that a skilled artisan who "endeavored" to make the recited conjugate composition would not have had a reasonable expectation of success. Appx44. The patent nowhere suggests that there was anything inventive, difficult, or unexpected about creating the recited conjugates. It says the opposite. The specification explains that the "[p]olysaccharides are prepared by standard techniques known to those skilled in the art." Appx309, 17:19-20. And it states that "[t]he chemical activation of the polysaccharides and subsequent conjugation to the carrier protein (i.e., a polysaccharide-protein conjugate) are achieved by conventional means." *Id.*, 17:43-45. Given that practicing the claim merely involved the

"predictable use of prior art elements according to their established functions," *KSR*, 550 U.S. at 417, a skilled artisan would have had every expectation that the conjugation would be successful.

The Board, however, did not address any of those issues or evidence. That is fatal to its decision. Such "refusal to consider evidence bearing on the issue before it is, by definition, arbitrary and capricious within the meaning of 5 U.S.C. §706." *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1325 (Fed. Cir. 2017). If the Board thought that, despite that long history of successful multi-valent vaccines using polysaccharides conjugated to CRM_{197}, there was something unique about the 13 polysaccharides recited in claim 18, the Board was required to "make the necessary findings" and provide "an adequate 'evidentiary basis'" to support that conclusion. *NuVasive*, 842 F.3d at 1382. Its failure to do so warrants reversal.

2. *To the Extent the Board Credited Wyeth's Immunogenicity Argument, the Board's Decision Is Unexplained, Unsupported, and Legally Erroneous*

Wyeth's primary argument was somewhat different—it had urged that a skilled artisan would not have had a "reasonable expectation of success in using CRM_{197} as the sole carrier for a 13-valent vaccine" based on concerns that the composition would not exhibit a particular level of ***immunogenicity***. Appx4336. But if the Board credited that argument, it cannot be "reasonably . . . discerned" from the Board's opinion. *NuVasive*, 842 F.3d at 1383 (alteration in original). As

an initial matter, the word "immunogenicity"—or even the concept of immunogenicity—appears nowhere in the Board's discussion of claim 18. The Board's decision cannot be upheld based on "'grounds'" that were not "'clearly disclosed'" in that decision. *See id.* at 1382 (quoting *Chenery*, 318 U.S. at 94).

Besides, Wyeth's immunogenicity argument was hotly disputed. Wyeth had argued that an artisan would have had "significant concerns" that conjugating all 13 polysaccharide serotypes to CRM_{197} would result in "immune interference"—a decrease in immunogenicity from conjugating too many serotypes to one carrier called "carrier induced epitope suppression," or "CIES." Appx4333-4334. Wyeth asserted that CIES would have prevented an artisan from having a "reasonable expectation of success in using CRM_{197} as the sole carrier for a 13-valent vaccine." Appx4336.

Merck had presented contrary evidence—that the artisan would find those concerns minimal, and that CIES was no reason to avoid the claimed conjugate composition. Wyeth's expert, Dr. Fattom, admitted that "CIES is not something that will prevent you from developing any vaccine with any valency. It's a risk management and risk evaluation." Appx7159-7160, 77:25-78:21. Merck demonstrated that the patent defies Wyeth's argument. It contains no hint that the purported invention overcame CIES. *See* Appx303-304, 6:49-7:3; Appx310-311, 19:24-21:47; Appx312-315, 23:36-29:32. Wyeth's expert agreed. Appx7167-

7168, 85:23-86:5; Appx7166-7167, 84:25-85:6. To the contrary, the '999 Patent introduces a 13-valent conjugate composition within the scope of the claim as a known vaccine composition to be tested in its claimed formulation. *See* Appx303-403, 6:49-7:3; Appx310-311, 19:24-21:47. That composition is described with terms like "known" and "conventional." Appx309, 17:19-20, 45. If a skilled artisan actually would have had serious concerns about CIES, Merck explained, the '999 Patent's silence on the matter would be inexplicable.

This Court's "precedent dictates that the PTAB must make a finding of a motivation to combine when it is disputed." *NuVasive*, 842 F.3d at 1382. If the Board were to accept Wyeth's immunogenicity arguments (for claims that require no particular degree of immunogenicity), it had to "make the necessary findings" and provide "an adequate evidentiary basis" to support that decision, particularly given the conflicting evidence. *Id.* at 1382 (quotation marks omitted). But "[t]he Board's discussion does not cite, let alone explain or analyze or adopt," either party's evidence on this issue. *Pers. Web Techs.*, 848 F.3d at 993. For that reason too, the Board's decision cannot be upheld on an immunogenicity theory it never articulated.

Finally, Wyeth's immunogenicity arguments are foreclosed by the Board's claim construction. In the Institution Decision, the Board rejected Wyeth's argument that the claim term "polysaccharide-protein conjugate" required a particular

level of immunogenicity. Appx4204-4205. The Board concluded that Wyeth had not established that the claims require the "formulation to provide any particular 'level of immunogenicity' or effectiveness as a vaccine composition." Appx4207.

After institution, Wyeth raised a new claim-construction argument, urging that the term "polysaccharide-protein conjugate" required that the conjugate have a particular level of "antigenicity"—which Wyeth urged is a prerequisite for immunogenicity. *See* Appx7-9. In its Final Written Decision, the Board rejected that attempt to back-door the already-rejected immunogenicity requirement. Appx7-11. The Board stated that, "[a]lthough . . . the claimed invention is directed toward an immunogenic composition, we also note that the claims do not recite any specific level of immunogenicity for the composition." Appx10. The specification's focus was not on particular immunogenic compositions, but rather a stabilizing formulation: "The Specification explains that the invention 'broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions.'" *Id.* (quoting Appx301, 2:53-55). The Board thus held that the claims do not require a specific level of immunogenicity.

This Court has warned that one must "consider the appropriate scope of the . . . claimed invention in evaluating the reasonable expectation of success." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 966 (Fed. Cir. 2014). The claims here do not require any particular level of immunogenicity. As a result, immuno-

genicity concerns are irrelevant to reasonable expectation of success. For that reason, too, Wyeth's arguments about immunogenicity could not support the Board's decision. That would be true even if the Board had credited, and provided some basis for crediting, Wyeth's position over Merck's—which it did not.

CONCLUSION

The Board's decision upholding claim 18 of the '999 Patent should be reversed.

December 18, 2018

Respectfully submitted,

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ADDENDUM

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Paper No. 59
Entered: June 8, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

WYETH LLC,
Patent Owner.

Case IPR2017-00378
Patent 8,562,999 B2

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition (Paper 1; "Pet.") to institute an *inter partes* review of claims 1–6, 10, 11, 14, and 17–20 of U.S. Patent 8,562,999 B2 (Ex. 1001; "the '999 patent"). Wyeth LLC ("Patent Owner") filed a Patent Owner's Preliminary Response (Paper 6; ("Prelim. Resp.").

On June 13, 2017, we instituted an *inter partes* review of all challenged claims. Paper 9 ("Dec. Inst."). On September 13, 2017, Patent Owner filed a Patent Owner Response to the Petition. Paper 16 ("PO Resp."). On December 13, 2017, Petitioner filed a Reply to the Patent Owner Response. Paper 28 ("Reply").

Petitioner and Patent Owner each filed a Motion to Exclude Evidence. Papers 34 and 38. Each party filed an Opposition to the other party's motion. Papers 42 and 45. Each party also filed a Reply to the other party's Opposition. Papers 49 and 55.[1] Patent Owner filed Motions for Observation on Cross-Examination Testimony. Papers 39 and 40. Petitioner filed a Response to each of Patent Owner's Motions for Observation. Paper 43 and 46.

On February 27, 2018, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 56 ("Tr.").

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Having considered the record before us, we

[1] We authorized Patent Owner to file a Revised Reply to Petitioner's Opposition to Patent Owner's Motion to Exclude Evidence that complied with the page limit set forth in 37 C.F.R. § 42.24(c)(2). *See* Paper 54.

determine that Petitioner has shown by a preponderance of the evidence that claims 1–6, 10, 11, 14, 17, 19, and 20 are unpatentable. *See* 35 U.S.C. § 316(e). Petitioner has not shown by a preponderance of the evidence that claim 18 is unpatentable. Additionally, the Motions to Exclude Evidence by Petitioner and Patent Owner have been decided below in Section III.

A. Related Proceedings

We have instituted two additional *inter partes* reviews of claims of the '999 patent in IPR2017-00380 and IPR2017-00390. Petitioner and Patent Owner explain that they are unaware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding. Pet. 5–6; Paper 4, 2.

B. The '999 patent

In some aspects, the '999 patent relates to formulations comprising an immunogen in the form of a polysaccharide-protein conjugate, a pH buffered saline solution, and an aluminum salt. Ex. 1001, 2:62–64, 12:9–15. The Specification defines the term "polysaccharide" as including "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." *Id*. at 16:32–38.

In certain embodiments, the compositions further comprise a surfactant. *Id*. at 12:65–67. The Specification explains that a suitable surfactant is one that "stabilizes and inhibits aggregation of an immunogenic composition described herein." *Id*. at 13:9–12. According to the Specification, in one aspect, the "invention relates to the unexpected and

surprising results that formulating an immunogenic composition with a surfactant such as Tween™80 significantly enhances the stability and inhibits precipitation of an immunogenic composition." *Id*. at 10:35–39.

The container means includes, among other items, syringes and vials. *Id*. at 3:2–8. The Specification explains that "silicone oil is a necessary component of plastic syringes, as it serves to lubricate the rubber plunger and facilitate transfer of the plunger down the syringe barrel." *Id*. at 2:31–34. Additionally, silicone oil is used as a coating for glass vials to minimize protein adsorption, and as a lubricant. *Id*. at 2:37–41. According to the Specification, "[i]t has been suggested in the art, that silicone oil, which induces protein secondary and tertiary conformational changes, might be responsible for the aggregation/precipitation seen in certain protein pharmaceutical preparations." *Id*. at 2:17–20 (citation omitted). To address that issue, the Specification states that the invention "broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions." *Id*. at 2:53–55. More specifically, certain embodiments of the invention relate to formulations that inhibit precipitation of immunogenic compositions comprised in siliconized container means. *Id*. at 5:44–50.

C. Illustrative Claims

Independent claim 1 and dependent claim 18 of the '999 patent are illustrative and reproduced below:

> 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.

> 18. The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises an *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 1 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 3 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 5 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6A polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 7F polysaccharide conjugated to a CRM197 polypeptide and an *S. pneumoniae* serotype 19A polysaccharide conjugated to a CRM197 polypeptide.

Ex. 1001, 31:7–12, 32:24–44.

In addition to claim 18, claims 2–6, 10, 11, 14, 17, and 19 depend directly from claim 1. Claim 20 depends from claim 19.

D. The Instituted Grounds of Unpatentability

Petitioner challenges the patentability of the claims as follows:

Claims	Basis	References
1–6, 10, 11, 14, and 17–20	pre-AIA § 103(a)	Chiron,[2] Smith,[3] and Elan[4]
17 and 18	pre-AIA § 103(a)	Chiron, Smith, Elan, and Peña[5]

Petitioner also relies on the Declarations of Dennis L. Kasper, M.D. (Ex. 1007), Devendra Kalonia, Ph.D. (Ex. 1008), Christopher Jones, Ph.D. (Ex. 1118), and Harm HogenEsch, D.V.M., Ph.D. (Ex. 1121). Patent Owner relies on the Declarations of Paul Dalby Ph.D. (Ex. 2115), Ali Fattom, Ph.D. (Ex. 2118), Lakshmi Khandke, Ph.D. (Ex. 2119), Garry Morefield, Ph.D. (Ex. 2120), and James W. Thomson, Ph.D. (Ex. 2123).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016)

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[2] Patent Application Publication No. WO 2003/009869 A1 by Mario Contorni et al., published February 6, 2003. Ex. 1011 ("Chiron").
[3] Smith et al., *Technical Report No. 12: Siliconization of Parenteral Drug Packaging Components*, 42 (4S) J. PARENTERAL SCI. & TECH. S3–S13 (1988). Ex. 1012 ("Smith").
[4] Patent Application Publication No. WO 2004/071439 A2 by David Burke et al., published August 26, 2004. Ex. 1013 ("Elan").
[5] de la Peña et al., *Present and future of the pneumonia vaccination*, 24(4) PEDIATRIKA 47–55 (2004) (English Translation). Ex. 1015 ("Peña").

(affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner and Patent Owner propose constructions for certain claims terms. Pet. 37–42; PO Resp. 11–20. As relevant to this Decision, we address the following claim terms.

1. "polysaccharide" and "polysaccharide-protein conjugates"

Petitioner asserts that the broadest reasonable interpretation of the claim term "polysaccharide" is set forth in the Specification. Pet. 37–42. In particular, the Specification defines "polysaccharide" as including "any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including, but not limited to, a 'saccharide', an 'oligosaccharide', a 'polysaccharide', a 'liposaccharide', a 'lipo-oligosaccharide (LOS)', a 'lipopolysaccharide (LPS)', a 'glycosylate', a 'glycoconjugate' and the like." Ex. 1001, 16:32–38. Patent Owner similarly acknowledges that the term "polysaccharide" is expressly defined in the Specification. PO Resp. 11.

Petitioner does not propose a separate construction for the claim phrase "polysaccharide-protein conjugates." Patent Owner, however, asserts that the broadest reasonable interpretation of that claim phrase is:

> a conjugate resulting from reacting 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 lipooligosaccharide, a liposaccharide, a glycosylate, a glycoconjugate, and the like with a carrier protein, that is amenable to standard conjugation procedures, wherein the antigenic saccharide element retains antigenicity after conjugation.

PO Resp. 12 (underlining removed). Patent Owner notes that its proposed construction is "rooted in the preliminary construction adopted by the Board," but adds the requirement that the antigenic saccharide element retains antigenicity after conjugation. *Id.*

Patent Owner asserts that "a purpose of the invention is to provide formulations that preserve the antigenicity of immunogenic formulations." *Id.* According to Patent Owner, the "inhibition of aggregation/precipitation" described in the Specification is a "proxy for whether there is a loss of antigenicity in the formulation." *Id.* Patent Owner asserts that it would be "improper to ignore the properties (i.e., antigenicity) of the conjugate" when construing the claim. *Id.* In support of its proposed construction, Patent Owner identifies various instances in the Specification wherein the polysaccharide-protein conjugate is referred to as an "immunogen" or "immunogenic" composition. *Id.* at 13 (citing, e.g., Ex. 1001, 14:19–23) ("the immunogen (i.e., a polysaccharide-protein conjugate . . .)").

Patent Owner draws our attention to the Specification discussion in the "Background of the Invention" section that "the immunogenic composition must be active throughout its 'expected' shelf life, wherein any breakdown of the immunogenic composition to an inactive or otherwise

undesired form (e.g., an aggregate) lowers the total concentration of the product." PO Resp. 13 (quoting Ex. 1001, 1:41–46). According to Patent Owner and its declarant, Dr. Thomson, a person of skill in the art would have understood an active polysaccharide-protein conjugate composition to mean an active immunogenic composition. *Id.* (citing Ex. 2123 ¶ 39). Patent Owner asserts that "[f]or an immunogen to be capable of inducing an immune response in a body, the immunogen must be antigenic." *Id.* Patent Owner asserts that "[a]ntigenicity is a prerequisite for immunogenicity." *Id.* at 14. According to Patent Owner, although immunogenicity is not recited in the claims, it is related to a property recited in the claims, i.e., that the formulation "inhibits aggregation induced by the siliconized container means." *Id.* Patent Owner asserts that "silicone-induced aggregation is assessed by measuring antigenicity to determine the extent of the loss of antigenicity due to silicone-induced aggregation." *Id.* (citing Ex. 1001, Example 4).

Petitioner asserts that the "Board should reject Patent Owner's proposed 'antigenicity' limitation for the same reasons it rejected the importation of an 'immunogenicity' requirement" in the Institution Decision because Patent Owner refers to "antigenicity" as a "prerequisite for immunogenicity." Reply at 5–6 (citing PO Resp. 14).

Based on the record as a whole, we determine that the Specification sets forth with reasonable clarity, deliberateness, and precision the definition of the term "polysaccharide," as accurately represented by Petitioner, and acknowledged by Patent Owner. With respect to the phrase "polysaccharide-protein conjugates," the Specification does not provide a similarly precise definition. However, the Specification generally describes

such conjugates in a manner that is consistent with the plain and ordinary meaning of the phrase. For example, the Specification explains that polysaccharides are "chemically activated (e.g., via reductive amination) to make the saccharides capable of reacting with the carrier protein." Ex. 1001, 17:35–37. The Specification also explains that "[c]arrier proteins should be amenable to standard conjugation procedures." *Id.* at 17:47–50. In particular, the Specification states, "[t]he chemical activation of the polysaccharides and subsequent conjugation to the carrier protein (i.e., a polysaccharide-protein conjugate) are achieved by conventional means." *Id.* at 17:43–45. Moreover, as Patent Owner asserts, the Specification describes the polysaccharide-protein conjugates as an example of an "immunogenic composition." Ex. 1001, 1:29–30.

In light of those Specification descriptions, we determine that the broadest reasonable construction of the claim phrase "polysaccharide-protein conjugates" refers to an immunogenic composition resulting from reacting 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, a lipopolysaccharide, a glycosylate, a glycoconjugate, and the like with a carrier protein that is amenable to standard conjugation procedures.

Although we recognize that the claimed invention is directed toward an immunogenic composition, we also note that the claims do not recite any specific level of immunogenicity for the composition. The Specification explains that the invention "broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions." Ex. 1001,

2:53–55. The Specification describes aggregation as an indicator of physical/thermal stability of the immunogenic composition. *Id*. at 2:7–8. Breakdown of the composition to an undesired form (e.g., an aggregate) lowers the total concentration of the product. *Id*. at 1:43–46.

Insofar as Patent Owner asserts that the claims require "measuring antigenicity to determine the extent of the loss of antigenicity due to silicone-induced aggregation," as in Example 4 of the Specification, PO Resp. 14, we disagree. Although Example 4 discusses total antigenicity (and loss), the claims do not require the formulation to retain a particular degree of immunogenicity. Instead, the claims are directed to a formulation comprising a polysaccharide-protein conjugate, i.e., an "immunogen," *see*, *e.g.*, Ex. 1001, 14:19–23, wherein the formulation inhibits aggregation[6] induced by the siliconized container means. The presence of a polysaccharide-protein conjugate confers the immunogenic element of the claim. While performing an immunoassay to measure loss of antigenicity, as in Example 4, may provide information regarding whether silicone-induced aggregation has occurred, such an assay is not required to meet the "protein-polysaccharide conjugate" element of the claim. Moreover, as explained in each example described in the Specification, the occurrence of aggregation/precipitation may be detected upon visual inspection. *See, e.g.*, Ex. 1001, 27:6–11 (discussing visual inspection for precipitation).

[6] *See* Ex. 1001, 12:38–40 (describing interchangeable use of the terms "precipitation" and "aggregation").

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

Petitioner asserts this claim phrase "recites a property of the formulation as a whole, without attributing inhibitory effect to any specific ingredient recited in the claim." Pet. 41 (citing Ex. 1008 ¶ 95). For example, Petitioner asserts that the plain language of the claim does not require that the aluminum salt inhibits silicone-induced aggregation. *Id.* (citing Ex. 1008 ¶ 97). According to Petitioner, because independent claim 1 recites a "formulation" followed by an open-ended term, "comprising," any element(s) comprised in the formulation may contribute the required inhibition, so long as the formulation as a whole "inhibits aggregation induced by the siliconized container means." *Id.*

Patent Owner asserts that this claim phrase means that "the formulation inhibits antigenicity loss of the polysaccharide component of the polysaccharide-protein conjugate that can occur as a result of aggregation induced by the siliconized container." PO Resp. 15. In support of that construction, Patent Owner relies again upon the antigenicity assessment described in Example 4 of the Specification. *Id.* at 16. According to Patent Owner, although visual inspection is used in the Specification examples to observe particulates, such inspection did not indicate whether the polysaccharide components of the vaccine maintained or lost antigenicity as a result of aggregation. *Id.* at 17.

Further, Patent Owner asserts that the "broadest reasonable interpretation of claim 1 should go no further than to read on embodiments that contain the three recited ingredients in a formulation that meets the functional property limitation." *Id.* at 19. According to Patent Owner, the

functional requirement of inhibiting aggregation induced by the siliconized container means must be satisfied by "a formulation of the three specifically recited ingredients [buffered saline solution, aluminum salt, and polysaccharide-protein conjugate], without any un-recited ingredient(s)." *Id.*

Having considered the arguments and evidence, we agree with Petitioner's rationale that claim 1 "recites a property of the formulation as a whole, without attributing inhibitory effect to any specific ingredient recited in the claim." Pet. 41. Further, we agree with Patent Owner that the claim element "the formulation . . . inhibits aggregation induced by the siliconized container means" may be interpreted to include an embodiment wherein the three specific ingredients recited in the claim, i.e., buffered saline solution, aluminum salt, and polysaccharide-protein conjugate, cause inhibition of aggregation induced by the siliconized container means. *See* PO Resp. 18–20. However, we do not agree with Patent Owner that the broadest reasonable interpretation ends there. Rather, we determine that by reciting the formulation using the open-ended term "comprising," along with attributing the aggregation inhibition property to "the formulation," the broadest reasonable construction also includes formulations comprising additional, unrecited ingredients, and such additional ingredient(s) may contribute to the required aggregation inhibition by the formulation. *See In re Baxter*, 656 F.2d 679, 686 (CCPA 1981) (use of the term "comprising" in a preamble of a claim permits inclusion of elements in addition to those specified in the claims); *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'").

Further, we do not determine that the claim phrase requires maintaining any specific level of antigenicity of the conjugate, as asserted by Patent Owner, PO Resp. 15–17, for the same reasons discussed above, with respect to Patent Owner's similar argument raised in connection with its proposed construction of the "polysaccharide-protein conjugate" term.

In view of our analysis, we determine that no additional claim terms require construction for the purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art at the time of the invention would have had either (a) "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," or (b) "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." Pet. 35–36 (citing Ex. 1008 ¶ 80).

Patent Owner relies upon its definition of the level of ordinary skill in the art set forth in the Patent Owner Preliminary Response. PO Resp. 20. In that filing, Patent Owner disagreed with Petitioner's definition insofar as it suggests the field of invention involved protein-based formulations. Prelim. Resp. 10–11. According to Patent Owner, a person of ordinary skill in the art at the time of the invention would have had either (a) "a Ph.D. degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least two years of work experience formulating polysaccharide-protein conjugate immunogenic compositions, and would have had familiarity or experience with the general components and formulation of bacterial vaccines," or (b) "a Master's degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least four years of work experience formulating polysaccharide-protein conjugate immunogenic compositions, and would have had familiarity or experience with the general components and formulation of bacterial vaccines." *Id.* at 11.

In the Institution Decision, we adopted Patent Owner's description of the level of ordinary skill at that stage in the proceeding because it included a requirement for experience relating to polysaccharide-protein conjugates. Dec. Inst. 12–13. Based on the record as a whole, we determine that a declarant having significant experience relating to protein-silicone oil interactions also offers useful information relating to the subject matter of the challenged claims. Thus, we also recognize those having ordinary skill in the art relating to silicone-induced interactions/aggregation in pharmaceuticals.

Thus, we adopt Patent Owner's description of one having ordinary skill in the art of formulating polysaccharide-protein conjugate

immunogenic compositions. Further, we describe one having ordinary skill in the art of silicone-induced interactions/aggregation in pharmaceuticals as either (a) a Ph.D. degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least two years of work experience involving researching silicone-induced interactions/aggregation in pharmaceuticals, or (b) a Master's degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least four years of work experience involving researching silicone-induced interactions/aggregation in pharmaceuticals.

We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). We recognize each of Petitioner's and Patent Owner's declarants as qualified to provide the offered opinions on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention with respect to formulating polysaccharide-protein conjugates and/or silicone-induced interactions/aggregation in pharmaceuticals. The relative weight that we assign such testimony, however, is subject to additional factors. *See, e.g.*, Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,763 (Aug. 14, 2012) ("Opinions expressed without disclosing the underlying facts or data may be given little or no weight.").

Petitioner does not challenge the expertise of any of Patent Owner's declarants. Patent Owner, however, asserts that Petitioner's declarants, Drs. Kalonia and Kasper, lack "experience in developing polysaccharide-protein conjugate formulations, and certainly not on a commercial scale." PO Resp. 20. Regarding Dr. Kalonia, Patent Owner asserts that his experience is "limited to the aggregation of proteins in formulations on a

laboratory scale." *Id*. However, as described in Dr. Kalonia's declaration, such experience involves "significant research experience in protein-interface, protein-protein, and protein-excipient interactions, including interactions among protein, silicone oil and surfactants," as well as co-authoring a book chapter describing applications and concerns relating to silicone oil in biopharmaceutical containers. Ex. 1008 ¶ 7.

We have determined that Dr. Kalonia's credentials and experience qualify him to provide expert testimony addressing protein-silicone oil interactions, which is precisely what Petitioner relies upon this declarant to do. *See, e.g.*, Pet. 5 (describing Dr. Kalonia as a "formulation expert specializing in protein-silicone oil interactions, including silicone-induced protein aggregation in pharmaceuticals"). Insofar as Dr. Kalonia's testimony discusses polysaccharide-protein conjugates, he expressly refers to and relies upon Dr. Kasper's testimony. *See, e.g.*, Ex. 1008 ¶¶ 18, 56, 87, 124, 157, 162, 170.

Regarding Dr. Kasper, Patent Owner asserts that he "has no experience in the development of commercial scale vaccine products," and "is not knowledgeable about vaccine formulation issues such as stability and aggregation." PO Resp. 21. We disagree. As Dr. Kasper explains in his declaration, he is a professor of medicine and microbiology at Harvard Medical School and runs his own research laboratory, wherein a "major focus" of his work is "the development of human vaccines, including polysaccharide-protein conjugate vaccines." Ex. 1007 ¶¶ 1, 5.

In support of its challenge of Dr. Kasper, Patent Owner directs us only to deposition testimony relating to Dr. Kasper's inexperience with using siliconized containers with his vaccine formulations. PO Resp. 21 (citing

Ex. 2035, 13:3–18, 35:20–23). However, as Petitioner has explained, Dr. Kasper's testimony is not offered to address silicone-induced aggregation in pharmaceuticals. Rather, Petitioner relies upon Dr. Kasper to provide testimony in his area of expertise, i.e., formulating polysaccharide-protein conjugate immunogenic compositions, and asserts that he would have had familiarity or experience with the general components and formulation of bacterial vaccines. *See* Pet. 5 (describing Dr. Kasper as "a renowned researcher focusing on the development of human vaccines, including polysaccharide-protein conjugate vaccines").

C. Obviousness over Chiron, Smith, and Elan

Petitioner asserts that claims 1–6, 10, 11, 14, and 17–20 are unpatentable over the combination of Chiron, Smith, and Elan. Pet. 43–62. Patent Owner disagrees. PO Resp. 22–48.

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) where in evidence, so-called secondary considerations. *Graham*, 383 U.S. at 17–18. If the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains, the claim is unpatentable under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

1. Chiron

Chiron discloses vaccine formulations comprising an antigen, aluminum salt, and histidine. Ex. 1011, Abstract. Chiron explains that the

"antigen is preferably a protein antigen or a saccharide antigen," preferably "from bacteria, with the bacterial genus *Neisseria* (e.g. *N.meningitidis*) being particularly preferred." *Id*. at 3. Chiron states, "[w]here a saccharide or carbohydrate antigen is used, it is preferably conjugated to a carrier protein in order to enhance immunogenicity." *Id*. at 4. Preferred carrier proteins are bacterial toxins or toxoids, with the CRM_{197} diphtheria toxoid being "particularly preferred." *Id*. The aluminum salt and histidine improve the stability of the vaccine by improving pH stability (buffering) and aluminum adjuvant adsorption, and/or improving antigen stability by reducing antigen hydrolysis. *Id*. at 2. Chiron teaches that its formulation may also comprise a detergent, e.g., Tween 80, to minimize adsorption of antigens to containers. *Id*. at 7.

2. Smith

Smith is a Technical Report published in the Journal of Parenteral Science and Technology by The Parental Drug Association. Ex. 1012, 1. The report describes siliconization of parenteral drug packaging components. *Id*. Smith explains that "[m]ost parenteral packaging components require the use of some form of lubrication in order to improve their processability and functionality." *Id*. at 4. According to Smith, silicone fluid is "[o]ne of the most commonly used lubricants for pharmaceutical packaging." *Id*. "Siliconization of packaging components such as glass, elastomeric closures, plastic, and metal, places an invisible water repellant film on the surface of the components" that "aid[s] in the free-draining characteristics, processing and machinability of vials and elastomeric closures." *Id*. Smith explains that "[s]ilicone fluid is commonly applied to plastic syringe barrels and glass cartridges used as plunger barrels

to facilitate easy movement of the plunger within the barrel." *Id.* When applied to hypodermic needles, silicone oil reduces the frictional drag and pain associated with such drag as the coated needle passes through body tissue. *Id.*

3. Elan

Elan discloses stable pharmaceutical immunoglobulin formulations comprising a therapeutically effective amount of an antibody, polysorbate 80, and a buffer. Ex. 1013, Abstract, 3. Elan explains that developing stable formulations that can maintain a small volume even with an increased concentration of antibody "has been hindered by the proteins or the antibodies themselves, which have a high tendency to aggregate and precipitate." *Id.* at 2. Elan explains that silicone oil was introduced into the product upon use of standard lubricated polypropylene syringes equipped with siliconized rubber stoppers. *Id.* at 15. Elan determined that the presence of the silicone oil was sufficient to cause discernible antibody precipitation in a formulation of antibody (natalizumab), histidine, and a buffer, upon gentle agitation and room temperature storage. *Id.* at 17. Elan reports that visual inspection confirmed that such precipitation was resolved by the addition of polysorbate 80. *Id.* at 17–18.

4. Obviousness Analysis

a. Claims 1–6, 10, 11, 14, 19, and 20

Petitioner contends that Chiron teaches or suggests every ingredient recited in the formulations of claims 1–6, 10, 11, 14, 19, and 20. Pet. 43–44. In particular, Petitioner asserts that Chiron teaches vaccine formulations comprising a bacterial saccharide antigen, histidine buffer, a sodium salt,

e.g., sodium phosphate or sodium chloride, and an aluminum salt. *Id*. at 44–45 (citing, e.g., Ex. 1011, 1:6–7, 2:1, 5:6–7, 15, 28). Petitioner asserts that Chiron's histidine buffer is inherently within the scope of the claim limitation requiring the buffer to have a pKa of about 3.5 to about 7.5 because "the pKa with respect to the side group proton is approximately 6.0." *Id*. at 45 (citing Ex. 1008 ¶ 28; Ex. 1045, 22). As for the saccharide antigen, Petitioner asserts that Chiron teaches that conjugation to a carrier protein is preferred to enhance immunogenicity. *Id*. at 45 (citing Ex. 1011, 3:20–21). Petitioner asserts that Chiron also teaches that its formulation comprises polysorbate 80. Pet. 50. Regarding dependent claims 2–6, 10, 11, 14, 19, and 20, Petitioner also asserts that Chiron teaches or suggests the additional limitations set forth in those claims. *See* Pet. 50–57 and 62.

