Trials@uspto.gov
571-272-7822

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

WYETH LLC,
Patent Owner.

Case IPR2017-00390
Patent 8,562,999 B2

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

HARLOW, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 7–9, 12, 13, 15, 16, 21, and 22 of U.S. Patent No. 8,562,999 B2 (Ex. 1001, "the '999 patent"). Paper 1 ("Pet."). Wyeth LLC ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp."). We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

For the reasons set forth below, we institute an *inter partes* review of claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent.

A. Related Matters

Petitioner has filed two additional petitions challenging claims of the '999 patent in IPR2017-00378 and IPR2017-00380. The parties have not identified any additional related proceedings concerning the '999 patent. Pet. 3–4; Paper 4, 2; Paper 7, 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. *Id*. at 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 'liposaccharide (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 which inhibit precipitation of immunogenic compositions comprised in siliconized container means. *Id*. at 5:44–50.

C. Illustrative Claim

Each of the challenged claims depends, directly or indirectly, from claim 1, which is reproduced below and is illustrative of the claimed subject matter.

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

Ex. 1001, 31:7–12. Claims 7–9, 12, 13, 15, 16, 21, and 22 impose further limitations on the recited buffered saline solution, aluminum salt, and/or polysaccharide-protein conjugates.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent on the following grounds:

Claims	Basis	References
7–9, 12, 13, 15, 16, 21, and 22	pre-AIA § 103(a)	Chiron,[1] Smith,[2] and Elan[3]
7–9, 12, 13, 15, 16, 21, and 22	pre-AIA § 103(a)	Prevenar[4] and Chiron
13 and 16	pre-AIA § 103(a)	Merck[5] and the '787 patent[6]

Petitioner also relies on the Declarations of Dennis L. Kasper, M.D. (Ex. 1007) and Devendra Kalonia, Ph.D. (Ex. 1010).

[1] Patent Application Publication No. WO 03/009869 A1 by Mario Contorni et al., published February 6, 2003. Ex. 1011 ("Chiron").
[2] *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").
[3] Patent Application Publication No. WO 04/041439 A2 by David Burke et al., published August 26, 2004. Ex. 1013 ("Elan").
[4] Summary of Product Characteristics for Prevenar Suspension for injection: Pneumococcal saccharide conjugated vaccine, adsorbed, Annex 1:1–15 (2005). Ex. 1017 ("Prevenar").
[5] Patent Application Publication No. WO 2011/100151 A1 by Michael J. Caulfield et al., published August 18, 2011.
[6] U.S. Patent No. 7,935,787 B2 by Lakshmi Khandke et al., issued May 3, 2011.

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) (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. 27–31; Prelim. Resp. 12–20. As relevant to this Decision, we address the following proposed constructions:

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

Petitioner asserts that the broadest reasonable interpretation of claim term "polysaccharide" is set forth by Specification definition for the term. Pet. 28–29. 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 'liposaccharide (LPS)', a 'glycosylate', a 'glycoconjugate' and the like." *Id*. at Ex. 1001, 16:32–38. Petitioner does not propose a separate construction for the claim phrase "polysaccharide-protein conjugates."

Patent Owner does not address the term "polysaccharide" alone, but instead as part of the claim phrase "polysaccharide-protein conjugate[s]." Prelim Resp. 13–16. According to Patent Owner, the broadest reasonable interpretation of that claim phrase is "an immunogen comprising a polysaccharide conjugated to a carrier protein." *Id*. at 14. In support of that proposed construction, Patent Owner identifies various instances in the Specification wherein the polysaccharide-protein conjugate is referred to as an immunogen. *Id*. at 14–15 (citing, e.g., Ex. 1001, 14:19–23) ("the immunogen (i.e., a polysaccharide-protein conjugate . . .)").

Further, Patent Owner asserts that "[w]hile the claims may not recite a level of immunogenicity, it is a property of the composition." *Id*. at 16. In support of that position, Patent Owner asserts that the Specification describes assays to measure loss of antigenicity as a measure of immunogenicity; immunogenicity and use as a vaccine is the utility of the claimed formulation; and a "polysaccharide-protein conjugate" is an immunogenic composition. *Id*. at 16. Additionally, Patent Owner states "[t]he compound (in this case a polysaccharide-protein conjugate in the formulation) and its properties are inseparable considerations, particularly in an obviousness context." *Id*. (citing *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086–90 (Fed. Cir. 2008)). According to Patent Owner,

under its proposed construction, "Petitioner must not only show that the formulations taught by the prior art formulations would inhibit silicone-induced aggregation of the polysaccharide-protein conjugates but also that at the time aggregation is inhibited, the immunogenicity of the conjugate compositions is retained." *Id*. at 14.

At this stage in the proceeding, and based on the current record, we determine that the Specification sets forth with reasonable clarity, deliberateness, and precision the definition of the term "polysaccharide," as accurately represented by Petitioner. 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. In light of those descriptions, at this stage in the proceeding, we determine that the broadest reasonable construction of the claim phrase "polysaccharide-protein conjugates" refers to the resulting product of 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 liposaccharide, a glycosylate, a glycoconjugate, and the like with a carrier protein that is amenable to standard conjugation procedures.

At this stage in the proceeding, we do not adopt Patent Owner's proposed construction as it does not reflect the Specification definition for the term "polysaccharide." *See* Prelim. Resp. 14. We acknowledge Patent Owner's assertion that "[w]hile the claims may not recite a level of immunogenicity, it is a property of the composition." *Id*. at 16. The Specification states that the invention "broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions." Ex. 1001, 2:53–55. Although Example 4 of the Specification discusses total antigenicity (and loss), the claims do not require the formulation to retain a particular degree of immunogenicity. Instead, the claims recite another property of the formulation, i.e., inhibition of aggregation/precipitation[7] induced by the siliconized container means. *Id*. at 5:44–50. Patent Owner has not established persuasively that the claims require the formulation to provide any particular "level of immunogenicity" or effectiveness as a vaccine composition by asserting that the claimed formulation comprises an immunogen. *Id*. at 5:44–50. The polysaccharide-protein conjugate confers the immunogen element of the claim, without regard to its level of functionality as such, so long as the formulation comprising that element

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

inhibits aggregation induced by the siliconized container. Thus, Patent Owner's reference to Specification descriptions of assays to measure loss of antigenicity as a measure of immunogenicity is misplaced, as the Specification explains that the formulation property relevant to the challenged claims (aggregation/precipitation) may be detected upon visual inspection. *See*, *e.g.*, Ex. 1001, 27:6–11 (discussing visual inspection for precipitation).

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 30 (citing Ex. 1010 ¶ 97). Petitioner contends that this construction is consistent with the plain language of the claim, as well as the Specification, "which expressly teaches that the invention includes the use of surfactants to inhibit silicone-induced aggregation", and the prosecution history, "where Patent Owner uniformly referred to the invention as inhibition of silicone-induced aggregation by the 'formulation,' not an individual ingredient." Pet. 30–31 (citing Ex. 1010 ¶¶ 98–102).

Patent Owner agrees that a proper construction of the claim 1 "does not focus on the action of any particular ingredient per se," and that the open-ended aspect of the claim "permits additional ingredients." Prelim. Resp. 18. Patent Owner, however, asserts that "[t]he plain language of the claim [1] requires that a formulation containing the three specifically recited ingredients inhibits aggregation induced by the siliconized container while

maintaining the antigenicity of the conjugate." *Id*. at 16–17. According to Patent Owner, "at a minimum, the claim must be construed to include an embodiment where the three ingredients (buffered saline solution, aluminum salt, and polysaccharide-protein conjugate) in formulation without more inhibit aggregation induced by the siliconized container means while maintaining antigenicity." *Id*. at 17. Thus, Patent Owner asserts that, based upon the language of the claim and the disclosure in the Specification, the claim phrase means "the formulation with at least the recited ingredients inhibits aggregation induced by the siliconized container." *Id*. at 17. According to the Patent Owner, under that construction, "the claim therefore is not rendered obvious by a reference or combination of references achieving the same result with additional components." *Id*.