Having reviewed the cited evidence, and the record as a whole, we find that Petitioner has accurately described the above-stated disclosures of Chiron. Indeed, Patent Owner does not challenge Petitioner's assertion that Chiron teaches a formulation comprising the ingredients recited in independent claim 1. Nor does Patent Owner challenge Petitioner's assertions that Chiron teaches or suggests the additional limitations set forth in dependent claims 2–6, 10, 11, 14, 19, and 20. Instead, regarding independent claim 1 and dependent claims 2–6, 10, 11, 14, 19, and 20, the parties' disputes center upon whether the combined prior art teaches or suggests (a) placing Chiron's formulation in "siliconized container means," and (b) the formulation "inhibits aggregation induced by the siliconized container means." Thus, our following analysis focuses on those issues.

Siliconized container means

Petitioner acknowledges that Chiron does not expressly teach that its formulations are comprised in a siliconized container means. *See* Pet. 46. Petitioner asserts, however, that it would have been obvious to a person of ordinary skill to provide those formulations in such known container means. *Id*. at 46–47 (citing Ex. 1008 ¶¶ 133–136). In particular, Petitioner asserts that Chiron discloses storing the polysaccharide-protein conjugated formulations of Example 8 in vials for at least one month. *Id*. at 47 (citing Ex. 1011, 15:1–6). According to Petitioner and Dr. Kalonia, a person of skill in the art would have sealed such vials with rubber stoppers for that long-term storage. *Id*. (citing Ex. 1008 ¶ 134). Petitioner asserts also that it would have been obvious to place the formulations in syringes, as it was designed to be injected. *Id*. (citing Ex. 1008 ¶ 135; Ex. 1011, 8:37, 15:9–10). Similarly, Petitioner asserts that it would have been obvious to store Chiron's formulations in pre-filled syringes, as that was a common method of supplying vaccines, as evidence by the commercialized Chiron polysaccharide-protein vaccine, Vaxem Hib. *Id*. (citing Ex. 1008 ¶ 136; Ex. 1051; Ex. 1053).

According to Petitioner and Dr. Kalonia, a person of ordinary skill in the art would have understood that standard pharmaceutical vial stoppers, syringe plungers, and syringe barrels were siliconized. Pet. 47 (citing Ex. 1008 ¶ 138). Additionally, Petitioner asserts that Smith teaches that "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*. at 46 (citing Ex. 1008 ¶ 133).

Patent Owner asserts that a person of ordinary skill in the art would

not have found it obvious to place Chiron's formulations "into siliconized containers as a commercial product." PO Resp. 24. According to Patent Owner, unlike "commercial, mass-produced pharmaceutical products," formulations created in a development laboratory for testing, like those disclosed by Chiron, are not commonly placed in siliconized containers. *Id.* (citing Ex. 2123 ¶ 55, Ex. 2120 ¶¶ 37–38). Patent Owner asserts that although vials are used in Example 8 of Chiron, there is no teaching whether they were siliconized. *Id.* According to Patent Owner, Dr. Kalonia confirmed during his deposition that laboratories working with protein formulations would specifically avoid using siliconized containers. *Id.* (citing Ex. 2036, 87:12–88:13). Further, Patent Owner asserts that if siliconized stoppers were used, a person of ordinary skill "would have taken steps to ensure the formulation did not contact the stoppers and compromise the study." *Id.* at 24–25 (citing Ex. 2120 ¶¶ 36–38; Ex. 2115 ¶¶ 55, 70–73). Patent Owner notes that Chiron's Example 8 demonstrates that the MenW135 and MenY conjugates were highly unstable by industry standards, thus, a person of ordinary skill in the art would have been unlikely to put the formulations in siliconized containers. *Id.* at 25 (citing Ex. 2120 ¶¶ 40–42).

As for Chiron Example 9, Patent Owner asserts that the disclosed lyophilized component was unstable in solution, and that even if the syringes containing the formulation were siliconized, "the [reconstituted] formulation would not have been in the syringe for a time period long enough for silicone-induced aggregation to occur." *Id.* (citing Ex. 2120 ¶¶ 43–44; Ex. 2036, 164:14–19, 172:7–17 (describing reconstitution at the time of administration)). Patent Owner asserts that Petitioner's reference to

Chiron's Vaxem Hib, a haemophilus influenza b vaccine, marketed as a liquid formulation in prefilled syringes does not suggest that the meningococcal formulation disclosed in Chiron would be similarly marketed. *Id*. at 26.

According to Patent Owner, "[v]accines are provided as either liquid or lyophilized formulations largely because of stability issues," and a person of ordinary skill in the art would not have assumed that Chiron's formulation could be formulated as a liquid in a siliconized container, or that its exemplary vaccines would be suited for such storage. *Id*. (citing Ex. 2123 ¶¶ 55–56; Ex. 2120 ¶¶ 35–45; Ex. 2115 ¶¶ 40–44). Patent Owner asserts that although siliconized containers existed in the art, Petitioner's assertion that it would have been obvious to put Chiron's formulations into pre-filled siliconized syringes is conclusory and based on hindsight. *Id*. at 26–27.

Based upon our review of the record, as a whole, we determine that the preponderance of the evidence supports Petitioner's contention that a person of skill in the art would have found it obvious at the time of the invention to store Chiron's formulations in siliconized container means. As the parties acknowledge, Chiron disclosed placing the formulations in vials and storing them for at least one month. There is no dispute that a person of ordinary skill in the art would have had a reason to use a rubber stopper with such storage vials. Although Patent Owner asserts that a person of skill in the art would not have used rubber stoppers that were siliconized, persuasive evidence suggests otherwise. Dr. Kalonia provides testimony that, at the time of the invention, "it was well understood in the art that pharmaceutical containers required lubrication, and that the standard lubricant for that purpose was silicone oil." Ex. 1008 ¶ 138. The evidence reveals that such

use of silicone oil as a lubricant was ubiquitous by that time. In particular, as Petitioner and Dr. Kalonia assert, Smith discloses that not only was lubrication common in parenteral packaging, "[m]ost parenteral packaging components require the use of some form of lubrication in order to improve their processability and functionality," wherein such lubrication is essentially all based upon the use of "silicone fluid." Ex. 1012, 4 and 8; Pet. 31; Ex. 1008 ¶¶ 118–120, 138.

Petitioner also provides a persuasive reason why a person of ordinary skill in the art would have placed Chiron's formulation into a syringe, at some point, as Chiron explains that the formulation is intended to be injected. Like the rubber stopper, Smith also discloses the common, even necessary application of such lubrication to plastic syringe barrels and glass cartridges used as plunger barrels "to facilitate easy movement of the plunger within the barrel." Ex. 1012, 4.

Insofar as Patent Owner asserts that Dr. Kalonia provided deposition testimony that laboratories working with protein formulations would "specifically avoid" using siliconized containers, PO Resp. 24, we disagree. The testimony relates to Example 1 in the '999 patent, and reads as follows:

> Q. Pyrex beaker is siliconized or not? That's a question for you.
>
> A. I cannot opine on that because around the time there was a practice to siliconize any container which is used for protein. And it was recognized as siliconization could induce aggregation in these types of protein. In some cases in the labs, they stopped using that. So without any specific information, I cannot really opine on this.
>
> Q. So are you saying if it said -- if the text said a vial, are you saying you can't tell whether or not the vial is siliconized or not?

MS. CHOW: Objection to form.

Q. Without more information?

MS. CHOW: Objection to form.

A. I would use it -- unless the explicit language, I would be reluctant to use it.

Ex. 2036, 87:12–88:13.

The first portion of the above discussion refers to the description in the '999 patent Specification relating to the use of Pyrex beakers when combining formulation ingredients. Ex. 1001, 20:1–3. When asked if the Pyrex beaker was siliconized or not, Dr. Kalonia confirmed that "there was a practice to siliconize" such containers. Ex. 2036:16–21. However, because some labs stopped using such containers in "some cases," Dr. Kalonia explained that "without any specific information," he could not know whether the beakers described in the '999 patent were siliconized or not. After discussing the beakers, Dr. Kalonia was asked "if the text said a vial, are you saying you can't tell whether or not the vial is siliconized or not?" Ex. 2036, 88:4–7. Dr. Kalonia responded, "I would use it – unless the explicit language, I would be reluctant to use it." *Id*. at 88:11–13. That response is consistent with his declaration testimony that a person of skill in the art would have found it obvious to use a siliconized container for Chiron's formulation, at the time of the invention, because such container means were commonly lubricated with silicone oil. *See, e.g.*, Ex. 1008 ¶ 118. In other words, in view of that common practice, a skilled artisan would have had a reason to use such a siliconized container to store Chiron's formulations, and, absent some caution in Chiron that the storage container means should not be siliconized, the artisan would have had a reasonable expectation of successfully storing the formulations in that manner.

We credit Dr. Kalonia's testimony that a skilled artisan would have used a siliconized container to store Chiron's formulation with persuasive weight, as that testimony is supported by Smith's disclosure, as discussed above. On the other hand, we find that Patent Owner's assertions and the related opinions by its declarants, e.g., Drs. Morefield (Ex. 2120) and Thomson (Ex. 2123), that a person of ordinary skill would not have found it obvious to use siliconized containers to store Chiron's formulations are inadequately supported. For example, Patent Owner relies upon Dr. Morefield's testimony that a siliconized container would not have been used in Chiron's Example 8 because (a) the example involved a saccharide stability study, and introducing a siliconized container would have injected an unknown parameter into the experiment, and (b) the data demonstrates that the formulation was highly unstable. PO Resp. 25 (citing Ex. 2120 ¶¶ 36–42). However, Dr. Morefield has not provided any evidence to suggest that a siliconized container represented an "unknown" parameter. Rather, as evidenced by Smith and Elan, it was a known parameter, with a known solution. Nor has Dr. Morefield accurately characterized the data disclosed in Chiron's Example 8 as demonstrating Chiron's formulation was "highly unstable." Chiron expressly concludes from the data in Example 8 that "[f]ree saccharide levels are thus stable for at least 1 month at 2–8°C, before and after packaging," and that stability issues arose for two formulations, MenW125 and Men Y, only "[u]nder thermal stress conditions." Ex. 1011, 16:3–6.

Similarly, Patent Owner relies upon Dr. Thomson's opinion that siliconized containers are "avoided in a research setting to minimize secondary effects while developing a formulation." Ex. 2123 ¶ 56. In line

with this argument, Patent Owner asserts also that a person of ordinary skill in the art would not have combined the teachings of Smith with Chiron because Smith provided information concerning the use of lubrication on pharmaceutical packaging components whereas Chiron is directed to research stage formulations that are not commonly placed in siliconized containers. PO Resp. 31–34.

Here again, we determine that the preponderance of the evidence does not support Patent Owner's argument. As Petitioner explains, Chiron did not simply operate as a research laboratory, but instead as a major vaccine manufacturer, as confirmed by Dr. Thomson, a former Chiron scientist. Reply 9 (citing Ex. 1094, 72:8–16, 72:24–73:5). As Petitioner also explains, Dr. Thomson acknowledged that Chiron would have considered marketing the disclosed formulations in siliconized pre-filled syringes. *Id*. at 10 (citing Ex. 1094, 74:20–25). Further, Petitioner directs us to Dr. Thomson's testimony that, in addition to Vaxem Hib, Chiron also marketed Menjugate, a meningococcal conjugate vaccine, in a vial with a siliconized stopper. *Id*. (citing Ex. 1094, 75:21–77:3). Dr. Thomson additionally confirmed that each of those products contains all the ingredients recited in claim 1. *Id*. at 10–11 (citing Ex. 1094, 43:11–15, 43:23–44:4, 44:9–12, 75:7–10, 75:21–76:8). Thus, we determine that a skilled artisan would have had a reason to use siliconized containers with Chiron's formulation because it had previously done so for other conjugate vaccines including similar ingredients. Moreover, the skilled artisan would have had a reason to consider the teachings of Smith, directed to parenteral drug packaging components, when formulating and storing Chiron's parenteral vaccine, as it would have been reasonable to expect that Chiron prepared the formulation

not simply for research purposes, but instead with a goal of ultimately commercializing the formulation and distributing it in siliconized containers, consistent with industry standards at the time.

Most problematic with Patent Owner's position are its competing assertions that a person of skill in the art would have viewed Chiron's formulations "to be unsuited for storage in siliconized containers," and that a person of ordinary skill in the art "would have doubted that the formulation in Chiron [] would be susceptible to silicone-induced aggregation" of the meningococcal conjugate formulations in siliconized containers. PO Resp. 26, 30. When these apparently contradictory positions were addressed at the oral hearing, no clarity was provided. *See* Tr. 49:1–51:7 (explaining only that one skilled in the art would not use siliconized containers because Chiron's formulations were allegedly unstable and partially in a lyophilized form). In any event, as discussed above, the preponderance of the evidence, involving teachings of the prior art, and testimony of each parties' experts, demonstrates persuasively that a person of ordinary skill in the art would have had reason to provide Chiron's formulation in a siliconized container means, and would have had a reasonable expectation of successfully doing so, as had been done with other Chiron conjugate vaccines.

Inhibition of aggregation induced by the siliconized container means

Petitioner asserts that a person of ordinary skill in the art would have understood that Chiron's polysaccharide-protein conjugate formulations inhibit aggregation induced by the siliconized container means because Chiron's formulation contains a surfactant, such as polysorbate/Tween® 80. Pet. 48 (citing Ex. 1011, 6:14–15, 14:3–17:4, Examples 7–9 with 0.0005% Tween® 80). According to Petitioner, a person of ordinary skill in the art

would have known that such a surfactant inhibits silicone-induced aggregation, as taught by Elan. *Id*. (citing Ex. 1008 ¶ 139; Ex. 1013, 16:13–15, 17:6–14). Based on this knowledge, Petitioner asserts that a person of ordinary skill in the art would have been further motivated to provide Chiron's formulations in a siliconized container and would have had a reasonable expectation of successfully doing so, as Elan taught that a formulation including a surfactant, such as in Chiron, would successfully address silicone-induced protein aggregation. *Id*. at 49–50 (citing Ex. 1008 ¶¶ 143–144).

Patent Owner asserts that Chiron discloses using a surfactant, polysorbate 80, to minimize adsorption of antigens to containers, but contains no disclosure that the surfactant would inhibit silicone-induced aggregation. PO Resp. 28. However, Patent Owner asserts also that a person of skill in the art would not have expected Chiron's formulation, even without the surfactant, to undergo silicone-induced aggregation because "[o]ther conjugate vaccines similar to the formulations of Chiron . . . but without surfactant, did not suffer from silicone-induced aggregation." *Id*. (citing Ex. 2120 ¶¶ 31–34; Ex. 2115 ¶¶ 49–50) (discussing Menactra, a commercially available product comprising conjugates similar to those disclosed in Chiron Examples 7–9 and packaged in siliconized single dose vials but having no reports of recalls due to aggregation).

Additionally, Patent Owner asserts that a person of ordinary skill in the art would not have been motivated to combine the teachings of Elan and Chiron. According to Patent Owner, Elan only addresses aggregation in proteins and, at the time of the invention, "it was understood that the protein component of the conjugate was not the only factor in, and would not 'drive'

the aggregation, including the silicone-induced aggregation, of the conjugate." PO Resp. 34. Patent Owner asserts that the artisan would have understood that the aggregation of polysaccharide-protein conjugates proceeded through mechanisms that were instead dominated by the polysaccharide component of the conjugate. *Id.* Patent Owner asserts that because Elan only addresses aggregation in proteins, its teachings would not apply to Chiron's formulations "because simply affecting the protein moiety would be insufficient to inhibit the overall aggregation of the conjugate." *Id.* at 34 (citing Ex. 2115 ¶¶ 27–30, 31–36, 75, 98; Ex. 2123 ¶ 62).

Patent Owner asserts also that a person of ordinary skill in the art "would not have had any reasonable expectation that polysorbate 80 would inhibit aggregation, let alone silicone-induced aggregation," in Chiron's formulation, based upon Elan's disclosure. *Id.* at 48. According to Patent Owner, "[p]olysorbate's effects were unpredictable and its anti-aggregation effects were formulation and protein dependent." *Id.* Patent Owner asserts that a "vaccine formulator would not have added polysorbate to a formulation without a reason related to its known properties." *Id.*

Further, according to Patent Owner, Elan teaches away from combining polysorbate 80 with the histidine buffer disclosed in Chiron by teaching that impurities arose from degradation of polysorbate 80 through an oxidation reaction involving metal ions and histidine. *Id.* at 42 (citing Ex. 1013, 18:19–20; Ex. 2123 ¶¶ 68–74; Ex. 2115 ¶ 83). Patent Owner asserts that, in view of Elan, "[h]istidine may be included only where a phosphate buffer is also present to inhibit auto-oxidation. . . ." *Id.* at 46. Further, Patent Owner asserts that "there would have been no motivation to use histidine as a buffer because Chiron [] teaches that histidine's effects on

stability are tied to its actions as a non-buffering excipient on the adjuvant." *Id*. According to Patent Owner, Chiron teaches away from inclusion of phosphate ions while Elan depends on it, thus dissuading a person of ordinary skill in the art from "combining . . . their opposite teachings regarding the critical role of a phosphate buffer." *Id*. at 47.

Based upon our review of the record, as a whole, we determine that the preponderance of the evidence supports Petitioner's contention that a person of ordinary skill in the art would have appreciated that Chiron's formulation inhibits aggregation induced by a siliconized container means. To begin, we address Patent Owner's assertion that Petitioner's position, i.e., that a person of ordinary skill in the art would have understood that the polysorbate 80 in Chiron's formulations inhibits silicone-induced aggregation, requires the artisan to have expected that the formulation would undergo such aggregation in the absence of polysorbate 80. PO Resp. 28. Based upon that rationale, Patent Owner asserts that a person of skill in the art would not have expected such formulations without polysorbate 80 to be susceptible to silicone-induced aggregation. *Id*. Patent Owner supports that assertion by referring to Dr. Morefield's testimony that Menactra, another Chiron product having a similar formulation as disclosed in Chiron, but without polysorbate 80 or any surfactant, was packaged in siliconized vials without any reports of recalls due to aggregation. *Id*. at 28–30 (citing Ex. 2120 ¶¶ 31–34).

We note that Patent Owner and Dr. Morefield do not address whether a person of ordinary skill in the art would have attributed the lack of such aggregation in Menactra to the formulation's ability to inhibit silicone-induced aggregation, in the absence of polysorbate 80. Based upon our

claim construction, the required inhibition of such aggregation may be attributable to any component, or combination of components, making up the formulation. Thus, Chiron's formulation may read on the functional claim requirement if one or more of the formulation ingredients contributes to the formulation's ability to inhibit silicone-induced aggregation.

Insofar as Patent Owner argues that Chiron's formulation does not inhibit silicone-induced aggregation because Petitioner has not established that it would have been subject to such aggregation, we do not find that argument supported by the evidence. Petitioner provides persuasive evidence that, at the time of the invention, it was well-known in the pharmaceutical industry that silicone oil lubricant in contact with pharmaceutical formulations, including vaccines, could lead to protein aggregation. Pet. 16 (citing Ex. 1008 ¶¶ 46–48). In addition to Dr. Kalonia's testimony describing the knowledge in the art at the time of the invention regarding silicone-induced aggregation, Petitioner also directs us to the following statement in the "Background of the Invention" section of the '999 patent describing what was known in the art at the time of the invention regarding silicone-induced aggregation:

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

Id. at 17 (citing Ex. 1001, 2:17–24); see also Ex. 1008 ¶ 48. Further, Petitioner provides evidence that during the prosecution of the '999 patent, Patent Owner confirmed that "[i]t was known at the time of the invention that silicone oil causes aggregation/precipitation." Pet. 17 (citing Ex. 1002, 291). Additionally, as Petitioner asserts, Elan teaches that the addition of polysorbate 80 to a formulation comprising an antibody, histidine, and a buffer resolved protein precipitation, i.e., aggregation, induced by the siliconized container, as confirmed by visual inspection. Ex. 1013, 17–18.

Based upon the foregoing, we are persuaded that Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have reasonably expected that (a) a formulation comprising a polysaccharide-protein conjugate may be subject to silicone-induced aggregation, and (b) any such aggregation would successfully be inhibited by polysorbate 80. *See In re O'Farrell*, 853 F.2d 894, 903–904 (Fed. Cir. 1988) (a proper obviousness inquiry focuses on *reasonable* expectations, as opposed to absolute certainty, that a skilled artisan would gain from the knowledge in the art, along with the teachings or suggestions of the combined prior art).

Moreover, in view of the above mentioned statements by Patent Owner during the prosecution of the '999 patent, we are not persuaded that a person of skill in the art would not have combined the teachings of Chiron and Elan because Elan addresses inhibiting aggregation in proteins and "simply affecting the protein moiety would be insufficient to inhibit the overall aggregation of the conjugate" in Chiron, as Patent Owner asserts here. PO Resp. 34. Further, we find Patent Owner's arguments that Elan

teaches away from combining polysorbate 80 with a histidine buffer, and that a vaccine formulator would not have added polysorbate to a formulation without a reason related to its known properties are misplaced, as Chiron's formulation already combines both of those elements successfully, wherein polysorbate 80 serves to "minimize adsorption of antigens to the containers." Ex. 1011, 2–4 and 7.

Regarding dependent claims 2–6, 10, 11, 14, 19, and 20, we have reviewed Petitioner's arguments and evidence that Chiron teaches or suggests that its formulations comprise each of the additional limitations set forth in those claims. *See* Pet. 50–57 and 62. Patent Owner does not separately challenge Petitioner's arguments and evidence as they relate to these claims. Thus, we determine that Petitioner has shown by a preponderance of the evidence that claims 2–6, 10, 11, 14, 19, and 20 are unpatentable.

b. Claim 17

Claim 17 depends from claim 1 and further requires that the "one or more polysaccharide-protein conjugate" comprises seven conjugates, with each having a different polysaccharide from a specific *S. pneumoniae* serotype (4, 6B, 9V, 14, 18C, 19F, 23F) conjugated to a CRM_{197} polypeptide. Petitioner asserts that it would have been obvious from the disclosure in Chiron for a person of ordinary skill in the art to have prepared Chiron's formulation wherein the conjugate comprises the recited seven valent conjugate. Pet. 57. In particular, Petitioner asserts that Chiron teaches that its formulation may comprise one or more bacterial antigens, including a saccharide antigen from *S. pneumoniae*. *Id*. at 57–58 (citing Ex.

1011, 2–3 and 6). Petitioner and Dr. Kalonia assert also that Rubin 2000,[7] referenced in Chiron, expressly discloses a vaccine comprising the same seven valent polysaccharide-protein conjugate recited in the claim. Pet. 57; Ex. 1008 ¶ 158; Ex. 1011, 3 (citing Ex. 1073, 14).

According to Petitioner and Dr. Kalonia, a person of skill in the art would have known that a commercially available vaccine, Prevnar, already comprised this seven valent conjugate (without the histidine buffer and surfactant of Chiron). Pet. 58–59; Ex. 1008 ¶ 158; Ex. 1058, 42. Petitioner and Dr. Kalonia assert that a person of skill in the art would have understood that modifying Chiron's formulation to include this disclosed seven valent conjugate would not change the aggregation characteristic of the formulation, as that characteristic is a function of the protein component and not the polysaccharide. Pet. 58; Ex. 1008 ¶ 157.

Patent Owner asserts that Petitioner's cited references do not disclose the conjugate recited in claim 17. PO Resp. 30. Patent Owner asserts also that Petitioner has not provided a reason for a person of skill in the art to modify the formulation disclosed in any of the asserted references to include the recited conjugates. *Id*. Additionally, Patent Owner asserts that Petitioner has failed to show that the modified formulation meets the limitations of independent claim 1, from which claim 17 depends, namely, that it "inhibits aggregation induced by the siliconized container means." *Id*. at 31. According to Patent Owner, Petitioner's declarants, Drs. Kalonia and Kasper, agree that modifying the polysaccharide-protein conjugate would

[7] Rubin, *Pneumococcal Vaccine*, 47(2) PEDIATRIC CLINICS OF NORTH AMERICA (20004). Ex. 1073 ("Rubin").

alter its behavior in the presence of silicone oil. *Id*. (citing Ex. 2036, 124:4–10; Ex. 2035, 32:4–25).

Having considered the record, as a whole, we determine that the preponderance of the evidence supports Petitioner's position that a person of ordinary skill in the art would have found it obvious to prepare Chiron's formulation in a manner that meets each limitation of claim 17. As previously discussed in Section II.C.4.a., Petitioner has shown by a preponderance of the evidence that a person of skill in the art would have found it obvious to prepare Chiron's formulation comprising a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, an aluminum salt, and one or more polysaccharide-protein conjugates in a siliconized container, wherein the formulation inhibits aggregation induced by the siliconized container, as required by independent claim 1. Further, based on the record, as a whole, we determine that the preponderance of the evidence also demonstrates that a person of ordinary skill in the art would have found it obvious to prepare Chiron's formulation comprising the seven valent conjugate recited in claim 17. Indeed, Chiron expressly discloses that its formulation may be prepared using a saccharide antigen from *S. pneumoniae*, and in that discussion specifically cited a reference disclosing a vaccine comprising the same seven valent polysaccharide-protein conjugate recited in the claim. Ex. 1011, 2–3 and 6 (citing Ex. 1073, 14).

Insofar as Patent Owner asserts that Drs. Kalonia and Kasper agree that modifying the polysaccharide-protein conjugate would alter its behavior in the presence of silicone oil, we are not persuaded that any such modified response would cause a person of skill in the art to no longer reasonably expect the polysorbate 80 component of the formulation would inhibit any

aggregation induced by a siliconized container means. To the contrary, as Petitioner asserts, Dr. Kalonia explained persuasively that a person of ordinary skill in the art "would have expected that the hydrophilic polysaccharide molecules would not have affected a surfactant's inhibition of silicone-induced protein aggregation," as the protein component is responsible for such aggregation. Reply 24–25 (quoting Ex. 1008 ¶ 50).

c. Claim 18

Claim 18 also depends from claim 1 and further requires the "one or more polysaccharide-protein conjugate" comprises thirteen conjugates, with each having a different polysaccharide from a specific *S. pneumoniae* serotype (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A) conjugated to a CRM_{197} polypeptide. Petitioner asserts that it would have been obvious from the disclosure in Chiron for a person of ordinary skill in the art to have prepared Chiron's formulation wherein the conjugate comprises the recited thirteen valent conjugate for the same reasons asserted regarding claim 17. Pet. 59. In particular, Petitioner asserts that the thirteen pneumococcal serotypes recited in claim 18 were well known in the art. *Id.* (citing Ex. 1007 ¶ 44; Ex. 1033, 7; Ex. 1015, 7). According to Petitioner, a person of skill in the art would have understood that "the 13 conjugates in claim 18 are a natural progression from Patent Owner's prior art 7-valent vaccine." *Id.* at 60 (citing Ex. 1007 ¶ 45).

Patent Owner asserts that Petitioner's cited references do not disclose the conjugate recited in claim 18. PO Resp. 30. Patent Owner asserts also that Petitioner has not provided a reason that a person of skill in the art would have modified the formulation disclosed in any of the asserted

references to include the recited conjugates. *Id*. Additionally, Patent Owner asserts that Petitioner has failed to show that the modified formulation meets the limitations of independent claim 1, from which claim 18 depends, namely, that it "inhibits aggregation induced by the siliconized container means." *Id*. at 31. Further, according to Patent Owner, Petitioner's reliance on a "natural progression" from the seven valent to the recited 13 valent conjugate formulation represents impermissible hindsight, as it is requires using the inventor's disclosure as a blueprint to piece together prior art. *Id*. at 31, 51–52 (citing *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)).

Additionally, Patent Owner asserts objective evidence of non-obviousness for claim 18. *Id*. at 56. Patent Owner asserts that Prevnar13 includes all of the limitations of claim 18 and has been a commercial success, received industry praise, met a long-felt but unmet need, and has been copied by others. *Id*. at 57–63.

Having considered the record, as a whole, we determine Petitioner has not established by a preponderance of the evidence that a person of skill in the art would found it obvious to modify Chiron's formulation to comprise the thirteen valent conjugate recited in claim 18. Although Petitioner's declarant provides evidence that the thirteen pneumococcal serotypes recited in claim 18 were known in the art, Petitioner has not provided a reason that a person of skill in the art would have modified Chiron's formulation to comprise a thirteen valent conjugate.

Unlike with the seven valent conjugate recited by claim 17, Petitioner has not demonstrated that Chiron teaches or suggests incorporating a thirteen valent conjugate into its formulation. Nor does Petitioner establish persuasively, or even contend, that the other references cited in the

combination, or the knowledge one having skill in the art would have motivated the artisan to modify Chiron in a manner that yields the claimed invention with a reasonable expectation of successfully doing so. *See KSR,* 550 U.S. at 418 (reaffirming that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art"); *see also In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988) (obviousness must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to arrive at the claimed invention). Without such evidence, Petitioner's obviousness rationale based upon a so-called "natural progression" from a seven valent conjugate formulation suggested by Chiron to the thirteen valent conjugate recited in claim 18 resembles a contention guided impermissibly by hindsight reasoning. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1343, 1368 (Fed. Cir. 2012).

In view of our determination that Petitioner has not shown by a preponderance of the evidence that claim 18 is unpatentable as obvious, we need not reach the merits of Patent Owner's evidence of secondary considerations of nonobviousness.

Based on the foregoing, we determine that Petitioner has established by a preponderance of the evidence that claims 1–6, 10, 11, 14, 17, 19, and 20 of the '999 patent are unpatentable over the combination of Chiron, Smith and Elan. Petitioner, however, has not established by a preponderance of the evidence that claim 18 is unpatentable over the combined prior art.

D. Obviousness over Chiron, Smith, Elan, and Peña

Petitioner asserts that claims 17 and 18 are unpatentable over the combination of Chiron, Smith, Elan, and Peña. Pet. 63–66. Patent Owner disagrees. PO Resp. 49–56.

1. Peña

Peña discusses various aspects of pneumococcal vaccination. Ex. 1015, 2. In particular, Peña describes two available vaccines to prevent invasive pneumococcal illness in Spain: 23-valent polysaccharides (VNP-23V) and 7-valent conjugated (VNC-7V). *Id.* Peña explains that the 7-valent vaccine contains the purified saccharides of the capsular antigens of seven serotypes of *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F, and 23F) conjugated individually with a protein that is a nontoxic mutant of the diphtheria toxin, CRM_{197}. *Id.* at 3. Peña explains that the 23-valent vaccine contains *S. pneumoniae* serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17E, 18C, 19A, 19F, 20, 22F, 23F, and 33F. *Id.* at 7. Peña discusses the Prevnar 7-valent conjugated vaccine and "other pneumococcal conjugates that have not yet been marketed and that are in advanced phases of study," including a 9-serotype vaccine (adds 1 and 5), an 11-serotype vaccine (adds 3 and 7F), and a 13-serotype vaccine (adds 6A and 19A). *Id.*

2. Obviousness Analysis

As discussed with respect to the obviousness challenge over the combination of Chiron, Smith, and Elan, we have determined that Petitioner has established by a preponderance of the evidence that the combined teachings of Chiron, Smith, and Elan teach or suggest each of the limitations of independent claim 1. Here, Petitioner adds Peña to the combination to

demonstrate that it would have been obvious to prepare Chiron's formulation by using the 7-valent and 13-valent conjugates recited by claims 17 and 18. Pet. 63.