At this stage in the proceeding, and based on the current record, 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 30. Further, we agree with Patent Owner that the broadest reasonable construction of the claim phrase "the formulation . . . inhibits aggregation induced by the siliconized container means" should "*include* an embodiment where the three ingredients (buffered saline solution, aluminum salt, and polysaccharide-protein conjugate) in formulation without more inhibit aggregation induced by the siliconized container means while maintaining antigenicity." Prelim. Resp. 17 (emphasis added). While *including* such an embodiment, we also determine that by reciting the formulation using the open-ended term "comprising," along with attributing the aggregation inhibition to the

formulation, the broadest reasonable construction also includes formulations comprising additional unrecited ingredients, and such additional ingredient(s) may contribute the required aggregation inhibition to 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 particular level of the antigenicity of the conjugate, as asserted by Patent Owner, Prelim. Resp. 17, for the same reasons discussed, supra, with respect to Patent Owner's similar argument raised in connection with its proposed construction of the "polysaccharide-protein conjugate" term.[8]

3. Other terms

In view of the above 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)

[8] Patent Owner apparently relies on those earlier arguments, as its discussion of the instant claim phrase does not include arguments in support of the contention that independent claim 1 requires "maintaining the antigenicity of the conjugate." *See* Prelim. Resp. 16–20.

(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. 27 (citing Ex. 1010 ¶ 82).

Patent Owner disagrees with Petitioner's definition insofar as it suggests the field of invention involved protein-based formulations. Prelim. Resp. 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 this stage in the proceeding, we determine that Patent Owner's description of the level of ordinary skill in the art is a more precise assessment and is supported by the current record. For purposes of this Decision, we adopt Patent Owner's description. 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).

Moreover, we have reviewed Dr. Kalonia's credentials (Ex. 1010, Ex. A) and, at this stage in the proceeding, we consider Dr. Kalonia to be qualified to provide an opinion on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. Additionally, we have reviewed Dr. Kasper's credentials (Ex. 1007, Ex. A) and, at this stage in the proceeding, we consider Dr. Kasper to be qualified to provide an opinion on the state of the art of polysaccharide-protein conjugate vaccines at the time of the invention, as relevant to the challenged claims.

C. Obviousness Ground of Unpatentability Based on Chiron, Smith, and Elan

Petitioner asserts that claims 7–9, 12, 13, 15, 16, 21, and 22 are unpatentable under § 103(a) as obvious in view of Chiron, Smith, and Elan. Pet. 31–46. Patent Owner disagrees. Prelim. Resp. 22–35.

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. 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 vaccines formulations comprising an antigen, aluminum salt and histidine. Ex. 1011, Abstract. Chiron explains that the "antigen is preferably a protein or a saccharide, 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.

2. Smith

Smith is a Technical Report published in the Journal of Parental 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

Petitioner contends that Chiron teaches or suggests every ingredient of the formulation recited in claim 1, from which each of the challenged claims ultimately depends. Pet. 32–34. Petitioner further asserts that the instantly challenged claims themselves "recite nothing more than obvious details of the vaccine components recited in sole independent claim 1, *i.e.*, buffer, saline, aluminum salt and polysaccharides." Pet. 31. In particular, Petitioner states 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 32–34 (citing, e.g., Ex. 1011, 1:6–7; 2:1; 5:15, 5:28). 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 33 (citing Ex. 1010 ¶ 138;[9] Ex. 1045, 22). As for the saccharide antigen, Petitioner asserts that Chiron teaches that conjugation to a carrier protein is preferred, and points to Chiron's disclosure that such conjugation enhances immunogenicity. *Id*. at 33 (citing Ex. 1011, 3:20–21).