With respect to claim 17, Petitioner asserts that Peña expressly discloses the 7 conjugates recited by the claim. *Id*. (citing Ex. 1015, 3). According to Petitioner, a person of ordinary skill in the art would have been motivated to include the 7 conjugates disclosed by Peña in Chiron's formulation because Chiron (a) explains that the invention is directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus, (b) teaches that its formulation may include "a saccharide antigen from *Streptococcus pneumonia*," (c) states that "the composition may comprise one or more of these bacterial . . . antigens," and (d) refers to a journal article that discloses the 7-pneumococcal CRM_{197}-conjugate of claim 17. *Id*. at 64 (citing Ex. 1011, 6:32–35, 2:15, 3:14; Ex. 1073, 14).

Further, Petitioner asserts that a person of ordinary skill in the art would have had a reasonable expectation of successfully using the known 7-valent conjugate in Chiron's formulation without disrupting the formula's ability to inhibit aggregation induced by the siliconized container means because (a) the artisan would have understood that it is the protein component of the formulation that is responsible for such aggregation, (b) the same protein component is used in the referenced 7-pneumococcal CRM_{197}-conjugate, and (c) there was a known solution for inhibiting aggregation induced by siliconized containers, i.e., a surfactant. *Id*. (citing Ex. 1008 ¶ 166).

Patent Owner asserts that the Petition only addresses the additional limitations of dependent claim 17, without addressing the limitations of

independent claim 1 from which it depends. We disagree, as Petitioner expressly relies upon its assertions in Ground 1 as demonstrating how the combination of Chiron, Smith, and Elan teaches or suggests each limitation of independent claim 1. Pet. 63. Patent Owner's remaining arguments mirror those raised regarding the challenge of claim 17 over the combination of Chiron, Smith and Elan.

For the same reasons discussed regarding the ground challenging claim 17 over the combination of Chiron, Smith, and Elan, we determine here that Petitioner has demonstrated by a preponderance of the evidence that a person of ordinary skill in the art would have found it obvious to prepare Chiron's formulation comprising the seven valent conjugate recited in claim 17—that is, the suggestion to do so is provided in Chiron and a disclosure of such conjugate is referenced in Chiron. Petitioner relies on Peña as further evidence that the recited seven valent conjugate was known in the art at the time of the invention and that a person of skill in the art would have had been motivated with a reasonable expectation of successfully incorporating it into Chiron's formulation.

With respect to claim 18, Petitioner asserts that Peña discloses a 13-valent pneumococcal conjugate vaccine with the same serotypes recited by the claim. Pet. 65 (citing Ex. 1015, 7). According to Petitioner, a person of ordinary skill in the art would have understood that those conjugates each contain the CRM_{197} protein carrier, "based on the published progression from 7-valent Prevnar®, to 9- and 11- valent iterations; each version contained CRM_{197} as the sole carrier protein." *Id.* (citing Ex. 1007 ¶¶ 45–46).

Patent Owner's arguments mirror those raised regarding the challenge of claim 18 over the combination of Chiron, Smith and Elan.[8] In view of those arguments and for similar reasons discussed regarding that ground, we determine here that Petitioner has not demonstrated by a preponderance of the evidence that a person of ordinary skill in the art would have found it obvious to prepare Chiron's formulation comprising the thirteen valent conjugate recited in claim 18.

In particular, Petitioner has not provided a reason that a person of skill in the art would have modified Chiron's formulation to comprise a thirteen valent conjugate. Instead, Petitioner simply directs us to Peña's disclosure of a 13-valent pneumococcal conjugate vaccine with the same serotypes recited by claim 18 that is described as being in an "advanced phase of study." Pet. 59 (citing Ex. 1015, 2). Petitioner does not direct us to any disclosure in Peña, or other evidence of record, further characterizing the vaccine or the study, nor do we see such disclosures in the reference. Without such information, we are unable to assess whether the study involved a formulation comprising each of the thirteen known serotypes conjugated to a CRM_{197} polypeptide, as required by the claim, or if such an attempt was even considered, tried and successful. As a result, Petitioner has not provided sufficient evidence for us to determine whether a skilled artisan who endeavored to modify Chiron's formulation to yield a 13-valent pneumococcal conjugate vaccine with the same serotypes as in Peña would have had a reasonable expectation of successfully doing so.

[8] Additionally, Patent Owner asserts objective evidence of non-obviousness for claim 18. *Id*. at 56.

To the extent that Petitioner relies on a so-called "natural progression" from a seven valent conjugate to the thirteen valent conjugate recited in claim 18, we remain unpersuaded, as it appears to be guided impermissibly by hindsight reasoning. *See Kinetic Concepts*, 688 F.3d at 1368.

In view of our determination that Petitioner has not shown by a preponderance of the evidence that claim 18 is unpatentable as obvious, we need not reach the merits of Patent Owner's evidence of secondary considerations of nonobviousness.

Based on the foregoing, we determine that Petitioner has established by a preponderance of the evidence that claim 17 of the '999 patent is unpatentable over the combination of Chiron, Smith, Elan and Peña. Petitioner, however, has not established by a preponderance of the evidence that claim 18 is unpatentable over the combined prior art.

III. MOTIONS TO EXCLUDE

Petitioner and Patent Owner have each filed a motion to exclude evidence. Papers 34 and 38.

A. Petitioner's Motion

Petitioner moves to exclude Patent Owner's Exhibits 2033, 2113, 2114, 2150–2159, and portions of Exhibits 2123 (¶¶ 78–79) and 2119 (¶¶ 9, 12–17, 25, and 27–28). Paper 34. Patent Owner opposes the motion. Paper 45. As the moving party, Petitioner has the burden of proof to establish that it is entitled to the requested relief.

Petitioner challenges Exhibits 2033, 2113, 2114, and portions of Exhibit 2123 (¶¶ 78–79) as they relate to Patent Owner's assertion of commercial success with respect to claim 18. Paper 34, 2. As we have not

reached the merits of Patent Owner's evidence of secondary considerations of nonobviousness, we dismiss Petitioner's Motion to Exclude regarding those exhibits as moot.

Petitioner challenges Exhibit 2119 (¶¶ 9, 12–17, 25, and 27–28) as allegedly "unreliable and unsupported testimony" by Patent Owner's declarant, Dr. Khandke, regarding the state of the art of conjugate vaccine formulation at the time of the invention. Paper 34, 2 (citing Federal Rules of Evidence "FRE" 702). In this *inter partes* review proceeding, we find that such matters go to the probative weight of Dr. Khandke's testimony, as opposed to its admissibility. *See, e.g.*, Office Patent Trial Practice Guide, 77 Fed. Reg. at 48,763 ("Opinions expressed without disclosing underlying facts or data may be given little or no weight."). Although we acknowledge Petitioner's reference to FRE 702 and 703 in seeking to exclude Dr. Khandke's testimony, generally, unlike a lay jury, by design, the Board is composed of individuals with "competent scientific ability" (35 U.S.C. § 6), and is thus capable of evaluating such testimony. Accordingly, the danger of prejudice in this proceeding is considerably lower than in a conventional district court trial. Accordingly, we deny Petitioner's Motion to Exclude the designated portions of Exhibit 2119.

Petitioner challenges Exhibits 2150–2159 as allegedly untimely submitted at the depositions of Petitioner's Reply witnesses. Paper 34, 2. According to Petitioner, those exhibits "impermissibly introduce new arguments and evidence which Petitioner and its experts have had no opportunity to address." *Id.* at 2–3. Further, Petitioner asserts that the exhibits are inadmissible under FRE 401 and 402 as lacking relevance, under FRE 801 and 802 as hearsay, and under FRE 901 as lacking

authentication and having no foundation. *Id.* at 3. We have not relied upon those exhibits in this Final Written Decision, however, as Patent Owner does not refer to them in the Patent Owner Response. Accordingly, we dismiss Petitioner's Motion to Exclude those exhibits as moot.

B. Patent Owner's Motion

Patent Owner moves to exclude Petitioner's Exhibits 1037, 1065, 1083–1085, 1092–1093, and 1109. Paper 38. Petitioner opposes the motion. Paper 42. As the moving party, Patent Owner has the burden of proof to establish that it is entitled to the requested relief.

Exhibit 1065 is a copy of a book chapter included in the "Concise Encyclopedia of High Performance Silicones," titled "Silicone Oil in Biopharmaceutical Containers: Applications and Recent Concerns." Patent Owner challenges the admissibility of the exhibit by asserting that it is legally irrelevant because it is not prior art. Paper 38, 3. Patent Owner notes that Petitioner describes the reference as being published in 2014. *Id.* According to Patent Owner, Petitioner has not established that the exhibit was a "printed publication" available before the April 26, 2006 priority date of the '999 patent. *Id.*

Petitioner responds by asserting that Exhibit 1065 is relevant to establishing the specific expertise of Dr. Kalonia, a co-author of the book chapter, regarding an aspect of the claimed invention, i.e., silicone-induced aggregation. Paper 42, 5.

Having considered the evidence and the arguments, we agree with Patent Owner that Petitioner has not established that Exhibit 1065 is relevant regarding the knowledge of those skilled in the art at the time of the invention. Based upon our review, Dr. Kalonia refers to the book chapter

submitted as Exhibit 1065 in his declaration discussion of his credentials. Ex. 1008 ¶ 7. Additionally, Petitioner and Dr. Kalonia refer to Exhibit 1065 when discussing certain arguments relating to the state of the art at the time of the invention. *See, e.g.*, Pet. 12 (referring to Exhibit 1065). We note that in such instances, those contentions are equally supported by other references, e.g., Smith.

Insofar as Exhibit 1065 is relied upon to demonstrate Dr. Kalonia's expertise regarding silicone oil in biopharmaceutical containers, we find such use permissible, and do not interpret Patent Owner's motion to seek to exclude use of Exhibit 1065 in that context. In the Final Written Decision, we have considered Exhibit 1065 only to assess Dr. Kalonia's qualifications to offer testimony regarding the ordinary skill in the art. The exhibit, however, is not available to establish what was known in the art at the time of the invention. Indeed, we have not relied on Exhibit 1065 in the Final Written Decision with respect to any patentability challenge. Accordingly, Patent Owner's motion is dismissed as moot.

We also have not relied upon Exhibits 1037, 1083–1085, 1092, 1093, and 1109 in this Final Written Decision, as they were cumulative to previously submitted evidence, or related to issues disposed upon other bases. Accordingly, we dismiss Patent Owner's Motion to Exclude these exhibits as moot.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has shown by a preponderance of the evidence that claims 1–6, 10, 11, 14, 17, 19, and 20 are unpatentable. Petitioner has not shown by a preponderance of the evidence that claim 18 is unpatentable.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–6, 10, 11, 14, 17, 19, and 20 of the '999 patent are unpatentable under 35 U.S.C. § 103 as obvious over Chiron, Smith, and Elan;

FURTHER ORDERED that claim 17 is also unpatentable under 35 U.S.C. § 103 as obvious over Chiron, Smith, Elan and Peña;

FURTHER ORDERED that Petitioner's Motion to Exclude is *dismissed* and moot with regard to Exhibits 2033, 2113, 2114, 2150–2159, and designated portions of Exhibit 2123 (¶¶ 78–79), and *denied* with regard to the designated portions of Exhibit 2119 (¶¶ 9, 12–17, 25, 27–28);

FURTHER ORDERED that Patent Owner's Motion to Exclude is *dismissed* as moot; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2017-00378
Patent 8,562,999 B2

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Paper No. 59
Entered: June 8, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

WYETH LLC,
Patent Owner.

Case IPR2017-00380
Patent 8,562,999 B2

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition (Paper 1; "Pet.") to institute an *inter partes* review of claims 1–6, 10, 11, 14, and 17–20 of U.S. Patent 8,562,999 B2 (Ex. 1001; "the '999 patent"). Wyeth LLC ("Patent Owner") filed a Patent Owner's Preliminary Response (Paper 6; ("Prelim. Resp.").

On June 13, 2017, we instituted an *inter partes* review of all challenged claims. Paper 9 ("Dec. Inst."). On September 13, 2017, Patent Owner filed a Patent Owner Response to the Petition. Paper 16 ("PO Resp."). On December 13, 2017, Petitioner filed a Reply to the Patent Owner Response. Paper 28 ("Reply").

Petitioner and Patent Owner each filed a Motion to Exclude Evidence. Papers 34 and 38. Each party filed an Opposition to the other party's motion. Papers 43 and 47. Each party filed also a Reply to the other party's Opposition. Papers 50 and 55.[1] Patent Owner filed Motions for Observation on Cross-Examination Testimony. Papers 39 and 40. Petitioner filed a Response to each of Patent Owner's Motions for Observation. Paper 44 and 45.

On February 27, 2018, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 56 ("Tr.").

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Having considered the record before us, we

[1] We authorized Patent Owner to file a Revised Reply to Petitioner's Opposition to Patent Owner's Motion to Exclude Evidence that complied with the page limit set forth in 37 C.F.R. § 42.24(c)(2). *See* Paper 54.

determine that Petitioner has shown by a preponderance of the evidence that claims 1–6, 10, 11, 14, 17, 19, and 20 are unpatentable. *See* 35 U.S.C. § 316(e). Petitioner has not shown by a preponderance of the evidence that claim 18 is unpatentable. Additionally, the Motions to Exclude Evidence by Petitioner and Patent Owner have been decided below in Section III.

A. Related Proceedings

Petitioner has filed two additional petitions challenging claims of the '999 patent in IPR2017-00378 and IPR2017-00390. Petitioner and Patent Owner explain that they are unaware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding. Pet. 4; Paper 4, 2.

B. The '999 patent

In some aspects, the '999 patent relates to formulations comprising an immunogen in the form of a polysaccharide-protein conjugate, a pH buffered saline solution, and an aluminum salt. Ex. 1001, 2:62–64, 12:9–15. The Specification defines the term "polysaccharide" as including "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." *Id.* at 16:32–38.

In certain embodiments, the compositions further comprise a surfactant. *Id.* at 12:65–67. The Specification explains that a suitable surfactant is one that "stabilizes and inhibits aggregation of an immunogenic composition described herein." *Id.* at 13:9–12. According to the Specification, in one aspect, the "invention relates to the unexpected and

surprising results that formulating an immunogenic composition with a surfactant such as Tween™80 significantly enhances the stability and inhibits precipitation of an immunogenic composition." *Id*. at 10:35–39.

The container means includes, among other items, syringes and vials. *Id*. at 3:2–8. The Specification explains that "silicone oil is a necessary component of plastic syringes, as it serves to lubricate the rubber plunger and facilitate transfer of the plunger down the syringe barrel." *Id*. at 2:31–34. Additionally, silicone oil is used as a coating for glass vials to minimize protein adsorption, and as a lubricant. *Id*. at 2:37–41. According to the Specification, "[i]t has been suggested in the art, that silicone oil, which induces protein secondary and tertiary conformational changes, might be responsible for the aggregation/precipitation seen in certain protein pharmaceutical preparations." *Id*. at 2:17–20 (citation omitted). To address that issue, the Specification states that the invention "broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions." *Id*. at 2:53–55. More specifically, certain embodiments of the invention relate to formulations that inhibit precipitation of immunogenic compositions comprised in siliconized container means. *Id*. at 5:44–50.

C. Illustrative Claims

Independent claim 1 and dependent claim 18 of the '999 patent are illustrative and reproduced below:

> 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.

> 18. The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises an *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 1 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 3 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 5 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6A polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 7F polysaccharide conjugated to a CRM197 polypeptide and an *S. pneumoniae* serotype 19A polysaccharide conjugated to a CRM197 polypeptide.

Ex. 1001, 31:7–12, 32:24–44.

In addition to claim 18, claims 2–6, 10, 14, 17, and 19 depend directly from claim 1. Claim 11 depends from claim 10. Claim 20 depends from claim 19.

D. The Instituted Grounds of Unpatentability

Petitioner challenges the patentability of the claims as follows:

Claims	Basis	References
1–6, 10, 11, 14, and 17–20	pre-AIA § 103(a)	Prevenar[2] and Chiron[3]
18	pre-AIA § 103(a)	Prevenar, Chiron, and Peña[4]

Petitioner also relies on the Declarations of Dennis L. Kasper, M.D. (Ex. 1007), Devendra Kalonia, Ph.D. (Ex. 1009), Christopher Jones, Ph.D. (Ex. 1119), and Harm HogenEsch, D.V.M., Ph.D. (Ex. 1122). Patent Owner relies on the Declarations of Paul Dalby Ph.D. (Ex. 2116), Ali Fattom, Ph.D. (Ex. 2118), Lakshmi Khandke, Ph.D. (Ex. 2119), Garry Morefield, Ph.D. (Ex. 2121), and James W. Thomson, Ph.D. (Ex. 2124).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016)

[2] Summary of Product Characteristics for Prevenar Suspension for injection: Pneumococcal saccharide conjugated vaccine, adsorbed, Annex 1:1–15 (2005). Ex. 1017 ("Prevenar").
[3] Patent Application Publication No. WO 2003/009869 A1 by Mario Contorni et al., published February 6, 2003. Ex. 1011 ("Chiron").
[4] de la Peña et al., *Present and future of the pneumonia vaccination*, 24(4) PEDIATRIKA 47–55(2004) (English Translation). Ex. 1015 ("Peña").

(affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner and Patent Owner propose constructions for certain claims terms. Pet. 33–38; PO Resp. 12–21. As relevant to this Decision, we address the following claim terms:

1. "polysaccharide" and "polysaccharide-protein conjugates"

Petitioner asserts that the broadest reasonable interpretation of the claim term "polysaccharide" is set forth in the Specification. Pet. 33–35. In particular, the Specification defines "polysaccharide" as including "any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including, but not limited to, a 'saccharide', an 'oligosaccharide', a 'polysaccharide', a 'liposaccharide', a 'lipo-oligosaccharide (LOS)', a 'lipopolysaccharide (LPS)', a 'glycosylate', a 'glycoconjugate' and the like." Ex. 1001, 16:32–38. Patent Owner similarly acknowledges that the term "polysaccharide" is expressly defined in the Specification. PO Resp. 12.

Petitioner does not propose a separate construction for the claim phrase "polysaccharide-protein conjugates." Patent Owner, however, asserts that the broadest reasonable interpretation of that claim phrase is:

> a conjugate resulting from reacting 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 lipooligosaccharide, a liposaccharide, a glycosylate, a glycoconjugate, and the like with a carrier protein, that is amenable to standard conjugation procedures, wherein the antigenic saccharide element retains antigenicity after conjugation.

PO Resp. 13 (underlining removed). Patent Owner notes that its proposed construction is "rooted in the preliminary construction adopted by the Board," but adds the requirement that the antigenic saccharide element retains antigenicity after conjugation. *Id*.

Patent Owner asserts that "a purpose of the invention is to provide formulations that preserve the antigenicity of immunogenic formulations." *Id*. at 14. According to Patent Owner, the "inhibition of aggregation/ precipitation" described in the Specification is a "proxy for whether there is a loss of antigenicity in the formulation." *Id*. Patent Owner asserts that it would be "improper to ignore the properties (i.e., antigenicity) of the conjugate" when construing the claim. *Id*. at 13–14 In support of its proposed construction, Patent Owner identifies various instances in the Specification wherein the polysaccharide-protein conjugate is referred to as an "immunogen" or "immunogenic" composition. *Id*. at 14 (citing, e.g., Ex. 1001, 14:19–23) ("the immunogen (i.e., a polysaccharide-protein conjugate . . .)").

Patent Owner draws our attention to the Specification discussion in the "Background of the Invention" section that "the immunogenic composition must be active throughout its 'expected' shelf life, wherein 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.* (quoting Ex. 1001, 1:41–46). According to Patent Owner and its declarant, Dr. Thomson, a person of skill in the art would have understood an active polysaccharide-protein conjugate composition to mean an active immunogenic composition. *Id.* (citing Ex. 2124 ¶ 39). Patent Owner asserts that "[f]or an immunogen to be capable of inducing an immune response in a body, the immunogen must be antigenic." *Id.* Patent Owner asserts that "[a]ntigenicity is a prerequisite for immunogenicity." *Id.* at 15. According to Patent Owner, although immunogenicity is not recited in the claims, it is related to a property recited in the claims, i.e., that the formulation "inhibits aggregation induced by the siliconized container means." *Id.* Patent Owner asserts that "silicone-induced aggregation is assessed by measuring antigenicity to determine the extent of the loss of antigenicity due to silicone-induced aggregation." *Id.* (citing Ex. 1001, Example 4).

Petitioner asserts that the "Board should reject Patent Owner's proposed 'antigenicity' limitation for the same reasons it rejected the importation of an 'immunogenicity' requirement" in the Institution Decision, because Patent Owner refers to "antigenicity" as a "prerequisite for immunogenicity." Reply 5–6 (citing PO Resp. 15).

Based on the record as a whole, we determine that the Specification sets forth with reasonable clarity, deliberateness, and precision the definition of the term "polysaccharide," as accurately represented by Petitioner, and acknowledged by Patent Owner. With respect to the phrase "polysaccharide-protein conjugates," the Specification does not provide a

similarly precise definition. However, the Specification generally describes such conjugates in a manner that is consistent with the plain and ordinary meaning of the phrase. For example, the Specification explains that polysaccharides are "chemically activated (e.g., via reductive amination) to make the saccharides capable of reacting with the carrier protein." Ex. 1001, 17:35–37. The Specification also explains that "[c]arrier proteins should be amenable to standard conjugation procedures." *Id.* at 17:47–50. In particular, the Specification states, "[t]he chemical activation of the polysaccharides and subsequent conjugation to the carrier protein (i.e., a polysaccharide-protein conjugate) are achieved by conventional means." *Id.* at 17:43–45. Moreover, as Patent Owner asserts, the Specification describes the polysaccharide-protein conjugates as an example of an "immunogenic composition." Ex. 1001, 1:29–30.

In light of those Specification descriptions, we determine that the broadest reasonable construction of the claim phrase "polysaccharide-protein conjugates" refers to an immunogenic composition resulting from reacting 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, a lipopolysaccharide, a glycosylate, a glycoconjugate, and the like with a carrier protein that is amenable to standard conjugation procedures.

Although we recognize that the claimed invention is directed toward an immunogenic composition, we also note that the claims do not recite any specific level of immunogenicity for the composition. The Specification explains that the invention "broadly relates to novel formulations which

stabilize and inhibit precipitation of immunogenic compositions." Ex. 1001, 2:53–55. The Specification describes aggregation as an indicator of physical/thermal stability of the immunogenic composition. *Id*. at 2:7–8. Breakdown of the composition to an undesired form (e.g., an aggregate) lowers the total concentration of the product. *Id*. at 1:43–46.

Insofar as Patent Owner asserts that the claims require "measuring antigenicity to determine the extent of the loss of antigenicity due to silicone-induced aggregation," as in Example 4 of the Specification, PO Resp. 15, we disagree. Although Example 4 discusses total antigenicity (and loss), the claims do not require the formulation to retain a particular degree of immunogenicity. Instead, the claims are directed to a formulation comprising a polysaccharide-protein conjugate, i.e., an "immunogen," *see*, *e.g.*, Ex. 1001, 14:19–23, wherein the formulation inhibits aggregation[5] induced by the siliconized container means. The presence of a polysaccharide-protein conjugate confers the immunogenic element of the claim. While performing an immunoassay to measure loss of antigenicity, as in Example 4, may provide information regarding whether silicone-induced aggregation has occurred, such an assay is not required to meet the "protein-polysaccharide conjugate" element of the claim. Moreover, as explained in each example described in the Specification, the occurrence of aggregation/precipitation may be detected upon visual inspection. *See, e.g.*, Ex. 1001, 27:6–11 (discussing visual inspection for precipitation).

[5] *See* Ex. 1001, 12:38–40 (describing interchangeable use of the terms "precipitation" and "aggregation").

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

Petitioner asserts this claim phrase "recites a property of the formulation as a whole, without attributing inhibitory effect to any specific ingredient recited in the claim." Pet. 37 (citing Ex. 1009 ¶ 95). For example, Petitioner asserts that the plain language of the claim does not require that the aluminum salt inhibits silicone-induced aggregation. *Id.* at 37–38 (citing Ex. 1009 ¶ 96). According to Petitioner, because independent claim 1 recites a "formulation" followed by an open-ended term, "comprising," any element(s) comprised in the formulation may contribute the required inhibition, so long as the formulation as a whole "inhibits aggregation induced by the siliconized container means." *Id.*

Patent Owner asserts that this claim phrase means that "the formulation inhibits antigenicity loss of the polysaccharide component of the polysaccharide-protein conjugate that can occur as a result of aggregation induced by the siliconized container." PO Resp. 16. In support of that construction, Patent Owner relies again upon the antigenicity assessment described in Example 4 of the Specification. *Id.* at 16–19. According to Patent Owner, although visual inspection is used in the Specification examples to observe particulates, such inspection did not indicate whether the polysaccharide components of the vaccine maintained or lost antigenicity as a result of aggregation. *Id.* at 18.

Further, Patent Owner asserts that the "broadest reasonable interpretation of claim 1 should go no further than to read on embodiments that contain the three recited ingredients in a formulation that meets the functional property limitation." *Id.* at 21. According to Patent Owner, the

functional requirement of inhibiting aggregation induced by the siliconized container means must be satisfied by "a formulation of the three specifically recited ingredients [buffered saline solution, aluminum salt, and polysaccharide-protein conjugate], without any un-recited ingredient(s)." *Id.* at 20.

Having considered the arguments and evidence, we agree with Petitioner's rationale that claim 1 "recites a property of the formulation as a whole, without attributing inhibitory effect to any specific ingredient recited in the claim." Pet. 37. Further, we agree with Patent Owner that the claim element "the formulation . . . inhibits aggregation induced by the siliconized container means" may be interpreted to include an embodiment wherein the three specific ingredients recited in the claim, i.e., buffered saline solution, aluminum salt, and polysaccharide-protein conjugate, cause inhibition of aggregation induced by the siliconized container means. *See* PO Resp. 19–20. However, we do not agree with Patent Owner that the broadest reasonable interpretation ends there. Rather, we determine that by reciting the formulation using the open-ended term "comprising," along with attributing the aggregation inhibition property to "the formulation," the broadest reasonable construction also includes formulations comprising additional, unrecited ingredients, and such additional ingredient(s) may contribute to the required aggregation inhibition by the formulation. *See In re Baxter*, 656 F.2d 679, 686 (CCPA 1981) (use of the term "comprising" in a preamble of a claim permits inclusion of elements in addition to those specified in the claims); *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'").

Further, we do not determine that the claim phrase requires maintaining any specific level of antigenicity of the conjugate, as asserted by Patent Owner, PO Resp. 16–18, for the same reasons discussed above, with respect to Patent Owner's similar argument raised in connection with its proposed construction of the "polysaccharide-protein conjugate" term.

In view of our analysis, we determine that no additional claim terms require construction for the purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art at the time of the invention would have had either (a) "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," or (b) "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." Pet. 32 (citing Ex. 1009 ¶ 80).

Patent Owner relies upon its definition of the level of ordinary skill in the art set forth in the Patent Owner Preliminary Response. PO Resp. 21. In that filing, Patent Owner disagreed with Petitioner's definition insofar as it suggests the field of invention involved protein-based formulations. Prelim. Resp. 10. According to Patent Owner, a person of ordinary skill in the art at the time of the invention would have had either (a) "a Ph.D. degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least two years of work experience formulating polysaccharide-protein conjugate immunogenic compositions, and would have had familiarity or experience with the general components and formulation of bacterial vaccines," or (b) "a Master's degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least four years of work experience formulating polysaccharide-protein conjugate immunogenic compositions, and would have had familiarity or experience with the general components and formulation of bacterial vaccines." *Id*. at 10–11.

In the Institution Decision, we adopted Patent Owner's description of the level of ordinary skill at that stage in the proceeding because it included a requirement for experience relating to polysaccharide-protein conjugates. Dec. Inst. 13. Based on the record as a whole, we determine that a declarant having significant experience relating to protein-silicone oil interactions also offers useful information relating to the subject matter of the challenged claims. Thus, we also recognize those having ordinary skill in the art relating to silicone-induced interactions/aggregation in pharmaceuticals.

Thus, we adopt Patent Owner's description of one having ordinary skill in the art of formulating polysaccharide-protein conjugate immunogenic compositions. Further, we describe one having ordinary skill

in the art of silicone-induced interactions/aggregation in pharmaceuticals as either (a) a Ph.D. degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least two years of work experience involving researching silicone-induced interactions/aggregation in pharmaceuticals, or (b) a Master's degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least four years of work experience involving researching silicone-induced interactions/aggregation in pharmaceuticals.

We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). We recognize each of Petitioner's and Patent Owner's declarants as qualified to provide the offered opinions on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention with respect to formulating polysaccharide-protein conjugates and/or silicone-induced interactions/aggregation in pharmaceuticals. The relative weight that we assign such testimony, however, is subject to additional factors. *See, e.g.*, Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,763 (Aug. 14, 2012) ("Opinions expressed without disclosing the underlying facts or data may be given little or no weight.").

Petitioner does not challenge the expertise of any of Patent Owner's declarants. Patent Owner, however, asserts that Petitioner's declarants, Drs. Kalonia and Kasper, lack "experience in developing polysaccharide-protein conjugate formulations, and certainly not on a commercial scale." PO Resp. 21–22. Regarding Dr. Kalonia, Patent Owner asserts that his experience is "limited to the aggregation of proteins in formulations on a laboratory scale." *Id*. at 20. However, as described in Dr. Kalonia's

declaration, such experience involves "significant research experience in protein-interface, protein-protein, and protein-excipient interactions, including interactions among protein, silicone oil and surfactants," as well as co-authoring a book chapter describing applications and concerns relating to silicone oil in biopharmaceutical containers. Ex. 1009 ¶ 7.

We have determined that Dr. Kalonia's credentials and experience qualify him to provide expert testimony addressing protein-silicone oil interactions, which is precisely what Petitioner relies upon this declarant to do. *See, e.g.*, Pet. 3–4 (describing Dr. Kalonia as a "formulation expert specializing in protein-silicone oil interactions, including silicone-induced protein aggregation in pharmaceuticals"). Insofar as Dr. Kalonia's testimony discusses polysaccharide-protein conjugates, he expressly refers to and relies upon Dr. Kasper's testimony. *See, e.g.*, Ex. 1009 ¶¶ 18, 56, 87, 121, 174, 181.

Regarding Dr. Kasper, Patent Owner asserts that he "has no experience in the development of commercial scale vaccine products," and "is not knowledgeable about vaccine formulation issues such as stability and aggregation." PO Resp. 22. We disagree. As Dr. Kasper explains in his declaration, he is a professor of medicine and microbiology at Harvard Medical School and runs his own research laboratory, wherein a "major focus" of his work is "the development of human vaccines, including polysaccharide-protein conjugate vaccines." Ex. 1007 ¶¶ 1, 5.

In support of its challenge of Dr. Kasper, Patent Owner directs us only to deposition testimony relating to Dr. Kasper's inexperience using siliconized containers with his vaccine formulations. PO Resp. 22–23 (citing Ex. 2035, 13:3–18, 35:20–23). However, as Petitioner has explained,

Dr. Kasper's testimony is not offered to address silicone-induced aggregation in pharmaceuticals. Rather, Petitioner relies upon Dr. Kasper to provide testimony in his area of expertise, i.e., formulating polysaccharide-protein conjugate immunogenic compositions, and asserts that he would have had familiarity or experience with the general components and formulation of bacterial vaccines. *See* Pet. 4 (describing Dr. Kasper as "a renowned researcher focusing on the development of human vaccines, including polysaccharide-protein conjugate vaccines").

C. Obviousness over Prevenar and Chiron

Petitioner asserts that claims 1–6, 10, 11, 14, and 17–20 are unpatentable over the combination of Prevenar and Chiron. Pet. 38–58. Patent Owner disagrees. PO Resp. 23–37.

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) where in evidence, so-called secondary considerations. *Graham*, 383 U.S. at 17–18. If the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains, the claim is unpatentable under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

1. Prevenar

Prevenar provides a summary of product characteristics for the Prevenar vaccine (marketed as "Prevnar"), a pneumococcal saccharide conjugated vaccine prepared as a suspension for injection. Ex. 1017, 1–2.

The vaccine comprises *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, each conjugated to the CRM_{197} carrier protein and adsorbed on aluminum phosphate. *Id*. at 2. The composition also comprises sodium chloride as an excipient. *Id*. at 7. The suspension is provided in a vial with Type I glass and a grey butyl rubber stopper, either without syringe or needles, or with syringe and one needle for withdrawal and one needle for injection. *Id*.

2. Chiron

Chiron discloses vaccine formulations comprising an antigen, aluminum salt, and histidine. Ex. 1011, Abstract. Chiron explains that the "antigen is preferably a protein antigen or a saccharide antigen, preferably from bacteria, with the bacterial genus *Neisseria* (e.g. *N.meningitidis*) being particularly preferred." *Id*. at 3. Chiron states, "[w]here a saccharide or carbohydrate antigen is used, it is preferably conjugated to a carrier protein in order to enhance immunogenicity." *Id*. at 4. Preferred carrier proteins are bacterial toxins or toxoids, with the CRM_{197} diphtheria toxoid being "particularly preferred." *Id*. The aluminum salt and histidine improve the stability of the vaccine by improving pH stability (buffering) and aluminum adjuvant adsorption, and/or improving antigen stability by reducing antigen hydrolysis. *Id*. at 2. Chiron teaches that its formulation may also comprise a detergent, e.g., Tween 80, to minimize adsorption of antigens to containers. *Id*. at 7.

3. Obviousness Analysis

a. Claims 1–6, 10, 11, 14, 17, 19, and 20

Petitioner contends that Prevenar teaches two of the three ingredients

recited in the formulations of independent claim 1 and dependent claims 6, 10, 11, 14, 17, 19, and 20. Pet. 39. In particular, Petitioner asserts that Prevenar teaches vaccine formulations comprising seven pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) each conjugated to the CRM_{197} carrier protein and adsorbed on aluminum phosphate. Pet. 39–43 (citing Ex. 1017, 11). Additionally, Petitioner asserts that Prevenar discloses using sodium chloride as an excipient. *Id*. at 40. Prevenar does not teach that its vaccine comprises a buffer. *Id*. at 39. Petitioner asserts, however, that "[b]uffer (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)." *Id*. at 40 (citing Ex. 1009 ¶ 128; Ex. 1011, 1:6–7).

Moreover, Petitioner asserts Chiron similarly discloses aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulations comprising a sodium salt such as sodium chloride and a histidine buffer. *Id*. at 40 (citing Ex. 1011, 1:27–2:3, 5:17–20, 28). Petitioner asserts that Chiron teaches that the addition of histidine buffer is advantageously biocompatible and safe, and enhances pH and antigen stability. *Id*. at 40–41 (citing Ex. 1011, 1:6–7, 5:6–7, 15, 11:30–12:15, 14:3–17:4).

According to Petitioner, it would have been obvious to a person of ordinary skill in the art to use the histidine buffer of Chiron in the Prevenar vaccine because Chiron teaches that histidine enhances the stability of vaccines which include aluminum salt adjuvants. Pet. 40 (citing Ex. 1009 ¶ 127; Ex. 1011, 1:31–2:3). Additionally, Petitioner asserts that Chiron teaches that "[t]he use of histidine in combination with an aluminum phosphate (particularly a hydroxyphosphate) is particularly advantageous for

acidic antigens." *Id*. at 42 (quoting Ex. 1011, 5:3–4). According to Petitioner and Dr. Kasper, because Prevenar's vaccine comprises acidic antigens, a person of skill in the art would have understood from Chiron that the formulation would benefit from histidine buffer. *Id*. (citing Ex. 1007 ¶ 55). Further, Petitioner asserts that Chiron's histidine buffer is inherently within the scope of the claim limitation requiring the buffer to have a pKa of about 3.5 to about 7.5 because "the pKa with respect to the side group proton is approximately 6.0." *Id*. at 42 (citing Ex. 1009 ¶ 131; Ex. 1045,[6] 22).

As for the siliconized container means, Petitioner asserts that an approved formulation of the Prevenar vaccine is provided in a "'pre-filled syringe (Type I glass),' which was known to be siliconized." Pet. 44 (citing Ex. 1009 ¶ 136 (citing Ex. 1017, 14; Ex. 1076, 7).

Petitioner asserts that Prevenar's formulation, modified to include Chiron's histidine buffer, inherently inhibits silicone-induced aggregation in siliconized containers. Pet. 44 (citing Ex. 1009 ¶ 137). According to Petitioner, Patent Owner conveys in the Specification of the '999 patent and during prosecution that adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation. *Id*. at 45. Petitioner asserts that such adsorption is taught by Prevenar and Chiron. *Id*. (citing Ex. 1017, 11; Ex. 1011, 4:5).

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[6] Akers et al., *Formulation Development of Protein Dosage Forms: Development and Manufacture of Protein Pharmaceuticals*, 14 PHARM. BIOTECH. 47–128 (2002).

Further, Petitioner asserts that a person of ordinary skill in the art would have had a reasonable expectation of successfully combining the teachings of Prevenar and Chiron to arrive at the claimed formulation because buffer was a common component of vaccines and Chiron teaches that histidine buffer confers pH and antigen stability to pneumococcal conjugate formulations such as Prevenar that have aluminum phosphate adjuvant. Pet. 45 (citing Ex. 1009 ¶ 142).

Patent Owner does not dispute that the only difference between the ingredients recited in claim 1 and Prevenar's formulation is that Prevenar does include a histidine buffer. Patent Owner also does not dispute Petitioner's contention that one of skill in the art would have understood that the Prevenar vaccine was provided in a siliconized container means because its approved formulation was distributed in a type of pre-filled syringe known to be siliconized. The parties' disputes instead center upon whether Petitioner has established by a preponderance of the evidence that (a) a person of ordinary skill in the art would have had a reason to combine Chiron's histidine buffer with the Prevenar vaccine with a reasonable expectation of success, and (b) the combined formula inherently inhibits silicone-induced aggregation.

Reason to Combine and Reasonable Expectation of Success

Patent Owner asserts that Petitioner fails to provide a reason to combine to Chiron's buffer to Prevenar's formulation, and that such combination is proposed only to reach the claimed invention and is, thus, based on hindsight. PO Resp. 31.

According to Patent Owner, a person of skill in the art would have recognized that a histidine buffer would not have provided any benefit to

Prevenar's formulation, as the formulation "did not suffer from the free phosphate issue described in Chiron[] as being solved by histidine." *Id*. at 31–32 (citing Ex. 2121 ¶¶ 33–36, 50; Ex. 2124 ¶¶ 55–56; Ex. 2116 ¶¶ 75–78). Patent Owner asserts that Prevenar's formulation was known to be stable, without a buffer, such that there would have been no reason to add one. *Id*. at 33.

Additionally, Patent Owner asserts, a person of skill in the art would have understood that histidine competes with at least serotypes 6B, 19F, and 23F in the Prevenar vaccine for binding positions on the aluminum phosphate adjuvant. PO Resp. 33 (citing Ex. 2121 ¶¶ 27–39; Ex. 2124 ¶¶ 55, 65). According to Patent Owner, the skilled artisan would have avoided adding histidine because it would "disrupt antigen binding to the aluminum adjuvant, rendering the formulation inferior to the Prevenar [] vaccine without histidine." *Id*. at 35. Additionally, Patent Owner asserts that "histidine could also disrupt the electrostatic attraction mechanism of antigen adsorption to aluminum phosphate." *Id*. (citing Ex. 2121 ¶ 40).

Further, Patent Owner asserts that Petitioner fails to address whether histidine would meet the optimal pH for the Prevenar vaccine. *Id*. at 37. According to Patent Owner, without knowing the optimal pH of the Prevenar vaccine, a person of skill in the art would have been dissuaded from combining histidine with Prevenar. *Id*. (citing Ex. 2124 ¶¶ 54–56; Ex. 2121 ¶¶ 27–51).

Each of those contentions by Patent Owner, however, are inadequately supported by the testimony of Drs. Morefield (Ex. 2121) and Thomson (Ex. 2124). The portions of the declarations of Drs. Morefield and Thomson relied upon by the Patent Owner do not refer to any evidence to

support their opinions that a histidine buffer would not be a beneficial addition to the Prevenar formulation. Rather, those discussions sound of unsubstantiated theoretical concerns, and are speculative at best. At worst, certain of those theories has been refuted in the art. For example, Petitioner directs us to the testimony of one of its declarants, Dr. HogenEsch, who has a Ph.D. in Pathology and Immunology. Reply 13–16. Dr. HogenEsch explains persuasively that, contrary to the speculation of Drs. Morefield and Thomson, "histidine buffer had specifically been reported . . . not to interact with aluminum adjuvant through ligand exchange." Ex. 1122 ¶ 43. In support of this testimony, Dr. HogenEsch quotes a disclosure from US Patent No. 6,251,678 B1[7] explaining that, although phosphate-containing buffers are generally not preferred because they may interact with aluminum adjuvants, "the non interaction of histidine . . . buffers with aluminum adjuvant was demonstrated by zeta potential measurements of the surface charge of the aluminum adjuvant." *Id*. (quoting Ex. 1109, 3:24–30).

We find that the unsupported testimony offered by Patent Owner's declarants to be outweighed by rebuttal testimony from Dr. HogenEsch and the express disclosures by Chiron relied upon by Petitioner. Generally, as Petitioner and Dr. Kalonia note, Chiron teaches that buffers are a standard component of vaccines. Pet. 40; Ex. 1009 ¶ 128 (citing Ex. 1011, 1:6–7). More specifically, as Petitioner asserts, Chiron teaches that adding histidine buffer to aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulations comprising a sodium salt is advantageously biocompatible and

[7] US Patent 6,251,678 B1 issued to David B. Volkin et al., June 26, 2001. (Ex. 1109).

safe, and enhances pH and antigen stability. Pet. 40–41 (citing Ex. 1011, 1:6–7, 5:6–7, 15, 11:30–12:15, 14:3–17:4). Chiron teaches also that "[t]he use of histidine in combination with an aluminum phosphate (particularly a hydroxyphosphate) is particularly advantageous for acidic antigens." Ex. 1011, 6:3–4. Prevenar's formulation represents such an aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulation comprising a sodium salt, wherein the aluminum phosphate adjuvant is a hydroxyphosphate, as recognized by Dr. Morefield. *See* Ex. 2121 ¶ 37. Thus, on balance, we determine that the preponderance of the evidence supports Petitioner's contention that a person of ordinary skill in the art would have had a reason to add a histidine buffer to the Prevenar vaccine with a reasonable expectation of enhancing the stability of the product.

Inhibition of aggregation induced by the siliconized container means

Patent Owner asserts that Petitioner "fails to show that the formulation resulting from the combination of Prevenar [] and Chiron [] was known to inhibit silicone-induced aggregation." PO Resp. 25. Additionally, Patent Owner asserts that the stated mechanism of action of the claimed formulation's ability to inhibit such aggregation, i.e., via adsorption of polysaccharide-protein conjugate to the aluminum salt, was not known in the prior art. *Id*. at 26. According to Patent Owner, Petitioner has not adequately established that Prevenar's formulation, modified to include Chiron's histidine, inherently possessed the properties of the claimed invention. *Id*. In support of that assertion, Patent Owner cites case law explaining that "[w]hat is important regarding properties that may be inherent, but unknown, is whether they are unexpected." *Id*. (quoting *Honeywell Int'l Inc. v. Mexichem Amanco Holding S. A.*, 865 F.3d 1348,

1355 (Fed. Cir. 2017).

To Patent Owner's point, we agree that an asserted inherent property in an obviousness challenge must be subjected to consideration of whether such property would have been unexpected. *See id*. Patent Owner, however, has not alleged, or provided any evidence demonstrating that the claimed formulations unexpectedly inhibit silicone-induced aggregation.[8]

In any event, we recognize that "the use of inherency in the context of obviousness [to supply a missing claim limitation] must be carefully circumscribed." *Id*. (citations omitted). We recognize also that "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (alteration in original) (quoting *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993)).

Here, Petitioner asserts that Prevenar's formulation, modified to include Chiron's histidine buffer, comprises every recited ingredient of independent claim 1. Petitioner's inherency argument is not based upon probabilities or possibilities. Rather, Petitioner relies on the fact that Prevenar's modified formulation is the formulation that is claimed, wherein the claims and the Specification of the '999 patent describe that the inhibition of silicone-induce aggregation is the natural result of the combination of elements disclosed in the prior art. Pet. 44–45; Ex. 1009

[8] At most, Patent Owner asserts that "[a]dding polysorbate 80 yielded the unexpected result of a decrease in the loss of antigenicity of the polysaccharide protein conjugate vaccine for all serotypes." PO Resp. 29. As discussed below, we determine that Patent Owner has not sufficiently supported that assertion.

¶ 137 (characterizing the '999 patent Specification as emphasizing that the adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation); *see PAR Pharm.*, 773 F.3d at 1196 (describing meeting high standard for inherency in an obviousness analysis when the claim limitation is the "natural result of the combination of elements explicitly disclosed by the prior art"). As Petitioner asserts, such adsorption is taught by Prevenar and Chiron. Pet. 45; Ex. 1017, 2 (polysaccharide-protein conjugates adsorbed on aluminum phosphate); Ex. 1011, 5:4 (antigen is preferably adsorbed to the aluminum salt). Thus, we determine that Petitioner has established persuasively that Prevenar's composition, as modified by the addition of Chiron's histidine, yields the formulation of claim 1, wherein the recited aggregation inhibition property of the formulation must be present, or is the natural result of the combination of elements disclosed by the prior art.

Accordingly, based on the foregoing, we determine that Petitioner has shown by a preponderance of the evidence that claim 1 would have been obvious over the combination of Prevenar and Chiron.

Claim 2 depends from claim 1 and further recites that the formulation "further comprises polysorbate 80, and wherein the final concentration of the polysorbate 80 in the formulation is at least 0.001% to 10% polysorbate 80 weight/volume of the formulation." Ex. 1001, 31:13–17. Petitioner asserts that a person of skill in the art would have had a reason to include Chiron's polysorbate 80 (e.g., 0.005% Tween 80) in the Prevenar formulation because the skilled artisan would have known that (a) Chiron taught that adding a surfactant, such as polysorbate 80, advantageously minimized adsorption of proteins to containers, and (b) such surfactant also inhibits silicone-induced

aggregation. Pet. 46–47 (citing Ex. 1011, 6:14–15 and Examples 7–9; Ex. 1009 ¶¶ 146–147(citing Ex. 1013 "Smith")). Further, in terms of a reasonable expectation of successfully adding a surfactant to Prevenar, Petitioner asserts that the skilled artisan would have known, and thus expected, that surfactants in low amounts were a safe and standard component of pharmaceuticals and had been included in other polysaccharide-protein conjugate vaccines. *Id*. at 47 (citing Ex. 1009 ¶147).

Patent Owner asserts that Chiron teaches away from using polysorbate to inhibit aggregation by teaching its use to minimize adsorption to containers. PO Resp. 27–28 (citing Ex. 2124 ¶ 68; *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). However, neither Patent Owner nor Dr. Thomson explain how Chiron's teaching regarding a benefit of adding a surfactant to a conjugate vaccine formulation may be said to lead a person of ordinary skill in the art "in a direction divergent from the path that was taken" by Patent Owner. Nor do we recognize such a teaching away. Indeed, both Chiron and Patent Owner include polysorbate 80 in their respective formulations.

Patent Owner asserts also that "polysorbates were associated with numerous risks that would have dissuaded a POSA to add polysorbate to an approved formulation such as Prevenar []." PO Resp. 28. In particular, Patent Owner asserts that ether linkages in polysorbates "can spontaneously and rapidly oxidize in aqueous solution to protein-damaging peroxides, epoxy acids, and reactive aldehydes, including formaldehyde and acetaldehyde," *id*. (citing Ex. 2124 ¶ 67); polysorbates oxidize histidine in a protein formulation that may cause a decrease in potency of the formulation, *id*. (citing Ex. 2124 ¶ 68); and polysorbates could cause aggregation, *id*.

(citing Ex. 2124 ¶ 68).

Those contentions by Patent Owner and Dr. Thomson appear to be theoretical and do not precisely relate to the use of polysorbate in a polysaccharide-protein conjugate formulation as taught by Chiron. Dr. Thomson relies on a 1978 journal article generally describing "autoxidation" of aqueous solutions of polysorbates. Ex. 2124 ¶ 67 (citing Ex. 2057, 3 and 8). The referenced portions of the article do not address the behavior of polysorbate in a polysaccharide-protein conjugate formulation. Nor does Dr. Thomson rely on another reference to address that point. In particular, he does not explain why a person of skill in the art would have viewed the referenced teaching relating to oxidation of polysorbate stored alone to be applicable to polysorbate in a formulation such as Chiron's polysaccharide-protein conjugate vaccine.

To support his opinion that polysorbate oxidizes histidine in a protein formulation, Dr. Thomson relies on a journal article abstract relating to the oxidation of histidine in a formulation also comprising polysorbate 80 and a monoclonal antibody ("mAb"). Ex. 2124 ¶ 68 (citing Ex. 2067, 4). Specifically, the abstract is directed to evaluating "[t]he role of histidine oxidation on mAb potency," and postulates that a "mAb formulated in histidine buffer not only gets oxidized but also interacts with histidine oxidation products thereby leading to an accelerated potency loss." Ex. 2067, 4. Dr. Thomson does not explain why a person of skill in the art would have viewed the referenced teaching to be applicable to a polysaccharide-protein conjugate formulation comprising polysorbate, histidine and an aluminum salt, such as Chiron's.

Similarly, Dr. Thomson has not explained why a person of skill in the

art would have viewed a journal article describing polysorbate 20 has enhancing aggregation in solutions comprising high concentrations of PEG-GCSF, PEG-MGDF, or OP-GFc protein stored in a quiescent shelf-life setting, or would have viewed a journal article describing Tween 80 and 0.1% HAS as having no stabilizing effect on an aqueous solution comprising interleukin-1 β, NaCl, and a citrate buffer applicable to Chiron's polysaccharide-protein conjugate formulation. *See* Ex. 2124 ¶ 68 (citing Ex. 2069, 3 and Ex. 2070, 2).

Patent Owner asserts also that "[a]dding polysorbate 80 yielded the unexpected result of a decrease in the loss of antigenicity of the polysaccharide-protein conjugate vaccine for all serotypes." PO Resp. 29 (citing Ex. 2119 ¶ 29). Neither Patent Owner nor Dr. Khanke adequately support that contention. For example, they have not compared the results described in the Specification of the '999 patent with the closest prior art. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Nor have they demonstrated what would have been expected upon adding polysorbate 80 to a polysaccharide-protein conjugate. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (expected properties must be considered before evaluating unexpected properties).

Thus, on balance, we determine that the inadequately supported testimony offered by Patent Owner's declarants, Drs. Thomson and Khandke, is outweighed by the express disclosures by Chiron relied upon by Petitioner. In other words, we determine that the preponderance of the evidence supports Petitioner's position that a person of skill in the art would have had a reason to add polysorbate 80 to the modified Prevenar formulation comprising histidine based upon Chiron's disclosure that adding

a surfactant, such as polysorbate 80, advantageously minimized adsorption of proteins to containers, and such a surfactant may be successfully combined with histidine in a polysaccharide-protein conjugate vaccine. Pet. 46–47 (citing Ex. 1011, 6:14–15 and Examples 7–9; Ex. 1009 ¶¶ 146–147). Moreover, Dr. Kalonia has explained persuasively that such surfactant was known in the art to inhibit silicone-induced aggregation, as evidence by Smith. *Id*. (citing Ex. 1009 ¶¶ 145–147(citing Smith)). Similarly, on balance, we determine that Petitioner has established by a preponderance of the evidence that, based upon those teachings of Chiron and Dr. Kalonia's testimony regarding the knowledge in the art, *see, e.g*. Ex. 1009 ¶147, a person of skill in the art would have had a reasonable expectation of successfully adding a surfactant to the modified Prevenar.

Patent Owner does not separately address Petitioner's related challenges to dependent claims 3–6, 10. 11, 14, 17, 19, and 20. Based upon our review of Petitioner's contentions regarding the additional limitations of those claims, Pet. 46–54 and 57–58, we determine that Petitioner has also shown by a preponderance of the evidence that each of those dependent claims would have been obvious over the combination of Prevenar and Chiron.

b. Dependent Claim 18

Claim 18 depends directly from claim 1, and further requires the one or more polysaccharide-protein conjugates to comprise thirteen conjugates, each with a different polysaccharide from a specific *S. pneumoniae* serotype (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A) conjugated to a CRM_{197} polypeptide. Regarding that additional limitation, Petitioner asserts that the thirteen pneumococcal serotypes recited in claim 18 were well known in the

art. Pet. 55 (citing Ex. 1007 ¶ 44). According to Petitioner, "[t]here is a natural progression in the development of multivalent vaccines." *Id.* Petitioner asserts that the 7-valent pneumococcal vaccine was expanded to a 9-valent vaccine, and subsequently to an 11-valent vaccine, wherein each polysaccharide is conjugated solely to CRM_{197}. *Id.* (citing Ex. 1007 ¶¶ 38, 45). According to Petitioner, a person of skill in the art "would have understood that a further step in the natural progression included the 13 serotypes of claim 18 (which were well-known), conjugated only to CRM_{197}." *Id.* (citing Ex. 1007 ¶¶ 44–46).

Patent Owner asserts that Prevenar and Chiron, alone or in combination, do not disclose the additional conjugates required by claim 18. PO Resp. 30. Patent Owner asserts also that Petitioner has not provided a reason for a person of skill in the art to further modify Prevenar's formulation to include the recited conjugates. *Id.* at 31. According to Patent Owner, Petitioner's reliance on a "natural progression" from the seven valent to the recited 13 valent conjugate formulation represents impermissible hindsight, as it requires using the inventor's disclosure as a blueprint to piece together prior art. *Id.* at 30, 40–41 (citing *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)). Further, Patent Owner asserts that Petitioner has failed to show that the modified formulation meets the limitations of independent claim 1, from which claim 18 depends, namely, that it "inhibits aggregation induced by the siliconized container means." *Id.* at 30.

Additionally, Patent Owner asserts objective evidence of non-obviousness for claim 18. *Id.* at 46. Patent Owner asserts that Prevnar13 includes all of the limitations of claim 18 and has been a commercial

success, received industry praise, met a long-felt but unmet need, overcame the failure of others, and has been copied by others. *Id*. at 47–53.

Having considered the record, as a whole, we determine Petitioner has not established by a preponderance of the evidence that a person of skill in the art would found it obvious to further modify Prevenar's formulation to comprise the thirteen valent conjugate recited in claim 18. Although Petitioner's declarant provides evidence that the thirteen pneumococcal serotypes recited in claim 18 were known in the art, Petitioner has not established persuasively, or even explained in any specific way, that the prior art, or the knowledge of one having skill in the art would have motivated the artisan to further modify Prevenar to include the recited 13 conjugates with a reasonable expectation of successfully doing so. *See KSR,* 550 U.S. at 418 (reaffirming that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art"); *see also In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988) (obviousness must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to arrive at the claimed invention).

Without such evidence, Petitioner's obviousness rationale based upon a so-called "natural progression" from a known seven valent conjugate formulation to the thirteen valent conjugate recited in claim 18 resembles a contention guided impermissibly by hindsight reasoning. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1343, 1368 (Fed. Cir. 2012) (care must be taken to avoid hindsight reasoning to reach the claimed invention without any explanation as to how or why the cited references

would be combined).

In view of our determination that Petitioner has not shown by a preponderance of the evidence that claim 18 is unpatentable as obvious, we need not reach the merits of Patent Owner's evidence of secondary considerations of nonobviousness.

Based on the foregoing, we determine that Petitioner has established by a preponderance of the evidence that claims 1–6, 10, 11, 14, 17, 19, and 20 of the '999 patent are unpatentable over the combination of Prevenar and Chiron. Petitioner, however, has not established by a preponderance of the evidence that claim 18 is unpatentable over the combined prior art.

D. Obviousness over Prevenar, Chiron, and Peña

Petitioner asserts that claim 18 is unpatentable over the combination of Prevenar, Chiron, and Peña. Pet. 58–59. Patent Owner disagrees. PO Resp. 37–53.

1. Peña

Peña discusses various aspects of pneumococcal vaccination. Ex. 1015, 2. In particular, Peña describes two available vaccines to prevent invasive pneumococcal illness in Spain: 23-valent polysaccharides (VNP-23V) and 7-valent conjugated (VNC-7V). *Id*. Peña explains that the 7-valent vaccine contains the purified saccharides of the capsular antigens of seven serotypes of *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F, and 23F) conjugated individually with a protein, a nontoxic mutant of the diphtheria toxin, CRM_{197}. *Id*. at 3. Peña explains that the 23-valent vaccine contains *S. pneumoniae* serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17E, 18C, 19A, 19F, 20, 22F, 23F, and 33F. *Id*. at 7. Additionally,

Peña discusses the Prevnar 7-valent conjugated vaccine and "other pneumococcal conjugates that have not yet been marketed and that are in advanced phases of study," including a 9-serotype vaccine (adds 1 and 5), an 11-serotype vaccine (adds 3 and 7F), and a 13-serotype vaccine (adds 6A and 19A). *Id*.

2. Obviousness Analysis

As discussed with respect to the obviousness challenge over the combination of Prevenar and Chiron, we have determined that Petitioner has established by a preponderance of the evidence that the combined teachings of those references teach or suggest each limitation of independent claim 1. Petitioner adds Peña to the combination to demonstrate that it would have been obvious to prepare Chiron's formulation by using the 13-valent conjugate recited by claim 18. Pet. 59.

Petitioner adds Peña to the combination to demonstrate that it would have been obvious to prepare Chiron's formulation by using the 13-valent conjugate recited by claim 18. Pet. 58. In particular, Petitioner asserts that Peña discloses a 13-valent pneumococcal conjugate vaccine with the same serotypes recited by the claim. *Id*. at 59; Ex. 1015, 7. According to Petitioner, a person of ordinary skill in the art would have understood that those conjugates each contain the CRM_{197} protein carrier, "based on the published progression from 7-valent Prevnar®, to 9- and 11- valent iterations; each version contained CRM_{197} as the sole carrier protein." *Id*. (citing Ex. 1007 ¶¶ 45–46).

Patent Owner's arguments mirror those raised regarding the challenge of claim 18 over the combination of Prevenar and Chiron.[9] In view of those arguments and for similar reasons discussed regarding that ground, we determine here that Petitioner has not demonstrated by a preponderance of the evidence that a person of ordinary skill in the art would have found it obvious to further modify Prevenar's formulation to comprise the thirteen valent conjugate recited in claim 18.

In particular, Petitioner directs us to Peña's disclosure of a 13-valent pneumococcal conjugate vaccine with the same serotypes recited by claim 18 that is described as being in an "advanced phase of study". Pet. 59 (citing Ex. 1015, 2). Petitioner, however, does not direct us to any disclosure in Peña, or other evidence of record, further characterizing the vaccine or the study, nor do we see such disclosures in the reference. Without such information, we are unable to assess whether the study involved a formulation comprising the each of thirteen known serotypes conjugated to a CRM197 polypeptide, as required by the claim, or if such an attempt was even considered, tried and successful. As a result, Petitioner has not provided sufficient evidence for us to determine whether a skilled artisan who endeavored to further modify Prevenar's formulation to yield a 13-valent pneumococcal conjugate vaccine with the same serotypes as in Peña would have had a reasonable expectation of successfully doing so. To the extent that Petitioner relies on a so-called "natural progression" from a seven valent conjugate to the thirteen valent conjugate recited in claim 18,

[9] Here again, Patent Owner also asserts objective evidence of non-obviousness for claim 18. *Id*. at 46.

we remain unpersuaded, as it appears to be guided only by impermissible hindsight. *See Kinetic Concepts*, 688 F.3d at 1368.

In view of our determination that Petitioner has not shown by a preponderance of the evidence that claim 18 is unpatentable as obvious, we need not reach the merits of Patent Owner's evidence of secondary considerations of nonobviousness.

Based on the foregoing, we determine that Petitioner has not established by a preponderance of the evidence that claim 18 of the '999 patent is unpatentable over the combination of Prevenar, Chiron, and Peña.

III. MOTIONS TO EXCLUDE

Petitioner and Patent Owner have each filed a motion to exclude evidence. Papers 34 and 38.

A. Petitioner's Motion

Petitioner moves to exclude Patent Owner's Exhibits 2033, 2113, 2114, 2150–2159, and portions of Exhibits 2124 (¶¶ 73–74) and 2119 (¶¶ 9, 12–17, 25, and 27–28). Paper 34. Patent Owner opposes the motion. Paper 47. As the moving party, Petitioner has the burden of proof to establish that it is entitled to the requested relief.

Petitioner challenges Exhibits 2033, 2113, 2114, and portions of Exhibit 2124 (¶¶ 73–74) as they relate to Patent Owner's assertion of commercial success with respect to claim 18. Paper 34, 2. As we have not reached the merits of Patent Owner's evidence of secondary considerations of nonobviousness, we dismiss Petitioner's Motion to Exclude regarding those exhibits as moot.

Petitioner challenges Exhibit 2119 (¶¶ 9, 12–17, 25, and 27–28) as allegedly "unreliable and unsupported testimony" by Patent Owner's declarant, Dr. Khandke, regarding the state of the art of conjugate vaccine formulation at the time of the invention. Paper 34, 2 (citing Federal Rules of Evidence "FRE" 702 and 703). In this *inter partes* review proceeding, we find that such matters go to the probative weight of her testimony, as opposed to its admissibility. *See, e.g.*, Office Patent Trial Practice Guide, 77 Fed. Reg. at 48,763 ("Opinions expressed without disclosing underlying facts or data may be given little or no weight."). Although we acknowledge Petitioner's reference to FRE 702 and 703 in seeking to exclude Dr. Khandke's testimony, generally, unlike a lay jury, by design, the Board is composed of individuals with "competent scientific ability" (35 U.S.C. § 6), and is thus capable of evaluating such testimony. Accordingly, the danger of prejudice in this proceeding is considerably lower than in a conventional district court trial. Accordingly, we deny Petitioner's Motion to Exclude the designated portions of Exhibit 2119.

Petitioner challenges Exhibits 2150–2159 as allegedly untimely submitted at the depositions of Petitioner's Reply witnesses. Paper 34, 2. According to Petitioner, those exhibits "impermissibly introduce new arguments and evidence which Petitioner and its experts have had no opportunity to address." *Id.* at 2–3. Further, Petitioner asserts that the exhibits are inadmissible under FRE 401 and 402 as lacking relevance, under FRE 801 and 802 as hearsay, and under FRE 901 as lacking authentication and having no foundation. *Id.* at 3. We have not relied upon those exhibits in this Final Written Decision, however, as Patent Owner does not refer to them in the Patent Owner Response.

Accordingly, we dismiss Petitioner's Motion to Exclude those exhibits as moot.