Chiron does not expressly teach that its formulations are comprised in a siliconized container means. Petitioner asserts, however, that it would have been obvious to a person of ordinary skill to provide those formulations in such container means. Pet. 34–36 (citing Ex. 1010 ¶¶ 143–148[10]). Petitioner asserts that Chiron discloses storing the polysaccharide-protein conjugated formulations of Example 8 in vials for at least one month. *Id*. at 34–35 (citing Ex. 1011, 15:1–6). According to Petitioner and its Declarant, Dr. Kalonia, a person of skill in the art would have sealed such vials with rubber stoppers for that long-term storage. *Id*. at 35 (citing Ex. 1010 ¶ 144). Petitioner asserts also that it would have been obvious to additionally store the formulations in syringes, as it was designed to be injectable. *Id*. (citing Ex. 1010 ¶ 145; 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 that was a common method of supplying vaccines, as

[9] Reference by the Petition to paragraph 1038 of Exhibit 1010, rather than paragraph 138, appears to be an inadvertent typographical error.
[10] Reference by the Petition on page 34 to paragraph 133 of Exhibit 1010, rather than paragraph 143, appears to be an inadvertent typographical error.

evidence by commercialized Chiron polysaccharide-protein vaccine, Vaxem Hib. *Id*. (citing Ex. 1010 ¶¶ 146–147; Ex. 1051; Ex. 1053).

According to Petitioner, a person of ordinary skill in the art would have understood also that standard pharmaceutical vial stoppers, syringe plungers, and syringe barrels were siliconized. Pet. 35 (citing Ex. 1010 ¶ 148). Relying on Dr. Kalonia, Petitioner asserts that Smith teaches that it was standard industry practice to lubricate the components of such containers with silicone oil. *Id*. at 35–36 (citing Ex. 1010 ¶ 148).

Petitioner further 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 also contains a surfactant, such as polysorbate/Tween® 80. Pet. 36 (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. 1010 ¶ 149; Ex. 1013, 16:13–15; 17:6–14). Thus, Petitioner asserts that a person of ordinary skill in the art would have been motivated to provide Chiron's formulations in a siliconized container means and would have had a reasonable expectation of successfully doing so, as Elan taught that a formulation including a surfactant, such as Chiron's, would successfully address silicone-induced protein aggregation. *Id*. at 36–38 (citing Ex. 1010 ¶¶ 151, 153–154).

Turning to the challenged dependent claims, Petitioner contends that Chiron discloses a preferred pH range of between 6 and 7, the use of

histidine as a buffer, and the use of a sodium salt, such as sodium phosphate or sodium chloride in the pH buffered saline solution of a vaccine formulation, and, therefore, satisfies the limitations recited in claims 7–9 of the '999 patent. Pet. 38–39 (citing Ex. 1011, 5:15, 5:28, 6:7–8, 11:30–12:15, 14:3–17:4 (Examples 2, 7–9)).

With regard to claims 12, 13, 15, and 16, Petitioner reiterates that Chiron teaches histidine as a preferred buffer, and asserts that Chiron further discloses that histidine is "a useful additive for improving the adsorption of antigens to aluminium hydroxyphosphate." *Id*. at 39 (quoting Ex. 1011, 12:14–15). Petitioner also contends that Chiron describes the combination of histidine with an aluminum phosphate adjuvant as "particularly advantageous for acidic antigens" *id*. (quoting Ex. 1011, 5:3–4), and represents that "CRM_{197}, as well as the majority of bacterial polysaccharides, including, pneumococcal and meningococcal polysaccharides, are acidic antigens" *id*. at 39–40 (citing Ex. 1011, 12:2–3; Ex. 1007 ¶ 55). In addition, concerning the particular species of aluminum adjuvant used in the disclosed vaccine formulation, Petitioner asserts that Chiron states "a preference for aluminum phosphate over aluminum hydroxide with respect to conjugate vaccine formulations, because of concerns that aluminum hydroxide would hydrolyze polysaccharide antigens, decreasing vaccine immunogenicity." *Id*. (citing Ex. 1007 ¶ 54; Ex. 1011, 1:22–24, 11:31–12:5). Furthermore, as described above with respect to claim 9, Petitioner states that Chiron teaches the use of sodium chloride in a pH buffered saline solution. *Id*. at 40 (citing Ex. 1011, 5:28, 14:3–17:4 (Examples 7–9).