B. Patent Owner's Motion

Patent Owner moves to exclude Petitioner's Exhibits 1037, 1065, 1084, 1085, and 1108. Paper 38. Petitioner opposes the motion. Paper 43. As the moving party, Patent Owner has the burden of proof to establish that it is entitled to the requested relief.

Exhibit 1065 is a copy of a book chapter included in the "Concise Encyclopedia of High Performance Silicones," titled "Silicone Oil in Biopharmaceutical Containers: Applications and Recent Concerns." Patent Owner challenges the admissibility of the exhibit by asserting that it is legally irrelevant because it is not prior art. Paper 38, 4. Patent Owner notes that Petitioner describes the reference as being published in 2014. *Id.* According to Patent Owner, Petitioner has not established that the exhibit was a "printed publication" available before the April 26, 2006 priority date of the '999 patent. *Id.* Petitioner responds by asserting that Exhibit 1065 is relevant to establishing the specific expertise of Dr. Kalonia, a co-author of the book chapter, regarding an aspect of the claimed invention, i.e., silicone-induced aggregation. Paper 43, 5.

Having considered the evidence and the arguments, we agree with Patent Owner that Petitioner has not established that Exhibit 1065 is relevant regarding the knowledge of those skilled in the art at the time of the invention. Based upon our review, Dr. Kalonia refers to the book chapter submitted as Exhibit 1065 in his declaration discussion of his credentials. Ex. 1009 ¶ 7. Additionally, Petitioner and Dr. Kalonia refer to Exhibit 1065 when discussing certain arguments relating to the state of the art at the time

of the invention. *See, e.g.*, Pet. 12 (referring to Exhibit 1065). We note that in such instances, those contentions are equally supported by other references. Insofar as Exhibit 1065 is relied upon to demonstrate Dr. Kalonia's expertise regarding silicone oil in biopharmaceutical containers, we find such use permissible, and do not interpret Patent Owner's motion to seek to exclude use of Exhibit 1065 in that context. In the Final Written Decision, we have considered Exhibit 1065 only to assess Dr. Kalonia's qualifications to offer testimony regarding the ordinary skill in the art. The exhibit, however, is not available to establish what was known in the art at the time of the invention. Indeed, we have not relied on Exhibit 1065 in the Final Written Decision with respect to any patentability challenge. Accordingly, Patent Owner's motion is dismissed as moot.

We also have not relied upon Exhibits 1037, 1084, 1085, and 1108 in this Final Written Decision, as they were cumulative to previously submitted evidence, or related to issues disposed upon other bases. Accordingly, we dismiss Patent Owner's Motion to Exclude these exhibits as moot.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has shown by a preponderance of the evidence that claims 1–6, 10, 11, 14, 17, 19, and 20 are unpatentable. Petitioner has not shown by a preponderance of the evidence that claim 18 is unpatentable.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–6, 10, 11, 14, 17, 19, and 20 of the '999 patent are unpatentable under 35 U.S.C. § 103 as obvious over Prevenar and Chiron;

FURTHER ORDERED that claim 18 has not been shown by a preponderance of the evidence to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is *dismissed* and moot with regard to Exhibits 2033, 2113, 2114, 2150–2159, and designated portions of Exhibit 2124 (¶¶ 73–74), and *denied* with regard to the designated portions of Exhibit 2119 (¶¶ 9, 12–17, 25, 27–28);

FURTHER ORDERED that Patent Owner's Motion to Exclude is *dismissed* as moot; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2017-00380
Patent 8,562,999 B2

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US008562999B2

(12) **United States Patent**
Khandke et al.

(10) **Patent No.: US 8,562,999 B2**
(45) **Date of Patent: *Oct. 22, 2013**

(54) **FORMULATIONS WHICH STABILIZE AND INHIBIT PRECIPITATION OF IMMUNOGENIC COMPOSITIONS**

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(72) Inventors: **Lakshmi Khandke**, Nanuet, NY (US); **Ronald Malone**, Chapel Hill, NC (US); **Cindy Xudong Yang**, Tappan, NY (US); **Hanyoung Han**, Sunnyside, NY (US); **Jee Loon Look**, Boyds, MD (US); **Zhaowei Jin**, Chesterfield, MO (US); **Robert C. Seid, Jr.**, Chapel Hill, NC (US); **Ying Chen**, Apex, NC (US)

(73) Assignee: **Wyeth LLC**, Madison, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/631,573**

(22) Filed: **Sep. 28, 2012**

(65) **Prior Publication Data**

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Related U.S. Application Data

(62) Division of application No. 13/070,664, filed on Mar. 24, 2011, which is a division of application No. 11/737,674, filed on Apr. 19, 2007, now Pat. No. 7,935,787.

(60) Provisional application No. 60/795,261, filed on Apr. 26, 2006.

(51) **Int. Cl.**

A61K 39/00	(2006.01)
A61K 39/385	(2006.01)
C07K 1/00	(2006.01)

(52) **U.S. Cl.**
USPC **424/184.1**; 424/193.1; 424/197.11; 530/350

(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Albert Navarro
(74) *Attorney, Agent, or Firm* — Victoria S. Molenda

(57) **ABSTRACT**

The present invention addresses an ongoing need in the art to improve the stability of immunogenic compositions such as polysaccharide-protein conjugates and protein immunogens. The invention broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions. More particularly, the invention described hereinafter, addresses a need in the art for formulations which stabilize and inhibit particulate formation (e.g., aggregation, precipitation) of immunogenic compositions which are processed, developed, formulated, manufactured and/or stored in container means such as fermentors, bioreactors, vials, flasks, bags, syringes, rubber stoppers, tubing and the like.

22 Claims, 9 Drawing Sheets

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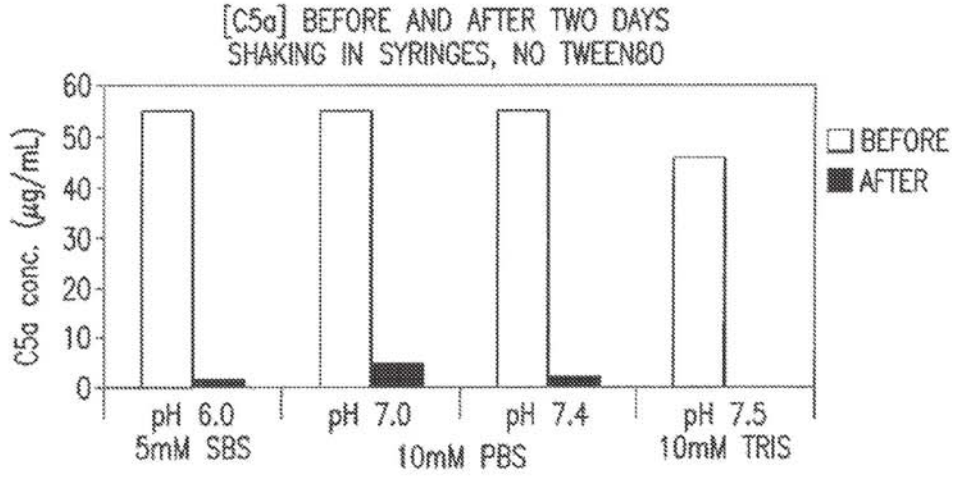
[C5a] BEFORE AND AFTER TWO DAYS
SHAKING IN SYRINGES, NO TWEEN80
C5a conc. (μg/mL)
60
50
40
30
20
10
0
BEFORE
AFTER
pH 6.0
5mM SBS
pH 7.0
10mM PBS
pH 7.4
pH 7.5
10mM TRIS

FIG.1A

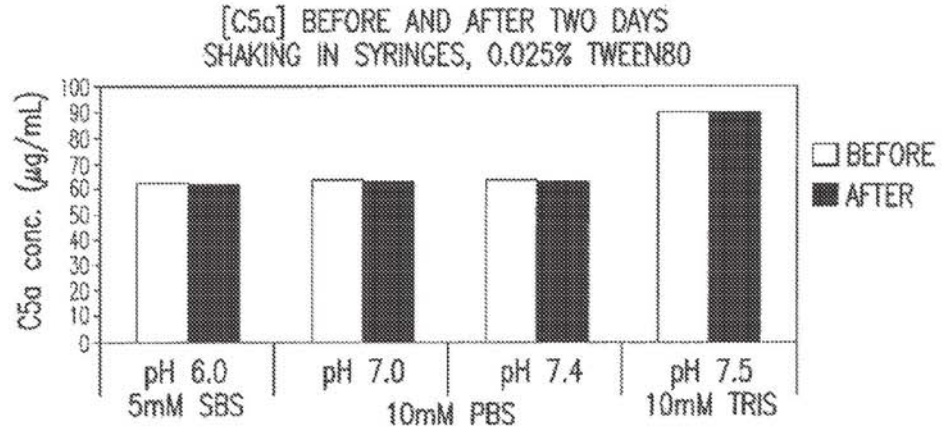
[C5a] BEFORE AND AFTER TWO DAYS
SHAKING IN SYRINGES, 0.025% TWEEN80
C5a conc. (μg/mL)
100
90
80
70
60
50
40
30
20
10
0
BEFORE
AFTER
pH 6.0
5mM SBS
pH 7.0
10mM PBS
pH 7.4
pH 7.5
10mM TRIS

FIG.1B

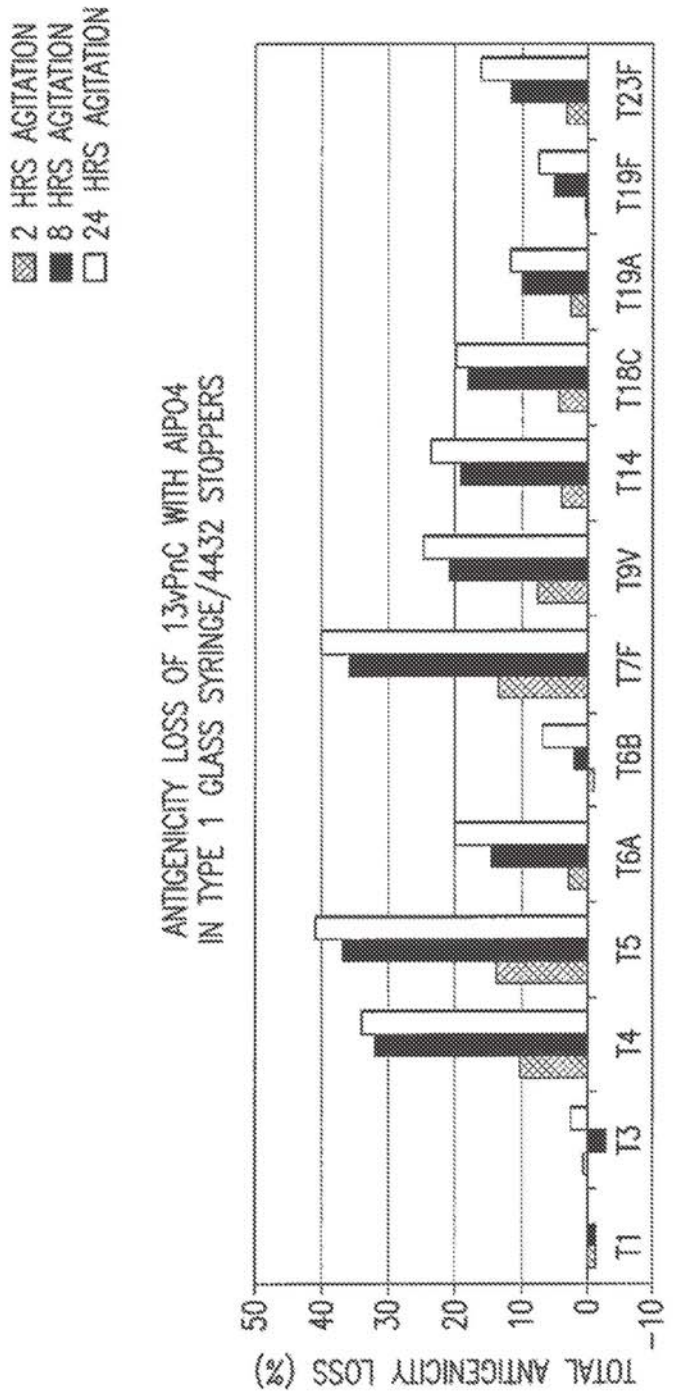
2 HRS AGITATION
8 HRS AGITATION
24 HRS AGITATION
ANTIGENICITY LOSS OF 13vPnC WITH AlPO4
IN TYPE 1 GLASS SYRINGE/4432 STOPPERS
TOTAL ANTIGENICITY LOSS (%)
50
40
30
20
10
0
-10
T1
T3
T4
T5
T6A
T8B
T7F
T9V
T14
T18C
T19A
T19F
T23F

FIG. 2

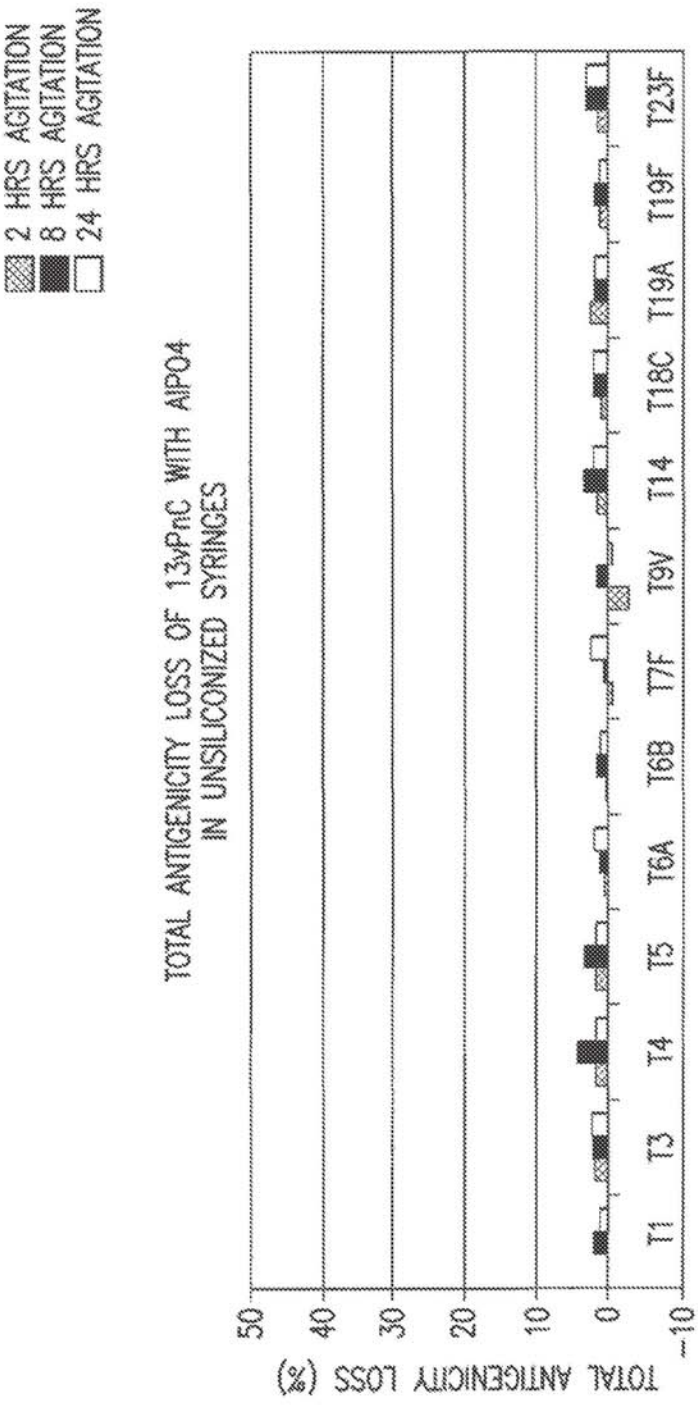
2 HRS AGITATION
8 HRS AGITATION
24 HRS AGITATION
TOTAL ANTIGENICITY LOSS OF 13vPnC WITH AlPO4
IN UNSILICONIZED SYRINGES
TOTAL ANTIGENICITY LOSS (%)
50
40
30
20
10
0
-10
T1
T3
T4
T5
T6A
T6B
T7F
T9V
T14
T18C
T19A
T19F
T23F

FIG.3

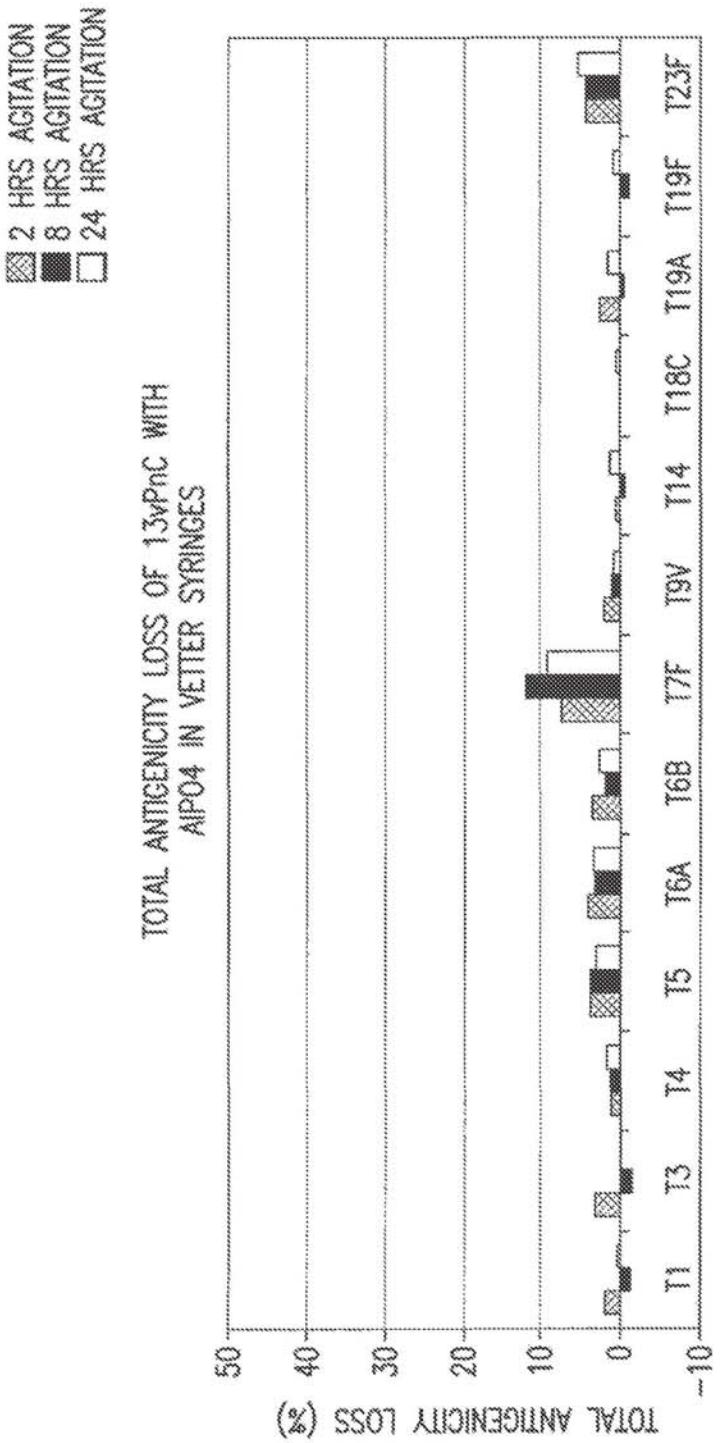
2 HRS AGITATION
8 HRS AGITATION
24 HRS AGITATION
TOTAL ANTIGENICITY LOSS OF 13vPnC WITH AlPO4 IN VETTER SYRINGES
TOTAL ANTIGENICITY LOSS (%)
50
40
30
20
10
0
-10
T1
T3
T4
T5
T6A
T6B
T7F
T9V
T14
T18C
T19A
T19F
T23F

FIG.4

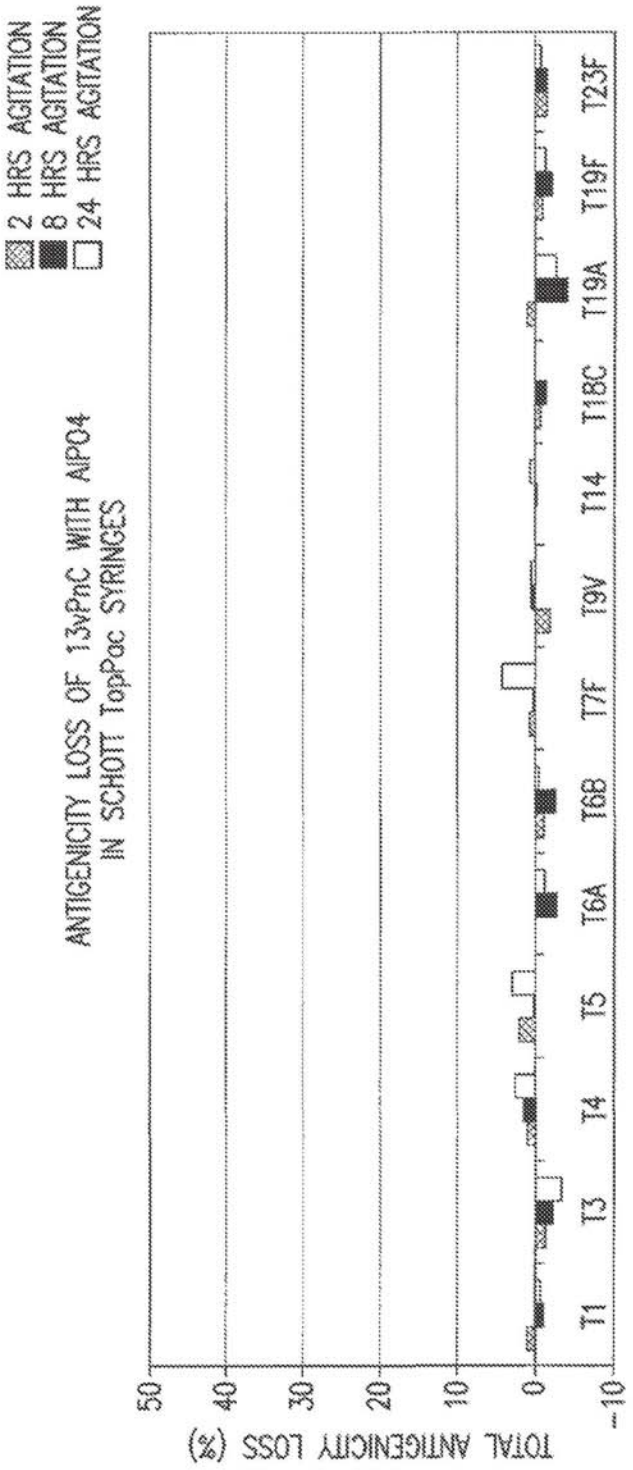
2 HRS AGITATION
8 HRS AGITATION
24 HRS AGITATION
ANTIGENICITY LOSS OF 13vPnC WITH AlPO4
IN SCHOTT TopPac SYRINGES
TOTAL ANTIGENICITY LOSS (%)
50
40
30
20
10
0
-10
T1
T3
T4
T5
T6A
T6B
T7F
T9V
T14
T18C
T19A
T19F
T23F

FIG.5

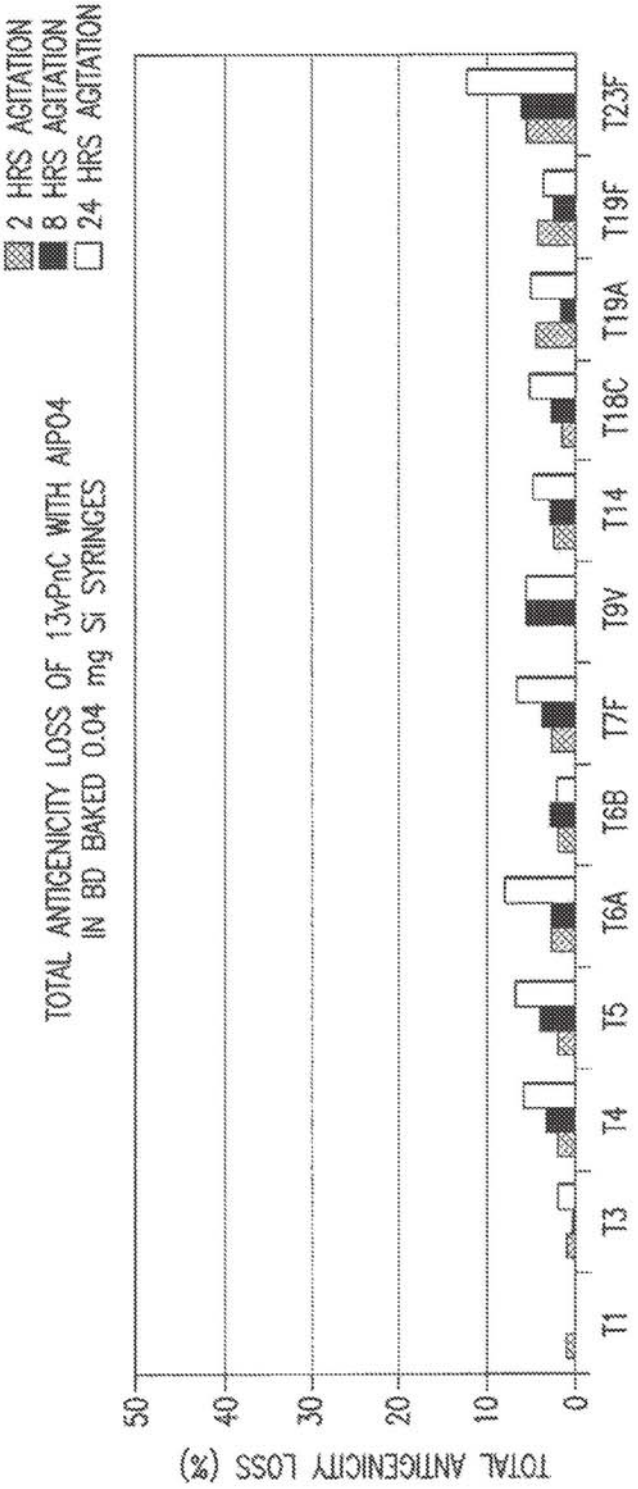
TOTAL ANTIGENICITY LOSS OF 13vPnC WITH AlPO4
IN BD BAKED 0.04 mg Si SYRINGES
2 HRS AGITATION
8 HRS AGITATION
24 HRS AGITATION
TOTAL ANTIGENICITY LOSS (%)
0
10
20
30
40
50
T1
T3
T4
T5
T6A
T6B
T7F
T9V
T14
T18C
T19A
T19F
T23F

FIG.6A

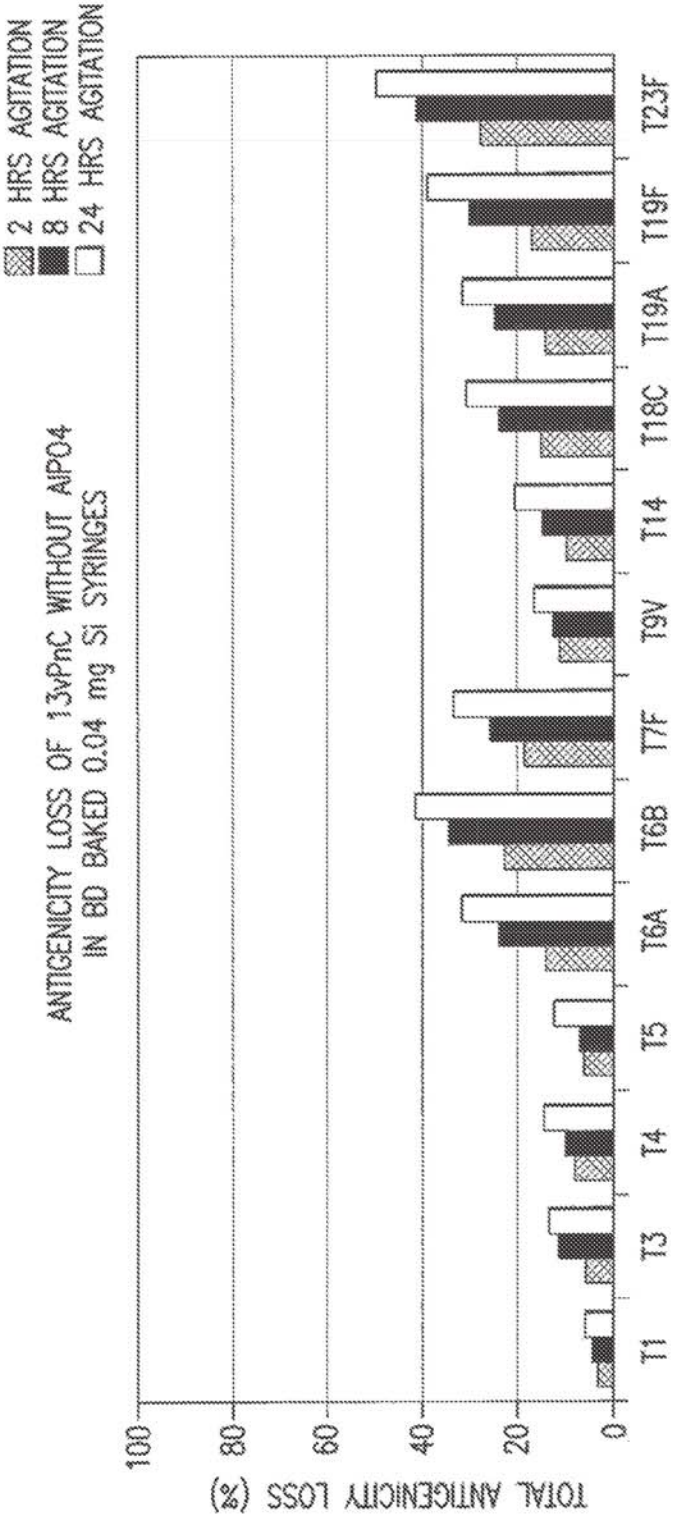
2 HRS AGITATION
8 HRS AGITATION
24 HRS AGITATION
ANTIGENICITY LOSS OF 13vPnC WITHOUT AlPO4
IN BD BAKED 0.04 mg Si SYRINGES
TOTAL ANTIGENICITY LOSS (%)
100
80
60
40
20
0
T1
T3
T4
T5
T6A
T6B
T7F
T9V
T14
T18C
T19A
T19F
T23F

FIG.6B

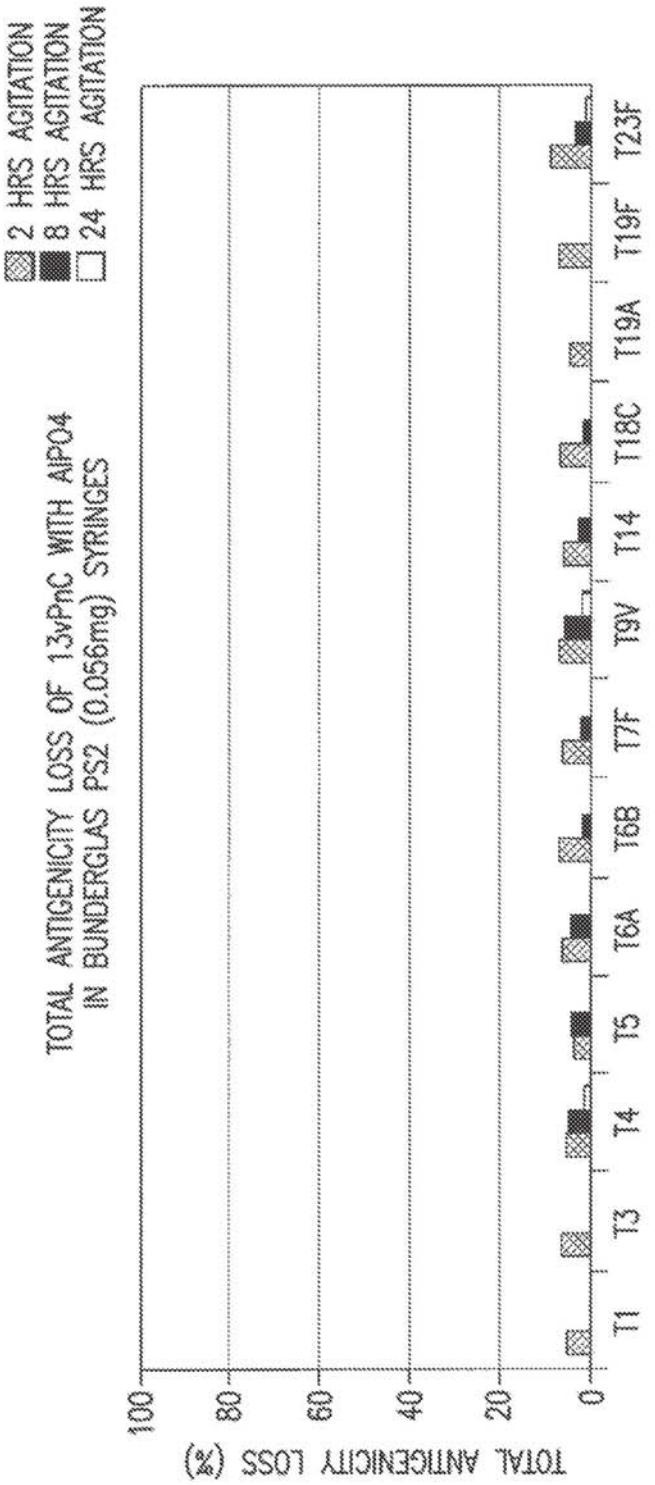
TOTAL ANTIGENICITY LOSS OF 13vPnC WITH AlPO4
IN BUNDERGLAS PS2 (0.056mg) SYRINGES
2 HRS AGITATION
8 HRS AGITATION
24 HRS AGITATION
TOTAL ANTIGENICITY LOSS (%)
100
80
60
40
20
0
T1
T3
T4
T5
T6A
T6B
T7F
T9V
T14
T18C
T19A
T19F
T23F

FIG. 7A

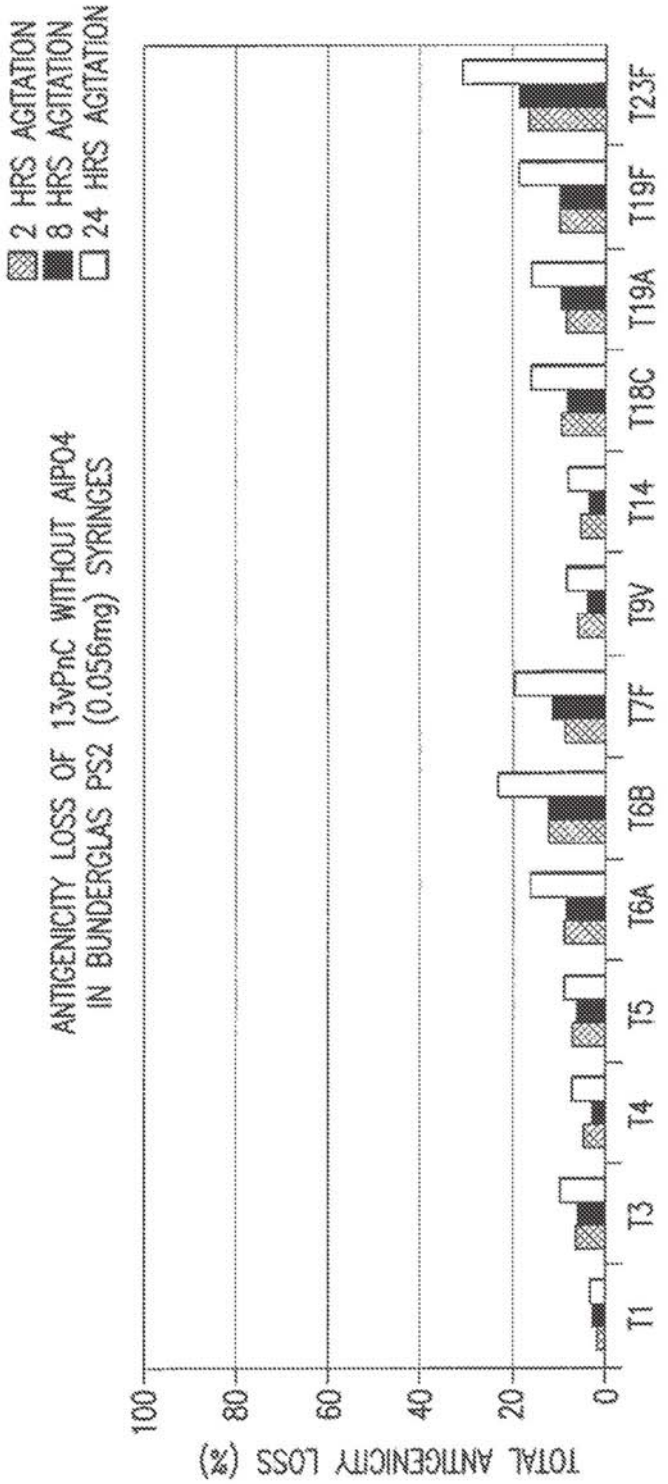
ANTIGENICITY LOSS OF 13vPnC WITHOUT AlPO4
IN BUNDERGLAS PS2 (0.056mg) SYRINGES
2 HRS AGITATION
8 HRS AGITATION
24 HRS AGITATION
TOTAL ANTIGENICITY LOSS (%)
100
80
60
40
20
0
T1
T3
T4
T5
T6A
T6B
T7F
T9V
T14
T18C
T19A
T19F
T23F

FIG.7B

FORMULATIONS WHICH STABILIZE AND INHIBIT PRECIPITATION OF IMMUNOGENIC COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of U.S. application Ser. No. 13/070,664, filed Mar. 24, 2011, which is a divisional application of U.S. application Ser. No. 11/737,674, filed Apr. 19, 2007, which claims the benefit of U.S. Provisional Application No. 60/795,261, filed Apr. 26, 2006. The contents of application Ser. Nos. 13/070,664; 11/737,674 and 60/795,261 are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention generally relates to the fields of immunology, bacteriology, vaccine formulation, protein stability and process development. More particularly, the invention relates to novel formulations which inhibit precipitation of immunogenic compositions.

BACKGROUND OF THE INVENTION

It is generally accepted in the bio-pharmaceutical arts, that improving the stability of an immunogenic composition (e.g., a protein immunogen, a polysaccharide-protein conjugate) is a necessary and highly desirable goal. For example, an immunogenic composition must appear fresh, elegant and professional when administered to a patient. Any changes in stability and/or physical appearance of the immunogenic composition, such as color change, clouding or haziness, may cause a patient or consumer to lose confidence in the product. Furthermore, because many immunogenic formulations are dispensed in multiple-dose containers, uniformity of dose content of the active ingredient (e.g., a polysaccharide-protein conjugate) over time must be assured (e.g., a cloudy solution can lead to a non-uniform dosage pattern). Additionally, the immunogenic composition must be active throughout its "expected" shelf life, wherein any breakdown of the immunogenic composition to an inactive or otherwise undesired form (e.g., an aggregate) lowers the total concentration of the product.

Several reports in the literature have suggested that the stability of a particular immunogenic composition (e.g., a protein immunogen, a polysaccharide-protein conjugate) is at least in part dependent upon the specific protein or carrier protein (Ho et al., 2001; Ho et al., 2002; Bolgiano et al., 2001). For example, stability analysis of meningococcal C (MenC) polysaccharides and *Haemophilus influenzae* type b (Hib) polysaccharides, conjugated to either a tetanus toxoid (TT) or a CRM_{197} carrier protein, revealed different stability profiles dependent on the carrier protein (Ho et al., 2002). In another study (Ho et al., 2001), MenC-CRM_{197} conjugates from two different manufacturers were analyzed (Ho et al., 2001), wherein the MenC-CRM_{197} conjugates differed in their conjugation chemistry and length of conjugate polysaccharide (both having the same carrier protein, CRM_{197}). Data from this study further indicated that factors such as conjugation chemistry (e.g., reductive amination either directly or via a chemical spacer group), number of conjugation sites, polysaccharide chain length, pH, storage buffer, storage temperature(s) and freeze/thaw cycles also influence the stability of an immunogenic composition.

Thus, when developing a formulation for an immunogenic composition, many factors must be considered to ensure a safe, stable, robust and cost effective product. Such considerations include, but are not limited to, chemical stability of the immunogenic composition (e.g., hydrolysis of saccharides, de-polymerization of polysaccharides, proteolysis or fragmentation of proteins), physical/thermal stability of the immunogenic composition (e.g., aggregation, precipitation, adsorption), compatibility of the immunogenic composition with the container/closure system, interactions between immunogenic composition and inactive ingredients (e.g., buffers, salts, excipients, cryoprotectants), the manufacturing process, the dosage form (e.g., lyophilized, liquid), the environmental conditions encountered during shipping, storage and handling (e.g., temperature, humidity, shear forces), and the length of time between manufacture and usage.

It has been suggested in the art, that silicone oil, which induces protein secondary and tertiary conformational changes, might be responsible for the aggregation/precipitation seen in certain protein pharmaceutical preparations (Jones et al., 2005). For example, several reports in the 1980s implicated the release of silicone oil from disposable plastic syringes as the causative agent in the aggregation of human insulin (Chantelau and Berger, 1985; Chantelau et al., 1986; Chantelau, 1989; Bernstein, 1987; Baldwin, 1988; Collier and Dawson, 1985). Chantelau et al. (1986) observed that after three or more withdrawals from a ten-dose preparation of insulin (using a siliconized disposable syringe), the vial would begin clouding due silicone oil contamination, thereby resulting in aggregation and deactivation of the insulin (Chantelau et al., 1986). Paradoxically, silicone oil is a necessary component of plastic syringes, as it serves to lubricate the rubber plunger and facilitate transfer of the plunger down the syringe barrel (i.e., silicone oil improves the syringeability of the formulation).

Furthermore, the use of silicone oil is not limited to syringes, as it is used as a coating for glass vials to minimize protein adsorption, as a lubricant to prevent conglomeration of rubber stoppers during filing procedures, as a lubricant critical to the processability/machinability of glass and elastomeric closures and as a lubricant to ease needle penetration of vial rubber stoppers. Additionally, the siliconization of syringes, glass vials, rubber stoppers and the like, is not a well controlled nor standardized process, and as such, there is a high degree of variability of the silicone oil content from one lot to another.

There is therefore an ongoing need in the art for formulations which enhance stability and inhibit precipitation of immunogenic compositions.

SUMMARY OF THE INVENTION

The present invention broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions. More specifically in certain embodiments, the present invention is directed to novel formulations which inhibit precipitation of immunogenic compositions comprised in container means. In one specific embodiment, the invention is directed to novel formulations which stabilize immunogenic compositions against silicone oil interactions, shear forces, shipping agitation, and the like.

Thus, in certain embodiments, the invention is directed to formulations which stabilize a polysaccharide-protein conjugate, the formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, (ii) a surfactant and (iii) one or more polysaccharide-protein conjugates. In one specific embodiment, the polysac-

charide-protein conjugate formulation is comprised in a container means. In certain embodiments, the container means is selected from one or more of the group consisting of a vial, a vial stopper, a vial closure, a glass closure, a rubber closure, a plastic closure, a syringe, a syringe stopper, a syringe plunger, a flask, a beaker, a graduated cylinder, a fermentor, a bioreactor, tubing, a pipe, a bag, a jar, an ampoule, a cartridge and a disposable pen. In certain embodiments, the container means is siliconized.

In certain embodiments, the pH buffered saline solution of the formulations has a pH of 5.5 to 7.5. In other embodiments, the buffer is phosphate, succinate, histidine or citrate. In certain embodiments, the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0. In one particular embodiment, the final concentration of the succinate buffer is 5 mM. In other embodiments, the salt in the pH buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof. In one particular embodiment, the salt in the pH buffered saline solution is sodium chloride.

In another embodiment, the surfactant of the formulations is selected from the group consisting of polysorbate 20 (Tween™20), polysorbate 40 (Tween™40), polysorbate 60 (Tween™60), polysorbate 65 (Tween™65), polysorbate 80 (Tween™80), polysorbate 85 (Tween™85), Triton™ N-101, Triton™ X-100, oxtoxynol 40, nonoxynol-9, triethanolamine, triethanolamine polypeptide oleate, polyoxyethylene-660 hydroxystearate (PEG-15, Solutol H15), polyoxyethylene-35-ricinoleate (Cremophor EL™), soy lecithin and a poloxamer. In one particular embodiment, the surfactant is polysorbate 80. In another embodiment, the final concentration of the polysorbate 80 in formulation is at least 0.01% to 10% polysorbate 80 weight/volume of the formulation. In other embodiments, the final concentration of the polysorbate 80 in the formulation is 0.01% polysorbate 80 weight/volume of the formulation. In yet other embodiments, the final concentration of the polysorbate 80 in the formulation is 0.05% polysorbate 80 weight/volume of the formulation. In another embodiment, the final concentration of the polysorbate 80 in the formulation is 0.1% polysorbate 80 weight/volume of the formulation. In certain other embodiments, the final concentration of the polysorbate 80 in the formulation is 1.0% polysorbate 80 weight/volume of the formulation. In yet other embodiments, the final concentration of the polysorbate 80 in the formulation is 10.0% polysorbate 80 weight/volume of the formulation.

In another embodiment, the polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides. In certain embodiments, the one or more pneumococcal polysaccharides are a *S. pneumoniae* serotype 4 polysaccharide, a *S. pneumoniae* serotype 6B polysaccharide, a *S. pneumoniae* serotype 9V polysaccharide, a *S. pneumoniae* serotype 14 polysaccharide, a *S. pneumoniae* serotype 18C polysaccharide, a *S. pneumoniae* serotype 19F polysaccharide, a *S. pneumoniae* serotype 23F polysaccharide, a *S. pneumoniae* serotype 1 polysaccharide, a *S. pneumoniae* serotype 3 polysaccharide, a *S. pneumoniae* serotype 5 polysaccharide, a *S. pneumoniae* serotype 6A polysaccharide, a *S. pneumoniae* serotype 7F polysaccharide and a *S. pneumoniae* serotype 19A polysaccharide. In certain embodiments, the protein of the polysaccharide-protein conjugate formulation is selected from the group consisting of CRM_{197}, a tetanus toxoid, a cholera toxoid, a pertussis toxoid, an *E. coli* heat labile toxoid (LT), a pneumolysin toxoid, pneumococcal surface protein A (PspA), pneumococcal adhesin protein A (PsaA), a C5a peptidase from *Streptococcus, Haemophilus influenzae* protein D, ovalbumin, keyhole limpet haemocyanin (KLH), bovine serum albumin (BSA) and purified protein derivative of tuberculin (PPD).

In one specific embodiment, the polysaccharide-protein conjugate formulation is a 7-valent pneumococcal conjugate (7vPnC) formulation comprising a *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM_{197} polypeptide and a *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM_{197} polypeptide.

In another specific embodiment, the polysaccharide-protein conjugate formulation is a 13-valent pneumococcal conjugate (13vPnC) formulation comprising a *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 1 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 3 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 5 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 6A polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 7F polysaccharide conjugated to a CRM_{197} polypeptide and a *S. pneumoniae* serotype 19A polysaccharide conjugated to a CRM_{197} polypeptide.

In other embodiments, the formulation further comprises one or more meningococcal polysaccharides, one or more meningococcal antigenic proteins, or a combination thereof. In yet other embodiments, the formulation further comprises one or more streptococcal polysaccharides, one or more streptococcal antigenic proteins, or a combination thereof.

In certain other embodiments, the formulation further comprises one or more adjuvants. Exemplary suitable adjuvants are described herein below.

In other embodiments, the invention is directed to formulations which stabilize a streptococcal C5a peptidase (SCP) composition, the formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 6.5, (ii) a surfactant and (iii) a streptococcal C5a peptidase. In one specific embodiment, SCP formulation is comprised in a container means. In certain embodiments, the container means is selected from one or more of the group consisting of a vial, a vial stopper, a vial closure, a glass closure, a rubber closure, a plastic closure, a syringe, a syringe stopper, a syringe plunger, a flask, a beaker, a graduated cylinder, a fermentor, a bioreactor, tubing, a pipe, a bag, a jar, an ampoule, a cartridge and a disposable pen.

In other embodiments, the pH buffered saline solution of the formulation has a pH of 5.5 to 7.5. In other embodiments, the buffer is succinate, histidine, phosphate or citrate. In one specific embodiment, the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0. In another specific embodiment, the final concentration of the succinate buffer is 5 mM. In yet other embodiments, the salt in the pH

buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof.

In certain embodiments, the surfactant in the formulations is selected from the group consisting of polysorbate 20 (Tween™20), polysorbate 40 (Tween™40), polysorbate 60 (Tween™60), polysorbate 65 (Tween™65), polysorbate 80 (Tween™80), polysorbate 85 (Tween™85), Triton™ N-101, Triton™ X-100, oxtoxynol 40, nonoxynol-9, triethanolamine, triethanolamine polypeptide oleate, polyoxyethylene-660 hydroxystearate (PEG-15, Solutol H15), polyoxyethylene-35-ricinoleate (Cremophor EL™), soy lecithin and a poloxamer. In one specific embodiment, the surfactant is polysorbate 80. In certain embodiments, the final concentration of the polysorbate 80 in formulation is 0.01% to 10% polysorbate 80 weight/volume of the formulation. In yet other embodiments, the final concentration of the polysorbate 80 in the formulation is 0.01% polysorbate 80 weight/volume of the formulation. In other embodiments, the final concentration of the polysorbate 80 in the formulation is 0.05% polysorbate 80 weight/volume of the formulation. In yet other embodiments, the final concentration of the polysorbate 80 in the formulation is 0.1% polysorbate 80 weight/volume of the formulation. In another embodiment, the final concentration of the polysorbate 80 in the formulation is 1.0% polysorbate 80 weight/volume of the formulation. In yet another embodiment, the final concentration of the polysorbate 80 in the formulation is 10.0% polysorbate 80 weight/volume of the formulation.

In certain other embodiments, the SCP composition further comprises one or more polypeptides selected from the group consisting of a streptococcal polypeptide, a pneumococcal polypeptide, a meningococcal polypeptide and a staphylococcal polypeptide. In still other embodiments, the SCP composition further comprises one or more polysaccharides selected from the group consisting of a streptococcal polysaccharide, a pneumococcal polysaccharide, a meningococcal polysaccharide and a staphylococcal polysaccharide.

In another embodiment, the formulation further comprises one or more adjuvants. Exemplary suitable adjuvants are described herein below.

In another embodiment, the invention is directed to formulations which inhibit silicone induced precipitation 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. In certain embodiments, the siliconized container means is selected from one or more of the group consisting of a vial, a vial stopper, a vial closure, a glass closure, a rubber closure, a plastic closure, a syringe, a syringe stopper, a syringe plunger, a flask, a beaker, a graduated cylinder, a fermentor, a bioreactor, tubing, a pipe, a bag, a jar, an ampoule, a cartridge and a disposable pen.

In certain embodiments, the pH buffered saline solution in the formulations has a pH of 5.5 to 7.5. In other embodiments, the buffer in the formulations is phosphate, succinate, histidine or citrate. In yet other embodiments, the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0. In one particular embodiment, the final concentration of the succinate buffer is 5 mM. In still other embodiments, the salt in the pH buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof. In one particular embodiment, the salt in the pH buffered saline solution is sodium chloride.

In other embodiments, the aluminum salt is aluminum hydroxide, aluminum phosphate or aluminum sulfate. In one specific embodiment, the aluminum salt is aluminum phosphate.

In certain other embodiments, the formulation further comprises polysorbate 80 (Tween™80). In one specific embodiment, the final concentration of the polysorbate 80 in formulation is at least 0.01% to 10% polysorbate 80 weight/volume of the formulation.

In another embodiment, the polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides. In certain embodiments, the one or more pneumococcal polysaccharides are a *S. pneumoniae* serotype 4 polysaccharide, a *S. pneumoniae* serotype 6B polysaccharide, a *S. pneumoniae* serotype 9V polysaccharide, a *S. pneumoniae* serotype 14 polysaccharide, a *S. pneumoniae* serotype 18C polysaccharide, a *S. pneumoniae* serotype 19F polysaccharide, a *S. pneumoniae* serotype 23F polysaccharide, a *S. pneumoniae* serotype 1 polysaccharide, a *S. pneumoniae* serotype 3 polysaccharide, a *S. pneumoniae* serotype 5 polysaccharide, a *S. pneumoniae* serotype 6A polysaccharide, a *S. pneumoniae* serotype 7F polysaccharide and a *S. pneumoniae* serotype 19A polysaccharide.

In certain other embodiments, the protein of the polysaccharide-protein conjugate formulation is selected from the group consisting of CRM_{197}, a tetanus toxoid, a cholera toxoid, a pertussis toxoid, an *E. coli* heat labile toxoid (LT), a pneumolysin toxoid, pneumococcal surface protein A (PspA), pneumococcal adhesin protein A (PsaA), a C5a peptidase from *Streptococcus, Haemophilus influenzae* protein D, ovalbumin, keyhole limpet haemocyanin (KLH), bovine serum albumin (BSA) and purified protein derivative of tuberculin (PPD).

In one particular embodiment, the polysaccharide-protein conjugate formulation is a 7-valent pneumococcal conjugate (7vPnC) formulation comprising a *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM_{197} polypeptide and a *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM_{197} polypeptide.

In another specific embodiment, the polysaccharide-protein conjugate formulation is a 13-valent pneumococcal conjugate (13vPnC) formulation comprising a *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 1 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 3 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 5 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 6A polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 7F polysaccharide

conjugated to a CRM_{197} polypeptide and a *S. pneumoniae* serotype 19A polysaccharide conjugated to a CRM_{197} polypeptide.

In yet other embodiments, the formulation further comprises one or more meningococcal polysaccharides, one or more meningococcal antigenic proteins, or a combination thereof.

In another embodiment, the formulation further comprises one or more streptococcal polysaccharides, one or more streptococcal antigenic proteins, or a combination thereof.

In certain other embodiments, the formulation further comprises one or more adjuvants. Exemplary suitable adjuvants are described herein below.

In other embodiments, the present invention is directed to formulations which inhibit silicone induced precipitation of a streptococcal C5a peptidase (SCP) composition 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 6.5, (ii) an aluminum salt and (iii) a streptococcal C5a peptidase. In certain embodiments, the container means is selected from one or more of the group consisting of a vial, a vial stopper, a vial closure, a glass closure, a rubber closure, a plastic closure, a syringe, a syringe stopper, a syringe plunger, a flask, a beaker, a graduated cylinder, a fermentor, a bioreactor, tubing, a pipe, a bag, a jar, an ampoule, a cartridge and a disposable pen.

In another embodiment, the pH buffered saline solution of the formulation has a pH of 5.5 to 7.5. In other embodiments, the buffer is succinate, histidine, phosphate or citrate. In certain embodiments, the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0. In another embodiment, the salt in the pH buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof.

In certain other embodiments, the formulation further comprises polysorbate 80 (Tween™80). In one specific embodiment, the final concentration of the polysorbate 80 in the formulation is 0.01% to 10% polysorbate 80 weight/volume of the formulation.

In yet other embodiments, the SCP composition further comprises one or more polypeptides selected from the group consisting of a streptococcal polypeptide, a pneumococcal polypeptide, a meningococcal polypeptide and a staphylococcal polypeptide.

In certain other embodiments, the SCP composition further comprises one or more polysaccharides selected from the group consisting of a streptococcal polysaccharide, a pneumococcal polysaccharide, a meningococcal polysaccharide and a staphylococcal polysaccharide.

In yet another embodiment, the formulation further comprises one or more adjuvants. Exemplary suitable adjuvants are described herein below.

In other embodiments, the invention is directed to formulations which stabilize a *N. meningitidis* 2086 protein composition, the formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 6.5, (ii) a surfactant and (iii) a *N. meningitidis* 2086 protein. Exemplary *N. meningitidis* 2086 proteins are described herein below. In one specific embodiment, the *N. meningitidis* 2086 protein formulation is comprised in a container means. In certain embodiments, the container means is selected from one or more of the group consisting of a vial, a vial stopper, a vial closure, a glass closure, a rubber closure, a plastic closure, a syringe, a syringe stopper, a syringe plunger, a flask, a beaker, a graduated cylinder, a fermentor, a bioreactor, tubing, a pipe, a bag, a jar, an ampoule, a cartridge and a disposable pen.

In other embodiments, the pH buffered saline solution of the formulation has a pH of 5.5 to 7.5. In other embodiments, the buffer is succinate, histidine, phosphate or citrate. In one specific embodiment, the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0. In another specific embodiment, the final concentration of the succinate buffer is 5 mM. In yet other embodiments, the salt in the pH buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof.

In certain embodiments, the surfactant in the formulations is selected from the group consisting of polysorbate 20 (Tween™20), polysorbate 40 (Tween™40), polysorbate 60 (Tween™60), polysorbate 65 (Tween™65), polysorbate 80 (Tween™80), polysorbate 85 (Tween™85), Triton™ N-101, Triton™ X-100, oxtoxynol 40, nonoxynol-9, triethanolamine, triethanolamine polypeptide oleate, polyoxyethylene-660 hydroxystearate (PEG-15, Solutol H15), polyoxyethylene-35-ricinoleate (Cremophor EL™), soy lecithin and a poloxamer. In one specific embodiment, the surfactant is polysorbate 80. In certain embodiments, the final concentration of the polysorbate 80 in the formulation is 0.01% to 10% polysorbate 80 weight/volume of the formulation. In yet other embodiments, the final concentration of the polysorbate 80 in the formulation is 0.01% polysorbate 80 weight/volume of the formulation. In other embodiments, the final concentration of the polysorbate 80 in the formulation is 0.05% polysorbate 80 weight/volume of the formulation. In yet other embodiments, the final concentration of the polysorbate 80 in the formulation is 0.1% polysorbate 80 weight/volume of the formulation. In another embodiment, the final concentration of the polysorbate 80 in the formulation is 1.0% polysorbate 80 weight/volume of the formulation. In yet another embodiment, the final concentration of the polysorbate 80 in the formulation is 10.0% polysorbate 80 weight/volume of the formulation.

In certain other embodiments, the *N. meningitidis* 2086 protein composition further comprises one or more polypeptides selected from the group consisting of a streptococcal polypeptide, a pneumococcal polypeptide, a meningococcal polypeptide and a staphylococcal polypeptide. In still other embodiments, the *N. meningitidis* 2086 protein composition further comprises one or more polysaccharides selected from the group consisting of a streptococcal polysaccharide, a pneumococcal polysaccharide, a meningococcal polysaccharide and a staphylococcal polysaccharide.

In another embodiment, the formulation further comprises one or more adjuvants. Exemplary suitable adjuvants are described herein below.

In other embodiments, the present invention is directed to formulations which inhibit silicone induced precipitation of a *N. meningitidis* 2086 protein composition 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 6.5, (ii) an aluminum salt and (iii) a *N. meningitidis* 2086 protein. In certain embodiments, the container means is selected from one or more of the group consisting of a vial, a vial stopper, a vial closure, a glass closure, a rubber closure, a plastic closure, a syringe, a syringe stopper, a syringe plunger, a flask, a beaker, a graduated cylinder, a fermentor, a bioreactor, tubing, a pipe, a bag, a jar, an ampoule, a cartridge and a disposable pen.

In another embodiment, the pH buffered saline solution of the formulation has a pH of 5.5 to 7.5. In other embodiments, the buffer is succinate, histidine, phosphate or citrate. In certain embodiments, the buffer is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0. In another

embodiment, the salt in the pH buffered saline solution comprises magnesium chloride, potassium chloride, sodium chloride or a combination thereof.

In certain other embodiments, the formulation further comprises polysorbate 80 (Tween™80). In one specific embodiment, the final concentration of the polysorbate 80 in the formulation is 0.01% to 10% polysorbate 80 weight/volume of the formulation.

In yet other embodiments, the *N. meningitidis* 2086 protein composition further comprises one or more polypeptides selected from the group consisting of a streptococcal polypeptide, a pneumococcal polypeptide, a meningococcal polypeptide and a staphylococcal polypeptide.

In certain other embodiments, the *N. meningitidis* 2086 protein composition further comprises one or more polysaccharides selected from the group consisting of a streptococcal polysaccharide, a pneumococcal polysaccharide, a meningococcal polysaccharide and a staphylococcal polysaccharide.

In yet another embodiment, the formulation further comprises one or more adjuvants. Exemplary suitable adjuvants are described herein below.

Other features and advantages of the invention will be apparent from the following detailed description, from the embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** shows the stability of Streptococcal C5a peptidase (SCP) formulations (filled in syringes) before and after two days of gentle agitation (60 cpm) on a horizontal orbital shaker. The data presented in FIG. **1**A is the two day stability of the SCP formulated without any Tween™80 (i.e., 0%), whereas the data in FIG. **1**B is the two day stability of the SCP formulated with 0.025% Tween™80. The buffers used in the formulations shown in FIGS. **1**A and **1**B are succinate buffered saline (SBS), phosphate buffered saline (PBS) and tris (hydroxymethyl)aminomethane (TRIS).

FIG. **2** shows the total antigenicity loss of the 13vPnC formulated with $AlPO_4$ (0.25 mg/ml) and filled in a BD Hypak syringe, after two hours, eight hours and twenty-four hours of agitation at 500 rpm and 2-8° C.

FIG. **3** shows the total antigenicity loss of the 13vPnC formulated with $AlPO_4$ (0.25 mg/ml) and filled in an unsiliconized syringe, after two hours, eight hours and twenty-four hours of agitation at 500 rpm and 2-8° C.

FIG. **4** shows the total antigenicity loss of the 13vPnC formulated with $AlPO_4$ (0.25 mg/ml) and filled in a Vetter syringe, after two hours, eight hours and twenty-four hours of agitation at 500 rpm and 2-8° C.

FIG. **5** shows the total antigenicity loss of the 13vPnC formulated with $AlPO_4$ (0.25 mg/ml) and filled in a Schott TopPac syringe, after two hours, eight hours and twenty-four hours of agitation at 500 rpm and 2-8° C.

FIG. **6** shows the total antigenicity loss of the 13vPnC formulated with (FIG. **6**A) and without (FIG. **6**B) $AlPO_4$ (0.25 mg/ml) and filled in a BD Baked syringe, after two hours, eight hours and twenty-four hours of agitation at 500 rpm and 2-8° C.

FIG. **7** shows the total antigenicity loss of the 13vPnC formulated with (FIG. **7**A) and without (FIG. **7**B) $AlPO_4$ (0.25 mg/ml) and filled in a BünderGlas PS2 syringe, after two hours, eight hours and twenty-four hours of agitation at 500 rpm and 2-8° C.