Focusing on the additional requirement recited in claims 13 and 16 that the histidine buffer have a pH of 5.8, relying on Dr. Kalonia, Petitioner asserts that "[t]he effective buffering range of histidine is approximately pH 5.0–7.0, and the choice of a specific pH within that range would have been a matter of routine optimization." *Id*. at 40–41 (citing Ex. 1010 ¶ 161). In this respect, Petitioner notes that the '999 patent neither expressly describes nor exemplifies a histidine buffer at pH 5.8; nor does the '999 patent suggest that such pH is critical to the invention or that it yields unexpectedly superior results. *Id*. Petitioner acknowledges that Chiron identifies a pH range for histidine buffer of pH 6–7 as preferred, but explains that an ordinarily skilled artisan "would have been motivated to choose histidine buffer with a pH below 6 to increase adsorption of acidic antigens (such as CRM_{197} and most bacterial polysaccharides) to aluminum phosphate adjuvant." *Id*. at 41 (citing Ex. 1010 ¶ 163). Petitioner also notes that the recited pH of 5.8 is close to the preferred range described by Chiron. *Id*. at 42.

Concerning the further requirement of claims 15 and 16 that the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, relying on Dr. Kalonia, Petitioner avers that "[i]t would have been obvious to use pneumococcal polysaccharide-protein conjugates in [the claimed] formulation, and that such formulations would still inhibit silicone-induced aggregation." *Id*. at 42 (citing Ex. 1010 ¶ 164). Petitioner asserts that Chiron expressly discloses the use of pneumococcal polysaccharides as antigens. *Id*. (citing Ex. 1007 ¶¶ 32, 34, 42–46; Ex. 1010 ¶ 165; Ex. 1011, 2:15, 3:14, 6:32–35). Petitioner additionally states that an

ordinarily skilled artisan "would have understood that the *protein* component of polysaccharide-protein conjugates (not the polysaccharide) is responsible for the claimed 'aggregation induced by the siliconized container means.'" *Id*. at 43 (citing Ex. 1010 ¶ 166).

Claims 21 and 22 require the use of succinate as a buffer, and further specify buffer concentration and pH. Petitioner recognizes that Chiron identifies histidine as a preferred buffer, but asserts that an ordinarily skilled artisan "would have found it obvious to use other well-known buffers (such as the claimed succinate buffer) during routine optimization." *Id*. at 44–45 (citing Ex. 1010 ¶ 170). Specifically, Petitioner contends that an ordinarily skilled artisan would have treated succinate as an acceptable substitute for histidine because "succinate has an effective buffering range (approximately pH 4.6 to 6.6) that overlaps in large part with both the buffering range for histidine (approximately pH 5.0 to 7.0) and the physiologically acceptable pH range (approximately pH 5.5 to 7.5)[.]" *Id*. at 44 (citing Ex. 1010 ¶ 170).

Relying on Dr. Kalonia, Petitioner further asserts that "[t]he choice of the specific buffer concentration and pH range is also a matter of routine optimization." *Id*. (citing Ex. 1010 ¶ 171). In this regard, Petitioner represents that the concentration range of 1 mM to 10 mM recited in claim 21 is a common range for buffers, and that the claimed pH range of pH 5.8 to pH 6.0 is obvious because it is close to the pKa of succinate and within the preferred pH range disclosed by Chiron. *Id*. (citing Ex. 1010 ¶ 171; Ex. 1011, 5:11–12).

Petitioner similarly contends that the 5 mM succinate buffer concentration required by claim 22 "is a matter of routine optimization and

5 mM is a standard one for buffers. *Id*. at 46 (citing Ex. 1010 ¶ 172; Ex. 1011, 5:12–13 ("most preferably, [concentration of histidine buffer] is about 5 mM").

Based upon our review of the current record, and in light of our preliminary claim constructions, we discern no deficiency in Petitioner's characterization of the cited references and the knowledge in the art, or in Petitioner's assertions as to the reasonable inferences an ordinary artisan would make from those references. Thus, based on the information presented at this stage of the proceeding, Petitioner has demonstrated sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of independent claims 7–9, 12, 13, 15, 16, 21, and 22 over the combined references.