DETAILED DESCRIPTION OF THE INVENTION

The present invention addresses an ongoing need in the art to improve the stability of immunogenic compositions such as polysaccharide-protein conjugates and protein immunogens. Thus, the present invention broadly relates to novel surfactant formulations and/or novel aluminum salt formulations which stabilize and inhibit precipitation of immunogenic compositions. More particularly, the invention described hereinafter, addresses a need in the art for formulations which stabilize and inhibit particulate formation (e.g., aggregation, precipitation) of immunogenic compositions which are processed, developed, formulated, manufactured and/or stored in container means such as fermentors, bioreactors, vials, flasks, bags, syringes, rubber stoppers, tubing and the like.

As set forth above in the Background of the Invention, various factors influence the stability of immunogenic compositions, including, but not limited to, chemical stability of the immunogenic composition, physical/thermal stability of the immunogenic composition, compatibility of the immunogenic composition with the container/closure system, interactions between immunogenic composition and inactive ingredients (e.g., buffers, salts, excipients, cryoprotectants), manufacturing processes, dosage form, environmental conditions encountered during shipping, storage and handling (e.g., temperature, humidity, shear forces), and the length of time between manufacture and usage.

The stability of an immunogenic composition of the invention is readily determined using standard techniques, which are well known and routine to those of skill in the art. For example, an immunogenic composition is assayed for stability, aggregation, immunogenicity, particulate formation, protein (concentration) loss, and the like, by methods including, but not limited to, light scattering, optical density, sedimentation velocity centrifugation, sedimentation equilibrium centrifugation, circular dichroism (CD), Lowry assay, bicinchoninic acid (BCA) assay, antibody binding, and the like.

As set forth in detail herein, the present invention relates to the unexpected and surprising results that formulating an immunogenic composition with a surfactant such as Tween™80 significantly enhances the stability and inhibits precipitation of an immunogenic composition. For example, it was observed in the present invention (e.g., see Example 2), that a thirteen-valent pneumococcal conjugate (13vPnC), formulated in buffered saline and filled in a single does syringe, would begin precipitating out of solution within ten minutes at 2-8° C. upon gentle agitation via a horizontal orbital shaker. (The horizontal orbital shaker was used to simulate typical process, shipping and storage conditions of a 13vPnC immunogenic composition). However, it was surprisingly observed that the 13vPnC, formulated in buffered saline and 0.001% Tween™80, filled in a single dose syringe and gently agitated at 2-8° C., was stable for twenty-five days with no visible signs of precipitation (data not shown). Thus, this data demonstrated that the addition of a surfactant (e.g., Tween™80) to an immunogenic composition formulation enhances the stability of the immunogenic composition.

A second stability study of the 13vPnC further confirmed that the addition of a surfactant to the formulation significantly enhanced the stability of the 13vPnC. For example, the stability (i.e., assayed by measuring change in 13vPnC antigenicity) of a 13vPnC formulation with 0.05% Tween™80 (Table 1) and without Tween™80 (0.0%, Table 1) was assessed over a two hour time period. As is shown in Table 1, there was a significant decrease in antigenicity of the thirteen serotype polysaccharides (formulated without Tween™80) within the two hour assay. Quite dramatically however, the 13vPnC formulation comprising 0.05% Tween™80 (Table 1), demonstrated robust stability throughout the two hour antigenicity assay. It was also observed that the 13vPnC for-

mulated in 250 mL glass bottles with either 0.01% Tween™80 or 0.05% Tween™80 could withstand significant shear forces induced via vortexing the formulations for thirty minutes at 2-8° C., with little or no loss in antigenicity (e.g., see Example 2, Table 2).

In other experiments (Example 3), it was demonstrated that the stability of an immunogenic streptococcal C5a peptidase (SCP) composition was greatly enhanced when formulated with a surfactant such as Tween™80. For example, as shown in FIG. **1**A, after two days of vortexing an SCP (55 μg/mL) formulated in either a 5 mM succinate buffer (pH 6.0), a 10 mM phosphate buffer (pH 7.0 and 7.4) or a 10 mM Tris buffer (pH 7.5), there was a significant decrease (e.g., greater than 90%) in the SCP concentration. However, as shown in FIG. **1** B, the addition of 0.025% Tween™80 to the SCP succinate, SCP phosphate and SCP Tris formulations, prior to vortexing for two days, completely inhibited the SCP loss which was observed in FIG. **1**A.

A 13vPnC immunogenic composition of the invention may also be formulated with or without an adjuvant, such as aluminum phosphate ($AlPO_4$). Thus, in a separate series of experiments (Example 4), 13vPnC immunogenic compositions were formulated in 5 mM succinate buffer (pH 5.8), 0.85% NaCl and $AlPO_4$ (0.25 mg aluminum/ml), without the addition of a surfactant (e.g., no Tween™80 was included in the formulation).

In these experiments, the 13vPnC immunogenic composition (formulated in the presence of $AlPO_4$) were filled in various siliconized and non-siliconized container means (e.g., see Table 3) and subjected to simulated shipping and handling conditions via agitation at 2-8° C. It was observed in these experiments (Example 4), that the container means with higher silicone content exhibited a higher degree of 13vPnC particulate formation and a higher percent of 13vPnC antigenicity loss. An FTIR analysis of the particulates indicated that the particulates consisted of protein and silicone (data not shown) and that about 85% of the 13vPnC is bound to the $AlPO_4$, wherein the remaining 15% was free (not bound to $AlPO_4$) 13vPnC in solution.

In another experiment comparing 13vPnC immunogenic compositions formulated with and without $AlPO_4$, which were then filled in identical syringes, it was observed that the 13vPnC formulated without $AlPO_4$ sustained greater antigenicity losses than 13vPnC with $AlPO_4$ in the syringes tested (e.g., see FIG. **6** and FIG. **7**).

Thus, the invention as set forth herein, is directed to novel formulations which stabilize and inhibit aggregation or precipitation of immunogenic compositions such as polysaccharide-protein conjugates (e.g., a 13vPnC) and protein immunogens (e.g., a streptococcal C5a peptidase, a *N. meningitidis* ORF 2086 protein), against the various factors which influence the stability of immunogenic compositions (e.g., shear forces, shipping agitation, silicone oil interactions, adsorption, manufacturing processes, temperature, humidity, length of time between manufacture and usage, etc.).

In certain embodiments, the invention is directed to a formulation which stabilizes a polysaccharide-protein conjugate, the formulation comprising a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, a surfactant and one or more polysaccharide-protein conjugates. In other embodiments, the polysaccharide-protein conjugate formulation is comprised in a container means. In another embodiment, the invention is directed to a formulation which stabilizes a streptococcal C5a peptidase (SCP) composition, the formulation comprising a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 6.5, a surfactant and a streptococcal C5a peptidase. In certain embodiments, the SCP formulation is comprised in a container means. In another embodiment, the invention is directed to a formulation which stabilizes a *N. meningitidis* 2086 protein composition, the formulation comprising a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, a surfactant and a *N. meningitidis* 2086 protein. In certain embodiments, the meningococcal 2086 formulation is comprised in a container means.

In certain other embodiments, the invention is directed to a formulation which inhibits silicone induced precipitation of a polysaccharide-protein conjugate comprised in a siliconized container means, the formulation comprising a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, an aluminum salt and one or more polysaccharide-protein conjugates. In another embodiment, the invention is directed to a formulation which inhibits silicone induced precipitation of a streptococcal C5a peptidase (SCP) composition comprised in a siliconized container means, the formulation comprising a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 6.5, an aluminum salt and a streptococcal C5a peptidase. In certain other embodiments, the invention is directed to a formulation which inhibits silicone induced precipitation of a *N. meningitidis* 2086 protein composition comprised in a siliconized container means, the formulation comprising a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, an aluminum salt and a *N. meningitidis* 2086 protein.

In yet other embodiments, the invention is directed to a formulation that optimizes antigen stability and binding percentage to an aluminum salt adjuvant (e.g., $AlPO_4$) of a *N. meningitidis* 2086 protein, the formulation comprising a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, a surfactant, an aluminum salt, and a *N. meningitidis* 2086 protein. In certain embodiments, the formulation is in a container means.

As defined hereinafter, the terms "precipitation", "precipitate" "particulate formation", "clouding" and "aggregation" may be used interchangeably and are meant to refer to any physical interaction or chemical reaction which results in the "aggregation" of a polysaccharide-protein conjugate or a protein (or polypeptide) immunogen. The process of aggregation (e.g., protein aggregation) is well known (but not well understood) and described in the art, and is often influenced by numerous physicochemical stresses, including heat, pressure, pH, agitation, shear forces, freeze-thawing, dehydration, heavy metals, phenolic compounds, silicon oil, denaturants and the like.

As defined hereinafter, a "polysaccharide-protein conjugate", a "pneumococcal conjugate", a "7-valent pneumococcal conjugate (7vPnC)", a "13-valent pneumococcal conjugate (13vPnC)", a "streptococcal C5a peptidase (SCP) immunogenic composition" and a "*N. meningitidis* 2086 protein immunogenic composition" of the invention includes liquid formulations, frozen liquid formulations and solid (e.g., freeze-dried or lyophilized) formulations.

A. Surfactants

As set forth above, the invention is directed to formulations which stabilize and inhibit aggregation of immunogenic compositions against the various factors which influence the stability of immunogenic compositions (e.g., shear forces, shipping agitation, silicone oil interactions, adsorption, manufacturing processes, temperature, humidity, length of time between manufacture and usage, etc.). In certain embodiments, the invention is directed to formulations comprising a surfactant.

A surfactant (or a surface-active agent) is generally defined as (a) a molecule or compound comprising a hydrophilic group or moiety and a lipophilic (hydrophobic) group or moiety and/or (b) a molecule, substance or compound that lowers or reduces surface tension of a solution. As defined herein, a "surfactant" of the present invention is any molecule or compound that lowers the surface tension of an immunogenic composition formulation.

A surfactant used in a formulation of the present invention comprises any surfactant or any combination of surfactants which stabilizes and inhibits aggregation of an immunogenic composition described herein. Thus, a surfactant of the invention includes, but is not limited to, polysorbate 20 (Tween™20), polysorbate 40 (Tween™40), polysorbate 60 (Tween™60), polysorbate 65 (Tween™65), polysorbate 80 (Tween™80), polysorbate 85 (Tween™85), Triton™ N-101, Triton™ X-100, oxtoxynol 40, nonoxynol-9, triethanolamine, triethanolamine polypeptide oleate, polyoxyethylene-660 hydroxystearate (PEG-15, Solutol H15), polyoxyethylene-35-ricinoleate (Cremophor EL™), soy lecithin, poloxamer, hexadecylamine, octadecylamine, octadecyl amino acid esters, lysolecithin, dimethyl-dioctadecylammonium bromide, methoxyhexadecylglycerol, pluronic polyols, polyamines (e.g., pyran, dextransulfate, poly IC, carbopol), peptides (e.g., muramyl peptide and dipeptide, dimethylglycine, tuftsin), oil emulsions, mineral gels (e.g., aluminum phosphate) and immune stimulating complexes (ISCOMS).

A person of skill in the art may readily determine a suitable surfactant or surfactant combination by measuring the surface tension of a particular immunogenic composition formulation in the presence and absence of the surfactant(s). Alternatively, a surfactant is evaluated qualitatively (e.g., visual inspection of particulate formation) or quantitatively (e.g., light scattering, sedimentation velocity centrifugation, optical density, antigenicity) for its ability to reduce, inhibit or prevent aggregation of an immunogenic composition.

B. Container Means

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

The skilled artisan will appreciate that the container means set forth above are by no means an exhaustive list, but merely serve as guidance to the artisan with respect to the variety of container means which are used to contain, hold, mix, blend, dispense, inject, transfer, nebulize, etc. an immunogen or immunogenic composition during research, processing, development, formulation, manufacture, storage and/or administration of the composition. Additional container means contemplated for use in the present invention may be found in published catalogues from laboratory equipment vendors and manufacturers such as United States Plastic Corp. (Lima, Ohio), VWR™ (West Chester, Pa.), BD Biosciences (Franklin Lakes, N.J.), Fisher Scientific International Inc. (Hampton, N.H.) and Sigma-Aldrich (St. Louis, Mo.).

Thus, the novel formulations of the present invention are particularly advantageous in that they stabilize and inhibit precipitation of immunogenic formulations comprised in a container means throughout the various stages of research, processing, development, formulation, manufacture, storage and/or administration of the composition. The novel formulations of the invention not only stabilize immunogenic compositions against physical/thermal stresses (e.g., temperature, humidity, shear forces, etc.), they also enhance stability and inhibit precipitation of immunogenic compositions against negative factors or influences such as incompatibility of the immunogenic composition with the container/closure system (e.g., a siliconized container means).

Thus, the novel formulations of the present invention are particularly useful in stabilizing the immunogen (i.e., a polysaccharide-protein conjugate, a protein or polypeptide antigen) against the silicon oil induced precipitation and precipitation described above. For example, co-pending U.S. Application No. 60/795,098, filed Apr. 26, 2006, specifically incorporated herein by reference, describes the aggregation of immunogenic compositions in the presence silicon oil found on container means such syringes, glass vials, rubbers stoppers and the like, wherein the addition of a surfactant to the container means prevented the silicon oil induced aggregation of these immunogenic compositions.

C. Adjuvants and Pharmaceutical Carriers/Excipients

In certain embodiments, the immunogenic compositions of the invention are further formulated with an adjuvant. An adjuvant is a substance that enhances the immune response when administered together with an immunogen or antigen. A number of cytokines or lymphokines have been shown to have immune modulating activity, and thus may be used as adjuvants, including, but not limited to, the interleukins 1-α, 1-β, 2, 4, 5, 6, 7, 8, 10, 12 (see, e.g., U.S. Pat. No. 5,723,127), 13, 14, 15, 16, 17 and 18 (and its mutant forms), the interferons-α, β and γ, granulocyte-macrophage colony stimulating factor (GMCSF, see, e.g., U.S. Pat. No. 5,078,996 and ATCC Accession Number 39900), macrophage colony stimulating factor (MCSF), granulocyte colony stimulating factor (GCSF), and the tumor necrosis factors α and β (TNF). Still other adjuvants useful in this invention include chemokines, including without limitation, MCP-1, MIP-1α, MIP-1β, and RANTES.

In certain embodiments, an adjuvant used to enhance an immune response of an immunogenic composition formulation includes, without limitation, MPL™ (3-O-deacylated monophosphoryl lipid A; Corixa, Hamilton, Mont.), which is described in U.S. Pat. No. 4,912,094, which is hereby incorporated by reference. Also suitable for use as adjuvants are synthetic lipid A analogs or aminoalkyl glucosamine phosphate compounds (AGP), or derivatives or analogs thereof, which are available from Corixa (Hamilton, Mont.), and which are described in U.S. Pat. No. 6,113,918, which is hereby incorporated by reference. One such AGP is 2-[(R)-3-Tetradecanoyloxytetradecanoylamino]ethyl 2-Deoxy-4-O-phosphono-3-O—[(R)-3-tetradecanoyoxytetradecanoyl]-2-[(R)-3-tetradecanoyloxytetradecanoyl-amino]-b-D-glucopyranoside, which is also known as 529 (formerly known as RC529). This 529 adjuvant is formulated as an aqueous form or as a stable emulsion (RC529-SE).

Still other adjuvants include mineral oil and water emulsions, aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate etc., Amphigen, Avridine, L121/squalene, D-lactide-polylactide/glycoside, pluronic polyols, muramyl dipeptide, killed *Bordetella*, saponins, such as Stimulon™ QS-21 (Antigenics, Framingham, Mass.), described in U.S. Pat. No. 5,057,540, which is hereby incorporated by reference, and particles generated therefrom such as ISCOMS (immunostimulating complexes), ISCOMATRIX (CSL Limited, Parkville, Australia), described in U.S. Pat. No. 5,254,339, Mycobacterium tuberculosis, bacterial lipopolysaccharides, synthetic polynucleotides such as oligonucleotides containing a CpG motif (U.S. Pat. No. 6,207,646, which is hereby incorporated by reference), IC-31 (Intercell AG, Vienna, Austria), described in European Patent Nos. 1,296,713 and 1,326,634, a pertussis toxin (PT), or an *E. coli* heat-labile toxin (LT), particularly LT-K63, LT-R72, PT-K9/G129; see, e.g., International Patent Publication Nos. WO 93/13302 and WO 92/19265, incorporated herein by reference.

Also useful as adjuvants (and carrier proteins) are cholera toxins and mutants thereof, including those described in published International Patent Application number WO 00/18434 (wherein the glutamic acid at amino acid position 29 is replaced by another amino acid (other than aspartic acid), preferably a histidine). Similar CT toxins or mutants are described in published International Patent Application number WO 02/098368 (wherein the isoleucine at amino acid position 16 is replaced by another amino acid, either alone or in combination with the replacement of the serine at amino acid position 68 by another amino acid; and/or wherein the valine at amino acid position 72 is replaced by another amino acid). Other CT toxins are described in published International Patent Application number WO 02/098369 (wherein the arginine at amino acid position 25 is replaced by another amino acid; and/or an amino acid is inserted at amino acid position 49; and/or two amino acids are inserted at amino acid positions 35 and 36).

In certain embodiments, the immunogenic composition formulations comprise a pharmaceutically acceptable diluent, excipient or a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutically acceptable diluent is sterile water, water for injection, sterile isotonic saline or a biological buffer. The polysaccharide-protein conjugates and/or protein immunogens are mixed with such diluents or carriers in a conventional manner. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with administration to humans or other vertebrate hosts. The appropriate carrier is evident to those skilled in the art and will depend in large part upon the route of administration.

For example, excipients that may be present in the immunogenic composition formulation are preservatives, chemical stabilizers and suspending or dispersing agents. Typically, stabilizers, preservatives and the like are optimized to determine the best formulation for efficacy in the targeted recipient (e.g., a human subject). Examples of preservatives include chlorobutanol, potassium sorbate, sorbic acid, sulfur dioxide, propyl gallate, the parabens, ethyl vanillin, glycerin, phenol, and parachlorophenol. Examples of stabilizing ingredients include casamino acids, sucrose, gelatin, phenol red, N—Z amine, monopotassium diphosphate, lactose, lactalbumin hydrolysate, and dried milk.

In certain embodiments, an immunogenic composition formulation is prepared for administration to human subjects in the form of, for example, liquids, powders, aerosols, tablets, capsules, enteric-coated tablets or capsules, or suppositories. Thus, the immunogenic composition formulations may also include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations.

The immunogenic compositions of the present invention, are not limited by the selection of the conventional, physiologically acceptable carriers, diluents and excipients such as solvents, buffers, adjuvants, or other ingredients useful in pharmaceutical preparations of the types described above. The 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.

D. Immunogens

In certain embodiments, a polysaccharide-protein conjugate formulation of the invention comprises one or more pneumococcal polysaccharides. In other embodiments, a polysaccharide-protein conjugate formulation of the invention comprises one or more streptococcal polysaccharides. In yet other embodiments, a polysaccharide-protein conjugate formulation of the invention comprises one or more meningococcal polysaccharides. In still other embodiments, a polysaccharide-protein conjugate formulation of the invention comprises a combination of one or more pneumococcal polysaccharides, one or more pneumococcal polypeptides, one or more streptococcal polysaccharides, one or more streptococcal polypeptides, one or more meningococcal polysaccharides, and/or one or more meningococcal polypeptides.

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

In one particular embodiment of the invention, the one or more pneumococcal polysaccharides are a *S. pneumoniae* serotype 4 polysaccharide, a *S. pneumoniae* serotype 6B polysaccharide, a *S. pneumoniae* serotype 9V polysaccharide, a *S. pneumoniae* serotype 14 polysaccharide, a *S. pneumoniae* serotype 18C polysaccharide, a *S. pneumoniae* serotype 19F polysaccharide, a *S. pneumoniae* serotype 23F polysaccharide, a *S. pneumoniae* serotype 1 polysaccharide, a *S. pneumoniae* serotype 3 polysaccharide, a *S. pneumoniae* serotype 5 polysaccharide, a *S. pneumoniae* serotype 6A polysaccharide, a *S. pneumoniae* serotype 7F polysaccharide and a *S. pneumoniae* serotype 19A polysaccharide.

In certain embodiments, a polysaccharide-protein conjugate formulation is a 7-valent pneumococcal conjugate (7vPnC) formulation comprising a *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM_{197} polypeptide and a *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM_{197} polypeptide.

In certain other embodiments, a polysaccharide-protein conjugate formulation is a 13-valent pneumococcal conjugate (13vPnC) formulation comprising a *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM_{197} polypeptide, a

S. pneumoniae serotype 6B polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 1 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 3 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 5 polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 6A polysaccharide conjugated to a CRM_{197} polypeptide, a *S. pneumoniae* serotype 7F polysaccharide conjugated to a CRM_{197} polypeptide and a *S. pneumoniae* serotype 19A polysaccharide conjugated to a CRM_{197} polypeptide.

Polysaccharides are prepared by standard techniques known to those skilled in the art. For example, the capsular polysaccharides set forth in the present invention are prepared from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F of *Streptococcus pneumoniae*, wherein each serotype is grown in a soy-based medium and the individual polysaccharides are then purified through centrifugation, precipitation, ultra-filtration, and column chromatography. Similarly, streptococcal polysaccharides (e.g., one or more polysaccharides (or oligosaccharides) from a (3-hemolytic *Streptococcus* such group A *Streptococcus*, group B *Streptococcus*, group C *Streptococcus* and group G *Streptococcus*) and meningococcal saccharides (e.g., an *N. meningitidis* lipo-oligosaccharide (LOS) or lipo-polysaccharide (LPS)) are prepared from clinically relevant serotypes or serogroups, using general techniques and methods known to one of skill in the art. The purified polysaccharides are then chemically activated (e.g., via reductive amination) to make the saccharides capable of reacting with the carrier protein. Once activated, each capsular polysaccharide is separately conjugated to a carrier protein (e.g., CRM_{197}) to form a glycoconjugate (or alternatively, each capsular polysaccharide is conjugated to the same carrier protein) and formulated into a single dosage formulation.

The chemical activation of the polysaccharides and subsequent conjugation to the carrier protein (i.e., a polysaccharide-protein conjugate) are achieved by conventional means. See, for example, U.S. Pat. Nos. 4,673,574 and 4,902,506.

Carrier proteins are preferably proteins that are non-toxic and non-reactogenic and obtainable in sufficient amount and purity. Carrier proteins should be amenable to standard conjugation procedures. In a particular embodiment of the present invention, CRM_{197} is used as the carrier protein.

CRM_{197} (Wyeth, Sanford, N.C.) is a non-toxic variant (i.e., toxoid) of diphtheria toxin isolated from cultures of Corynebacterium diphtheria strain C7 (β197) grown in casamino acids and yeast extract-based medium. CRM_{197} is purified through ultra-filtration, ammonium sulfate precipitation, and ion-exchange chromatography. Alternatively, CRM_{197} is prepared recombinantly in accordance with U.S. Pat. No. 5,614,382, which is hereby incorporated by reference. Other diphtheria toxoids are also suitable for use as carrier proteins.

In other embodiments, a carrier protein of the invention is an enzymatically inactive streptococcal C5a peptidase (SCP) (e.g., one or more of the SCP variants described in U.S. Pat. Nos. 6,951,653, 6,355,255 and 6,270,775).

Other suitable carrier proteins include inactivated bacterial toxins such as tetanus toxoid, pertussis toxoid, cholera toxoid (e.g., CT E29H, described in International Patent Application WO2004/083251), *E. coli* LT, *E. coli* ST, and exotoxin A from *Pseudomonas aeruginosa*. Bacterial outer membrane proteins such as outer membrane complex c (OMPC), porins, transferrin binding proteins, pneumolysin, pneumococcal surface protein A (PspA), pneumococcal adhesin protein (PsaA), or *Haemophilus influenzae* protein D, can also be used. Other proteins, such as ovalbumin, keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or purified protein derivative of tuberculin (PPD) can also be used as carrier proteins.

After conjugation of the capsular polysaccharide to the carrier protein, the polysaccharide-protein conjugates are purified (enriched with respect to the amount of polysaccharide-protein conjugate) by a variety of techniques. These techniques include concentration/diafiltration operations, precipitation/elution, column chromatography, and depth filtration.

After the individual glycoconjugates are purified, they are compounded to formulate the immunogenic composition of the present invention. Formulation of the polysaccharide-protein conjugates of the present invention can be accomplished using art-recognized methods. For instance, the 13 individual pneumococcal conjugates can be formulated with a physiologically acceptable vehicle to prepare the composition. Examples of such vehicles include, but are not limited to, water, buffered saline, polyols (e.g., glycerol, propylene glycol, liquid polyethylene glycol) and dextrose solutions.

In other embodiments, the invention is directed to formulations which stabilize a streptococcal C5a peptidase (SCP) immunogenic composition, wherein the formulations comprise a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 6.5, a surfactant and a streptococcal C5a peptidase. The C5a peptidase is a highly conserved serine protease and is expressed across all β-hemolytic Streptococci (e.g., streptococcal Groups A, B, C and G). For example, the nucleotide sequence encoding a Group B streptococci (GBS) C5a peptidase is 98% identical to the nucleotide sequence encoding a Group A streptococci (GAS) C5a peptidase. Thus, in certain embodiments of the invention, an immunogenic composition against infection caused by β-hemolytic Streptococci comprises a C5a peptidase immunogen (or antigen).

In one particular embodiment, a C5a peptidase of the invention is an enzymatically inactive streptococcal C5a peptidase (e.g., one or more of the SCP variants described in U.S. Pat. Nos. 6,951,653, 6,355,255 and 6,270,775, each specifically incorporated herein by reference). In another specific embodiment, the SCP used in the novel immunogenic composition formulations of the invention is cloned from a Group B streptococci. In another embodiment, the Group B streptococci SCP sequence has been genetically mutated to render it proteolytically inactive (e.g., see U.S. Pat. Nos. 6,951,653; 6,355,255 and 6,270,775) and is expressed as a recombinant protein in *E. coli*.

In another embodiment, the invention is directed to formulations which stabilize a *N. meningitidis* 2086 protein immunogenic composition, wherein the formulations comprise a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, a surfactant and a *N. meningitidis* 2086 protein. The *N. meningitidis* 2086 proteins are encoded by a nucleic acid sequence open reading frame (ORF) identified as "ORF 2086" (e.g., see International Publication No. WO 03/063766 A2 (International Application No. PCT/US02/32369), International Publication No. WO 04/094596 A2 (International Application No. PCT/US04/011901), and International Publication No. WO 04/065603 A2 (International Application No. PCT/US04/000800), each specifically incor-

porated herein by reference). In a further embodiment, the invention is directed to formulations that optimize antigen stability and binding percentage to an aluminum salt adjuvant (e.g., $AlPO_4$) of a *N. meningitidis* 2086 protein, wherein the formulations comprise a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, a surfactant, an aluminum salt, and a *N. meningitidis* 2086 protein.

All patents and publications cited herein are hereby incorporated by reference.

E. Examples

The following examples are carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. The following examples are presented for illustrative purpose, and should not be construed in any way as limiting the scope of this invention.

Example 1

Immunogenic Formulations Comprising 0.001%-0.05% Tween™80 Stabilize and Prevent Aggregation of the Immunogen

The polysaccharide-protein conjugate used in this example was a thirteen-valent pneumococcal polysaccharide conjugate (13vPnC) comprising capsular polysaccharides from *S. pneumoniae* serotypes 4, 6B, 9V, 18C, 19F, 14, 23F, 1, 3, 5, 6A, 7F and 19A, each of which were conjugated to CRM_{197}. The capsular polysaccharides were prepared by standard techniques known to those skilled in the art. Briefly, each pneumococcal polysaccharide serotype was grown in a soy-based medium, the individual polysaccharides were then purified through centrifugation, precipitation, ultra-filtration, and column chromatography. The purified polysaccharides were chemically activated for conjugation and each polysaccharide was separately conjugated to a CRM_{197} carrier protein to form a glycoconjugate and formulated into a single dosage formulation.

The chemical activation of the polysaccharides and subsequent conjugation to the carrier protein were achieved by conventional means (e.g., see U.S. Pat. Nos. 4,673,574 and 4,902,506). CRM_{197} (Wyeth, Sanford, N.C.) is a non-toxic variant (i.e., toxoid) of diphtheria toxin isolated from cultures of *Corynebacterium diphtheria* strain C7 (β197) grown in casamino acids and yeast extract-based medium. CRM_{197} is purified through ultra-filtration, ammonium sulfate precipitation, and ion-exchange chromatography.

The antigenicity experiments described below were performed by mixing the 13vPnC samples with one of thirteen antisera (Ab) specific to the each of the polysaccharide serotypes and detecting the immune complexes via light scattering measurements on an Array® 360 system (Beckman Coulter, Inc.; Fullerton, Calif.). The detected light scattering measurements for each of the thirteen serotypes were then compared to a standard curve and reported as antigenicity (μg/mL).

Syringes (BD Hypak SCF™) and syringe stoppers (BD Hypak SCF™) were purchased from BD Biosciences (Franklin Lakes, N.J.). Clear borosilicate vials (VWR Trace-Clean™, 40 mL) with Teflon®-lined closures were purchased from VWR™ (West Chester, Pa.). Polysorbate 80 (Tween™80) was purchased from J.T. Baker (Mallinckrodt Baker, Inc.; Phillipsburg, N.J.). Buffered saline was succinate (5 mM) and NaCl (0.85%) at pH 5.8.

The 13vPnC was formulated (500 mL total volume) at different surfactant concentrations (Tween™80; 0.001%, 0.005%, 0.01% and 0.05%, weight/volume) as follows: 0.85% saline (150 mM NaCl) was added to a one liter Pyrex® glass beaker, followed by 50 mM succinate buffer (final concentration 5 mM) and the 13vPnC. The final concentration of each serotype conjugate was 4.4 μg/mL (except for serotype 6B, which was 8.8 μg/mL). The 13vPnC formulation was then divided into five separate glass vials (50 mL per vial), wherein either 0.0%, 0.001%, 0.005%, 0.01% or 0.05% Tween™80 (w/v) was added to one of the five vials and each solution filtered through a 0.22 μm Durapore® filter (Millipore; Billerica, Mass.). Subsequently, 0.65 mL of each solution was filled in a separate 3 mL BD HYPAK™ SCF™ glass syringe with w4432 grey stoppers (BD Medical Pharmaceutical Systems; Franklin Lakes, N.J.), and the syringes placed on a horizontal orbital shaker (60 cpm) for 100 hours at 2° C. to 8° C.

It was observed by visual inspection (data not shown), that the 13vPnC formulated in the absence of Tween™80 (i.e., 0.0%), would begin precipitating out of solution within ten minutes at 2-8° C. upon gentle agitation via a horizontal orbital shaker. In contrast, the 13vPnC, formulated in 0.001%, 0.005%, 0.01% or 0.05% Tween™80 and gently agitated at 2-8° C., was stable for up to twenty-five days with no visible signs of precipitation (data not shown). Thus, this data demonstrated that the addition of a surfactant (e.g., Tween™80) to an immunogenic composition formulation enhances the stability of the immunogenic composition.

A second stability experiment of the 13vPnC further confirmed that the addition of surfactant to the formulation significantly enhanced the stability of the 13vPnC. In this experiment, the 13vPnC was formulated with and without 0.05% Tween™80. The 13vPnC formulated without Tween™80 (i.e., 0.0%) was prepared as follows: 0.85% saline (150 mM NaCl) was added to a one liter Pyrex® glass beaker, followed by 50 mM succinate buffer (final concentration 5 mM) and the 13vPnC, at a total volume of 500 mL. The 13vPnC formulation with 0.05% Tween™80 was prepared as follows: 0.85% saline (150 mM NaCl) was added to a one liter Pyrex® glass beaker, followed by 50 mM succinate buffer (final concentration 5 mM), 0.05% Tween™80 and the 13vPnC, at a total volume of 500 mL. The final concentration of each serotype conjugate in the 500 mL formulations was 4.4 μg/mL (except for serotype 6B, which was 8.8 μg/mL). The 500 mL formulations were homogenized via a rotor/stator homogenizer at 6,000 rpm (2-8° C.) for 120 minutes. The homogenization process created an air-liquid interface (with air bubbles).

The stability of the 13vPnC formulation with (Table 1) and without (Table 1) 0.05% Tween™80 was assessed over a two hour time period as follows: Samples (20-30 mL) were removed at zero, thirty and one hundred-twenty minutes from the 0.0% and 0.05% Tween™80 formulations, the samples were diluted 1:2 in protein diluent (Array® 360 protein diluent (Cat. No. 663630); Beckman Coulter Inc.; Fullerton, Calif.) and the antigenicity of all thirteen serotypes of the 13vPnC were assayed (see, Table 1) on an Array® 360 system.

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

TABLE 1

STABILITY ASSAY OF 13VPNC FORMULATED WITH AND WITHOUT TWEEN ™80

	13vPnC without Tween80				13vPnC with 0.05% Tween80		
Serotype	Antigenicity 0 minutes	Antigenicity 30 minutes	Antigenicity 120 minutes	Serotype	Antigenicity 0 minutes	Antigenicity 30 min	Antigenicity 120 min
1	4.8 µg/ml	4.2 µg/ml	2.4 µg/ml	1	5.1 µg/ml	5.0 µg/ml	5.2 µg/ml
3	4.8 µg/ml	4.1 µg/ml	1.7 µg/ml	3	5.0 µg/ml	5.0 µg/ml	5.2 µg/ml
4	5.8 µg/ml	5.0 µg/ml	3.1 µg/ml	4	6.1 µg/ml	6.1 µg/ml	6.2 µg/ml
5	3.4 µg/ml	3.0 µg/ml	2.0 µg/ml	5	3.6 µg/ml	3.6 µg/ml	3.7 µg/ml
6A	4.9 µg/ml	3.8 µg/ml	1.3 µg/ml	6A	5.4 µg/ml	5.4 µg/ml	5.6 µg/ml
6B	10.0 µg/ml	5.6 µg/ml	1.4 µg/ml	6B	10.6 µg/ml	10.6 µg/ml	10.5 µg/ml
7F	4.7 µg/ml	3.4 µg/ml	1.0 µg/ml	7F	5.3 µg/ml	5.2 µg/ml	5.3 µg/ml
9V	5.6 µg/ml	4.7 µg/ml	2.5 µg/ml	9V	6.1 µg/ml	6.1 µg/ml	6.2 µg/ml
14	7.6 µg/ml	6.4 µg/ml	3.0 µg/ml	14	8.2 µg/ml	8.3 µg/ml	8.3 µg/ml
18C	5.6 µg/ml	4.4 µg/ml	1.7 µg/ml	18C	6.2 µg/ml	6.1 µg/ml	6.2 µg/ml
19A	6.4 µg/ml	4.5 µg/ml	1.9 µg/ml	19A	6.8 µg/ml	6.8 µg/ml	6.8 µg/ml
19F	5.4 µg/ml	2.6 µg/ml	0.0 µg/ml	19F	6.1 µg/ml	6.2 µg/ml	6.0 µg/ml
23F	4.5 µg/ml	2.8 µg/ml	0.9 µg/ml	23F	5.2 µg/ml	5.2 µg/ml	5.2 µg/ml

The 13vPnC/Tween™80 formulation was further tested for stability against high shear forces. In this experiment, a 100 mL 13vPnC composition (4.4 µg/mL serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F and 8.8 µg/mL serotype 6B, 5 mM succinate buffer, 150 mM NaCl and 0.25 mg/mL $AlPO_4$) was added to three 250 mL glass bottles comprising either 0.0%, 0.01% or 0.05% Tween™80. The three bottles were then vortexed for thirty minutes (2-8° C.) on a vortexer (Vortex-Genie® 2; Scientific Industries, Inc.; Bohemia, N.Y.) and an air-liquid interface was created at the maximum speed setting. After thirty minutes 10-30 mL samples were taken from each bottle, diluted 1:2 in Array® 360 protein diluent and the antigenicity of the thirteen serotypes assayed on an Array® 360 system.

As seen in Table 2 below, the 13vPnC formulated without Tween™80 (0.0%) had on average a 20% decrease in antigenicity after vortexing. The 13vPnC formulated with 0.01% Tween™80 had a decrease in antigenicity ranging from 2-10% (average 8%) and the 13vPnC formulated with 0.05% Tween™80 had a decrease in antigenicity ranging from 0-8% (average 3%). Thus, the data presented in Table 2 demonstrate that the 13vPnC formulated with either 0.01% or 0.05% Tween™80 were significantly stabilized against shear forces, relative to the 13vPnC formulated in the absence of Tween™80.

TABLE 2

STABILIZING EFFECT OF TWEEN ™80 AGAINST SHEAR FORCES

Serotype	Antigenicity 0.0% tw80	Antigenicity 0.0% tw80 + vortex	Antigenicity 0.01% tw80	Antigenicity 0.01% tw80 + vortex	Antigenicity 0.05% tw80	Antigenicity 0.05% tw80 + vortex
1	4.7 µg/mL	3.6 µg/mL	4.8 µg/mL	4.3 µg/mL	4.7 µg/mL	4.6 µg/mL
3	4.6 µg/mL	3.4 µg/mL	4.7 µg/mL	4.2 µg/mL	4.7 µg/mL	4.4 µg/mL
4	5.5 µg/mL	4.4 µg/mL	5.9 µg/mL	5.4 µg/mL	5.9 µg/mL	5.6 µg/mL
5	3.2 µg/mL	2.5 µg/mL	3.5 µg/mL	3.2 µg/mL	3.3 µg/mL	3.3 µg/mL
6A	4.3 µg/mL	3.6 µg/mL	4.6 µg/mL	4.5 µg/mL	4.7 µg/mL	4.8 µg/mL
6B	9.7 µg/mL	7.7 µg/mL	10.2 µg/mL	9.6 µg/mL	10.2 µg/mL	10.1 µg/mL
7F	4.6 µg/mL	3.5 µg/mL	5.4 µg/mL	5.0 µg/mL	5.4 µg/mL	5.3 µg/mL
9V	5.3 µg/mL	4.1 µg/mL	5.7 µg/mL	5.1 µg/mL	5.6 µg/mL	5.3 µg/mL
14	6.8 µg/mL	5.4 µg/mL	7.3 µg/mL	6.7 µg/mL	7.4 µg/mL	6.8 µg/mL
18C	4.1 µg/mL	3.4 µg/mL	4.5 µg/mL	4.3 µg/mL	4.5 µg/mL	4.5 µg/mL
19A	5.1 µg/mL	4.2 µg/mL	5.5 µg/mL	5.3 µg/mL	5.6 µg/mL	5.4 µg/mL
19F	4.8 µg/mL	3.6 µg/mL	5.2 µg/mL	4.9 µg/mL	5.2 µg/mL	5.1 µg/mL
23F	3.0 µg/mL	2.4 µg/mL	3.4 µg/mL	3.3 µg/mL	3.5 µg/mL	3.4 µg/mL

Example 2

Formulations Comprising Surfactant Stabilize and Prevent Aggregation of Streptococcal C5a Peptidase

The streptococcal C5a peptidase (SCP) used in this example was expressed and purified as follows. The SCP was expressed recombinantly in *E. coli* using an arabinose inducible system. Standard fermentation protocols for *E. coli* using animal-free defined medium and subsequent cell lysis were followed. Recombinant SCP was purified from the soluble fraction of the cell lysate by saturation to 60% (approximately 3 M) ammonium sulfate while stirring for 12-24 hours. The saturated lysate was centrifuged, supernatant retained and loaded onto a phenyl Sepharose hydrophobic interaction column. Bound material was then eluted with 1 M ammonium sulfate, 20 mM Tris-CI, pH 7.5, concentrated, and diafiltered against PBS, pH 7.4. The purified recombinant SCP (rSCP) was diluted to ~10 mg/mL with PBS, pH 7.4 and passed through a Posidyne filter to remove endotoxin, followed by a final filtration (0.2 mM) for sterility and stored frozen (−25° C.).

The purified SCP (55 µg/mL) was then formulated with 0.025% Tween™80 or without Tween™80 (0.0%) in the following buffers: 5 mM succinate buffer at pH 6.0, 10 mM

phosphate buffer at pH 7.0, 10 mM phosphate buffer at 7.4 or 10 mM Tris buffer at pH 7.5 and filled in separate BD Hypak SCF™ syringes. The syringes were then placed on an a horizontal orbital shaker at 2-8° C., shaken at 180 cpm for two days and the SCP protein concentration determined by the modified Lowry assay.

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

The storage stability of the SCP/Tween™80 (0.025%) formulation was also assessed at 25° C. and 37° C. for eight weeks and six weeks, respectively (data not shown). Briefly, the SCP (200 μg) was formulated 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. The stability of the SCP/Tween™80 formulations were assayed by size-exclusion-HPLC, modified Lowry total protein assay and visual inspection for precipitation. 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).

Example 3

The Influence of Siliconized Container Means on the Stability of 13vPnC

Previous experiments indicated (data not shown) that 13vPnC immunogenic compositions precipitated and/or aggregated when filled in ready to use (single-dose) Becton Dickinson® (BD) Hypak Type 1 borosilicate glass syringes treated with Dow Corning® medical grade DC 360 silicone and capped with West 4432/50 latex free stoppers (chlorobutyl) and EZ tip cap West 7025/65 (Synthetic Isoprene Bromobutyl Blend; West Pharmaceutical®, Lionville, Pa.). In these experiments, the 13vPnC was formulated in 5 mM succinate buffer containing 0.85% NaCl and 4.4 μg/ml of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F and 8.8 μg/ml of *S. pneumoniae* serotype 6B, with and without 0.25 mg/mL aluminum phosphate as an adjuvant. It was observed that, in the absence of $AlPO_4$, the 13vPnC particulates were readily observable, whereas, in the presence of $AlPO_4$, the 13vPnC particulates were significantly diminished and more difficult to detect.

In the present example, a series of container and closure components (i.e., container means) were examined to identify what components were inducing or contributing to 13vPnC particulate formation. The container means tested comprised syringes, stoppers and vials and are listed below in Table 3. The BD and West stoppers listed in Table 3 were siliconized, using either the Huber or Jar process. The Huber process of siliconization is more controlled and yielded 30 to 60 μg/cm2 of silicone on the surface of the stopper, while the Jar process of siliconization resulted in 150 to 300 μg/cm2 of silicone on the surface of the stopper. Based on theoretical calculations, about 15% of the surface area of the stopper is exposed to the product in the syringe, suggesting that for the Huber and Jar process between 4.5 to 9 μg and 22.5 to 45 μg of silicone is extractable from the stoppers, respectively.

Materials

The silicone was Dow Corning® 360 Medical Fluid 1000 centistokes (batch No. 0001846266). The 7vPnC was formulated in 5 mM succinate buffer containing 0.85% NaCl and 4.4 μg/ml of *S. pneumoniae* serotypes 4, 9, 14, 18C, 19F and 23F and 8.8 μg/ml of *S. pneumoniae* serotype 6B, with and without 0.25 mg/ml aluminum phosphate. The 13vPnC was formulated in 5 mM succinate buffer containing 0.85% NaCl and 4.4 μg/ml of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F and 8.8 μg/ml of *S. pneumoniae* serotype 6B, with and without 0.25 mg/ml aluminum phosphate. Monovalent *S. pneumoniae* serotype 6B was formulated (5 mM succinate buffer containing 0.85% NaCl, without aluminum phosphate) at a concentration of 61 μg/ml to simulate the total saccharide concentration of the 13vPnC formulations.

Methods

The 7vPnC and 13vPnC were formulated as described above, and 35 ml of a given formulation was added to a clear 250 ml Nalgene® bottle. Into each Nalgene® bottle, the container means components listed in Table 3 were added. The Nalgene® bottles were then placed on a Labline® Orbit Shaker and swirled overnight at 50 rpm. The results are summarized in Table 3.

Visual Appearance. The Nalgene® bottles containing each of the container means components were held up to a fluorescence light in the laboratory. A path of a beam of light (Tindel effect) passing through the samples allowed for the detection of particulates.

Protein Assay. The total protein and protein bound to aluminum was determined by measuring the total protein concentration in the formulated immunogenic composition and the protein associated with the aluminum pellet, respectively (an aliquot of the immunogenic composition was centrifuged and the pellet was re-suspended in saline). Assays were performed using the Pierce Modified Lowry protein assay (catalog #23240) with bovine serum albumin as a standard.

Results

In the first series of experiments, the 13vPnC immunogenic compositions were formulated without $AlPO_4$ and exposed to a series of container means listed below in Table 3. It was clearly evident from the data (Table 3), that the container means components that were treated with silicone oil induced the formation of white particles. In contrast, no particulates were detected in the presence of the non-siliconized Daikyo® stoppers (Daikyo Seiko, Ltd., Japan) and Schott vials (Schott North America Inc.; Lebanon, Pa.).

TABLE 3

EFFECT OF DIFFERENT CONTAINER MEANS COMPONENTS ON 13VPNC, FORMULATED WITHOUT $ALPO_4$

Container Means Components	Number of Container Means Components Added	Appearance (Visual Inspection)
Control-13vPnC without AlPO4	None	No Particulate
BD Hypak BSCF 1-3 ml 4432/50 Grey Si WWD Stoppers	10	Particulates
BD Hypak BSCF 1-3 ml 4432/50 Grey Si Huber Processed Stoppers	10	Particulates
West 890 Ready to Sterilize Stoppers	10	Particulates
BD Hypak BSCF 1-3 ml W4416/50 Grey Si 1000 WWD Stoppers	10	Particulates
Helvoet 6213 Stoppers	10	Particulates
Daikyo Vial Stoppers (D777-1 B2-40 F451 plug stoppers)	10	No Particulate

TABLE 3-continued

EFFECT OF DIFFERENT CONTAINER MEANS COMPONENTS ON 13VPNC, FORMULATED WITHOUT $AlPO_4$

Container Means Components	Number of Container Means Components Added	Appearance (Visual Inspection)
BD Hypak BSCF 1-3 ml LLA EZGTC W7025/65 Syringe Barrels	4	Particulates
Hypak NSCF 1-3 ml 4023/50 B2-40 Daikyo Stoppers	10	No Particulate
Syringe E-Z Grip Tip Cap W7025/65 EZ IITC	10	No Particulate
2 ml, 13 mm Schott Type 1 glass vials	4	No Particulate
Silicone Oil (Dow Chemical Medical grade 360)	500 µL (1.43%)	Particulates
Schott TopPac Syringes	4	No Particulate

The monovalent *S. pneumoniae* serotype 6B was chosen as a model for the 13vPnC and was formulated at 61.6 µg/ml (without $AlPO_4$) to simulate the total saccharide concentration in the 13vPnC formulation. Silicone (Dow Corning 360 Medical Fluid) was added to aliquots of the formulated monovalent 6B, ranging from 2 ppm to 100 ppm. The mixtures were placed on a Labline® Orbit Shaker for 2 hours at 50 rpm. As indicated below in Table 4, fiber-like white particulates were observed at all silicone (Si) concentrations.

TABLE 4

EFFECT OF SILICONE CONCENTRATION ON THE FORMATION OF PARTICULATES

Silicone Concentration	Appearance (Visual Inspection)
2 ppm (1 µl of Si to 500 mL Formulation)	Fiber-like white particulates
5 ppm (2.5 µl of Si to 500 mL Formulation)	Fiber-like white particulates
10 ppm (5 µl of Si to 500 mL Formulation)	Fiber-like white particulates
15 ppm (7.5 µl of Si to 500 mL Formulation)	Fiber-like white particulates
20 ppm (10 µl of Si to 500 mL Formulation)	Fiber-like white particulates
100 ppm (2 µl of Si to 20 mL Formulation)	Fiber-like white particulates

The amount of silicone in 13vPnC formulations (without $AlPO_4$) was also examined. The silicone concentration was determined by DC Plasma Emission Spectroscopy (data not shown). In this method, the content of 25 syringes were pooled and extracted with two 50 ml portions of cyclohexane/isopropyl alcohol mixture. The extracts were combined and evaporated. The residual was solubilized and tested as per existing methods for silicone determination on rubber stoppers. The results indicated that between 15.8 to 19.0 µg of silicone is extractable from each syringe. This amount corresponds to 2.7% to 3.3% of silicone.

In a separate series of experiments, in which the 13vPnC was formulated in the presence of $AlPO_4$ and subjected to the same container means set forth in Table 3, it was elucidated that the silicone and the "free" protein (13vPnC) in solution was responsible for the formation of the particulates (data not shown). FTIR analysis of the particulates also indicated that the particulate consisted of protein and silicone (data not shown). It was determined in these experiments, that about 85% of the 13vPnC is bound to the $AlPO_4$, wherein the remaining 15% was free (not bound to $AlPO_4$) 13vPnC in solution. In contrast, it was observed that 7vPnC formulated with $AlPO_4$ was 100% bound to the $AlPO_4$ (data not shown).

To elucidate the effect of free protein-polysaccharide on the formation of particulates, 25 ml of both 7vPnC and 13vPnC were aliquoted and transferred to a 50 ml centrifuge tube. The samples were centrifuged for 10 minutes at 3,000 rpm and the supernatant was carefully extracted and transferred to a Nalgene® bottle. Ten siliconized stoppers (4432 Stoppers) were added to each bottle and placed on orbital shaker at 50 rpm. After careful visual inspection, it was observed that the 7vPnC supernatant exhibited no particulate formation, thereby remaining clear and colorless. However, the 13vPnC supernatant began to show low levels of particulate in the fourth hour of observation (data not shown). This result suggested that the free protein-polysaccharide in solution, in conjunction with silicone, is responsible for the formation of the particulates.

To further elucidate the contribution of the free protein-polysaccharide in solution to the formation of particulates, monovalent *S. pneumoniae* serotypes 4 and 6B were chosen for their high and low binding to aluminum, respectively. These two monovalents were formulated at protein concentration ranging from 25 µg/ml to 200 µg/ml in the absence and presence of $AlPO_4$. Ten siliconized stoppers (4432 stoppers) were placed in each formulation, which were then placed on the orbit shaker at 50 rpm. As indicated below in Table 5, fiber-like white particulates were observed for both monovalent serotypes at all protein concentrations in the absence of $AlPO_4$. However, in the presence of $AlPO_4$, particulates were detected at lower concentrations for serotype 4 (100 µg/ml) versus serotype 6B (200 µg/ml), data not shown.

TABLE 5

EFFECT OF PROTEIN CONCENTRATION ON THE FORMATION OF PARTICULATES

	Appearance (Visual Inspection)	
	Without $AlPO_4$	With $AlPO_4$
25 µg/mL of 6B	Fiber-like white particulates	No particulates
50 µg/mL of 6B	Fiber-like white particulates	No particulates
75 µg/mL of 6B	Fiber-like white particulates	No particulates
100 µg/mL of 6B	Fiber-like white particulates	No particulates
200 µg/mL of 6B	Fiber-like white particulates	Fiber-like white particulates
25 µg/mL of Type 4	Fiber-like white particulates	No particulates
50 µg/mL of Type 4	Fiber-like white particulates	No particulates
75 µg/mL of Type 4	Fiber-like white particulates	No particulates
100 µg/mL of Type 4	Fiber-like white particulates	Fiber-like white particulates
200 µg/mL of Type 4	Fiber-like white particulates	Fiber-like white particulates

Example 4

Aluminum Adjuvants Inhibit the Formation of 13vPnC Particulates in the Presence of Siliconized Container Means

As set forth above in Example 3, a 13vPnC immunogenic composition is a liquid formulation comprising 4.4 µg/mL of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A,

19F, 23F and 8.8 μg/mL of type 6B in 5 mM succinate buffer (pH 5.8) and 0.85% NaCl, which may also be formulated with or without an adjuvant (e.g., an aluminum adjuvant). The 13vPnC may also be formulated with or without an adjuvant, such as 0.25 mg aluminum/ml aluminum phosphate ($AlPO_4$). It was observed in Example 3, that 13vPnC formulated without $AlPO_4$ and filled in BD Hypak SCF™ syringes (capped with Hypak plungers) failed visual inspection due to the observation of particulates, wherein further studies revealed that the particulates were in part a result of protein-polysaccharide interactions with silicone. In the following example, syringes (and plungers) from various vendors were evaluated with 13vPnC formulations, wherein shipping and handling conditions were simulated via agitation (described below).

Materials

The 13vPnC was formulated in 5 mM succinate buffer containing 0.85% NaCl and 4.4 μg/ml of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F and 8.8 μg/ml of *S. pneumoniae* serotype 6B, with and without 0.25 mg/ml aluminum phosphate. The container means tested are listed below in Table 6.

TABLE 6

CONTAINER MEANS

	Container Means	Description
1	Vetter syringes Type 1 untreated glass	1 ml long bulk format
2	Schott TopPac ® syringes	Plastic syringes
3	BD Baked syringes Type 1 untreated glass	0.1 mg silicone/barrel
4	BD Baked syringes Type 1 untreated glass	0.04 mg silicone/barrel
5	BD High viscosity syringes Type 1 untreated glass	2.25 ml syringes 12500 cst silicone
6	BD High viscosity syringes Type 1 untreated glass	1.0 ml syringes 12500 cst silicone
7	BünderGlas syringes, PS2 Type 1 untreated glass	0.056 mg silicone/barrel
8	BünderGlas syringes, PS4 Type 1 untreated glass	0.14 mg silicone/barrel
1	West 4023/50 Flurotec ® B2-40 plungers	Flurotec ® plungers
2	West 4023/50 Flurotec ® B2-40 plungers	Flurotec ® plungers
1	13vPnC with $AlPO_4$ in BD Hypak syringes with West 4432 ready to use plungers and 7025/65 EZ tip caps	Positive control, high silicone
2	13vPnC with $AlPO_4$ in un-siliconized syringes with West 4023/50 Flurotec ® B2-40 plungers	Negative control, not treated with silicone

Methods

Formulation and Fill Procedure. Listed below in Table 7 is the recipe for a 2 liter 13vPnC formulation. Briefly, the 0.85% saline was first added to a glass beaker, followed by the 5 mM succinate buffer (pH 5.8), and then sequentially each of the *S. pneumoniae* serotype conjugates. The formulation was then gently mixed on a stirrer plate and filtered through a 0.22 μm Millipore® filter unit. For formulation comprising $AlPO_4$, the $AlPO_4$ (0.25 mg/ml final concentration) was then added and the formulation gently mixed. The test syringes were then filled (0.58 ml/syringe) and capped with plungers.

Shipping Simulation via Agitation. A VWR® signature Digital Multitube vortexer (Catalog No. 14005-826) was used to agitate the samples. The syringes filled with 13vPnC were placed horizontal and fixed by the two support plates of the vortexer. Samples were held at horizontal position and agitated at 500 rpm pause mode at 2-8° C. for twenty-four hours.

Nephelometry. Serotype specific antigenicities were determined by a rate nephelometry assay using type-specific antibodies. For 13vPnC with $AlPO_4$, the aluminum phosphate was solubilized by adding 1N NaOH. The solution was immediately neutralized by adding 1M citric acid. For 13vPnC without AlPO4, no solubilization and neutralization procedures were performed. The assay measures the rate of change of light scattering intensity derived from the antibody-antigen complex formed in the sample using Beckman Array 360 nephelometer.

TABLE 7

13VPNC FORMULATION TABLE

Component	Batch Size (L)	Bulk Conc (mg/mL)	Required Conc (ug/mL)	13vPnC with $AlPO_4$ Volume (mL)	13vPnC without $AlPO_4$ Volume (mL)
serotype 1	2.000	0.506	4.4	17.39	17.39
serotype 3	2.000	0.256	4.4	34.38	34.38
serotype 4	2.000	0.530	4.4	16.60	16.60
serotype 5	2.000	0.515	4.4	17.09	17.09
serotype 6A	2.000	0.519	4.4	16.96	16.96
serotype 6B	2.000	0.489	8.8	35.99	35.99
serotype 7F	2.000	0.500	4.4	17.60	17.60
serotype 9V	2.000	0.521	4.4	16.89	16.89
serotype 14	2.000	0.518	4.4	16.99	16.99
serotype 18C	2.000	0.509	4.4	17.29	17.29
serotype 19A	2.000	0.511	4.4	17.22	17.22
serotype 19F	2.000	0.520	4.4	16.92	16.92
serotype 23F	2.000	0.511	4.4	17.22	17.22
Succinate Buffer in 0.85% Saline, pH 5.8	2.000	50.0	5000	200.0	200.0
$AlPO_4$	2.000	3.250	250	153.85	NA
Saline	2.000	NA	NA	1387.62	1541.46

Results

In this study, syringes from different venders, having different silicone levels (Table 6), were subject to controlled agitation conditions. The total antigenicity of each serotype was measured by Nephelometry assay for both pre-agitation and post-agitation samples. Antigenicity loss following agitation (percentage) was calculated and is shown in FIG. **2** through FIG. **7**.

Prior to the study, the agitation conditions were optimized based on the antigenicity loss of the two controls: (1) the worst-case control (positive control, high silicone; FIG. **2**) and (2) the best-case control (negative control, no silicone; FIG. **3**). The conditions were then optimized such that the antigenicity loss was low in positive control, yet detectable in the negative control. This was to ensure that the agitation was neither too weak to produce precipitation in the syringes; nor too strong, such that the precipitation might be caused by factors other than the silicone interaction (e.g., by shear forces). Thus, agitation at 500 rpm (pause mode) for twenty-four hours was chosen as the most suitable agitation condition, while a temperature of 2-8° C. and a horizontal position were used to simulate the conditions in real time product shipping and handling.

The results of the study are summarized as follows: The largest antigenicity losses of the 13vPnC formulated with $AlPO_4$ occurred in the syringes with higher silicone levels (data not shown). For example, of the syringes listed in Table 6, the BD Hypak syringe (control 1), the BD baked syringe (syringe 3; 0.1 mg silicone), the BD high viscosity (syringe 5) and the BünderGlas PS4 syringe (syringe 8, 0.14 mg silicone), each had one or more of the 13vPnC serotypes with greater than 10% antigenicity loss. The smallest antigenicity

losses of the 13vPnC formulated with $AlPO_4$ occurred in the syringes with lower silicone levels. For example, the Vetter syringes (FIG. **4**) and the Schott TopPac plastic syringes (FIG. **5**) were most similar to un-siliconized syringes (FIG. **2**), both demonstrating minor antigenicity losses for 13vPnC formulated with $AlPO_4$.

The influence of the aluminum phosphate on stabilizing the 13vPnC and inhibiting particulate formation in the presence of siliconized syringes was analyzed in experiments using 13vPnC formulated with and without 0.25 mg/ml $AlPO_4$, wherein syringes used were the BD baked low silicone syringes (syringe 4 in Table 6) and the BünderGlas low silicone PS2 syringes (syringe 7 in Table 6). The BD baked low silicone syringes (0.04 mg silicone/barrel) typically had less than 10% antigenicity loss for the 13vPnC serotypes formulated with $AlPO_4$ (FIG. **6**A), whereas the antigenicity loss for the 13vPnC serotypes formulated without $AlPO_4$ (FIG. **6**B) had antigenicity losses ranging from 5% (serotype 1) up to about 50% (serotype 23F). The BunderGlas low silicone PS2 (0.056 mg silicone/barrel) syringes had less than 5-8% antigenicity loss (depending on serotype) for 13vPnC formulated with $AlPO_4$ (FIG. **7**A), whereas the antigenicity loss for the 13vPnC serotypes formulated without $AlPO_4$ (FIG. **7**B) had antigenicity losses ranging from about 5% to about 30% (depending on serotype).

Thus, these data taken together indicate that: (1) the antigenicity loss of 13vPnC was greater in the syringes with higher silicone levels and (2) the 13vPnC formulated without $AlPO_4$ sustained greater antigenicity losses than 13vPnC with $AlPO_4$ in all of the syringes tested.

Example 5

Formulations Comprising Surfactant Optimize the Binding of Meningococcal Antigenic Proteins to Aluminum Salt Adjuvants

The recombinant lipidated *N. meningitidis* 2086 protein (rLP2086) used in this example was expressed and purified as follows. The rLP2086 was expressed recombinantly in *E. coli* utilizing a native leader sequence. Standard fermentation protocols for *E. coli* using animal-free defined medium and subsequent cell lysis were followed. Recombinant lipidated *N. meningitidis* 2086 protein was purified from the membrane pellet with 50 mM Tris-HCl/5 mM EDTA/1% sarcosyl pH 8. This sarcosyl extract was adjusted to 1% Zwittergent 3-14 (Z3-14) and dialyzed twice against a 30 fold excess of 50 mM Tris-HCl/5 mM EDTA/1% Z3-14. The dialyzed rLP2086 extract was precipitated with 90% ethanol to remove remaining sarcosyl, and solubilized with 50 mM Tris-HCl/5 mM EDTA/1% Z3-14 pH 8. Insoluble material was removed by centrifugation, the supernatant was passed over an anion exchange chromatography column, and rLP2086 was collected in the unbound fraction. The unbound material was then dialyzed twice against a 30-fold excess of 25 mM NaAc/1% Z3-14 pH 4.5, and passed over a cation exchange chromatography column. The rLP2086 was eluted with a 0-0.3M NaCl gradient and stored frozen (−25° C.).

The purified rLP2086 was then formulated with 150 mM NaCl, 0.020% Tween™80, 0.25 mg Al/mL of $AlPO_4$, and in the following buffers: 10 mM phosphate buffer at pH 7.0 and 5 mM succinate buffer at pH 6.0. Table 8 compares protein binding percentage to the $AlPO_4$ adjuvant.

TABLE 8

RLP2086 BINDING TO ADJUVANT

Buffer	Total Protein Conc. (μg/mL)	$AlPO_4$ Bound Protein (%)
10 mM Phosphate buffer pH 7.0 containing 150 mM NaCl, 0.02% polysorbate 80 and 0.25 mg Al/mL of $AlPO_4$	400	68
	120	82
5 mM Succinate buffer pH 6.0 containing 150 mM NaCl, 0.02% polysorbate 80 and 0.25 mg Al/mL of $AlPO_4$	400	81
	120	100

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What is claimed is:

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

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

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

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

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

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

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.

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

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

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.

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

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.

17. The formulation of claim **1**, wherein the one or more polysaccharide-protein conjugate comprises an *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM197 polypeptide, and an *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM197.

18. The formulation of claim **1**, wherein the one or more polysaccharide-protein conjugate comprises an *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 1 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 3 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 5 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6A polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 7F polysaccharide conjugated to a CRM197 polypeptide and an *S. pneumoniae* serotype 19A polysaccharide conjugated to a CRM197 polypeptide.

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

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

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 SERVICE

I certify that today, December 18, 2018, I electronically filed the foregoing Opening Brief for Appellant Merck Sharp & Dohme Corp. with the Clerk of the Court for the U.S. Court of Appeals for the Federal Circuit using the appellate CM/ECF system. All participants in the case are registered CM/ECF users and will be served by the appellate CM/ECF system.

December 18, 2018 /s/ Jeffrey A. Lamken

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