Our remaining analysis of this asserted ground of unpatentability focuses on the deficiencies in Patent Owner's arguments in its Preliminary Response as to the challenged claims. Patent Owner focuses its arguments predominantly on sole independent claim 1; dependent claims 21 and 22 are the only challenged claims directly addressed.

Patent Owner arguments rely, to a great extent, upon claim constructions that we have not adopted at this stage in the proceeding. First, as explained in our preliminary claim construction discussion, contrary to Patent Owner's contention, the current record does not support construing independent claim 1 so as to require achieving or preserving some particular level of immunogenicity of the formulation. Although the Specification describes assays for stability and immunogenicity, Ex. 1001, 10:27–30, Patent Owner has not shown that "[i]mmunogenicity and use as a vaccine is

the utility of the claimed formulation." Prelim. Resp. 16. Instead, the challenged claims are directed toward another specific property of the formulation, i.e., the inhibition of aggregation induced by the siliconized container means.

Second, as explained in our preliminary claim construction discussion, the current record does not support construing claim 1 in a manner that excludes a formulation comprising an additional ingredient, such as a surfactant, that provides the formulation with the required aggregation inhibition. In claim 1, the open-ended transition term "comprising" is used to describe the formulation ingredients. Although only three ingredients are recited, i.e., a pH buffered saline solution, an aluminum salt, and one or more polysaccharide-protein conjugates, the "comprising" term signals that additional ingredients may be included. Indeed, claim 2 depends directly from claim 1 and adds an ingredient, polysorbate 80. Because the claim attributes the required aggregation inhibition to the formulation and not to any of the specific recited ingredient(s), a formulation comprising additional ingredients may read on the claim, whether or not such additional ingredient(s) contribute the required inhibition of aggregation induced by the siliconized container means, so long as the formation, as a whole achieves that inhibition.

Patent Owner asserts also that Petitioner has failed to establish that Smith and Elan are pertinent prior art. Prelim. Resp. 22–25. In support of those contentions, Patent Owner asserts that neither Smith nor Elan is in the same field of endeavor as the '999 patent, as they does not concern vaccine formulations, let alone polysaccharide-protein conjugate formulations. *Id*. at

23–25. We find that argument is short-sighted, as the Petition makes clear that Smith is relied upon to show the standard practice of lubricating pharmaceutical container means with silicone oil at the time of the invention. In other words, Smith addresses a key element of the challenged claims, siliconized container means. In the combination, Petitioner articulates sound reasoning that, based upon Smith's teaching, a person of skill in the art would have had a reason to believe any such container means used to store Chiron's formulation would have had siliconized surfaces. Pet. 1–2 n.1, 21, 34–36. As for Elan, the Petition explains that the reference teaches the addition of a surfactant (also used in Chiron) to prevent protein aggregation induced by the silicone in standard syringes. *Id*. at 1–2 n.1, 22, 36–38. In other words, Elan addresses another key element of the challenged claims, inhibiting aggregation induced by the siliconized container means. That Smith and Elan do not mention polysaccharide-protein conjugate formulations does not negate the relevance of their combined teachings in an obviousness analysis of the challenged claims. Moreover, as discussed, based on the current record, we do not construe the claims as being directed to the effectiveness of the formulation as an immunogen or vaccine.

For the same reasons, we are not persuaded by Patent Owner's assertion that the Petition failed to identify a reason to combine, or a reasonable expectation of success in combining Chiron with Smith or Elan. Prelim. Resp. *Id*. at 31–35. To the extent that Patent Owner asserts that "Elan 2004 teaches away from using polysorbate 80 and histidine together as in the Chiron 2003 formulation" (Prelim. Resp. 32), we disagree. Elan

explains that the source (lot) of histidine plays a role in the polysorbate 80 degradation. *See, e.g.*, Ex, 1013, 20 (describing minimal levels of trace impurities for a particular histidine lot). Moreover, Elan teaches that its formulation comprising polysorbate 80 "may further comprise histidine." *Id*. at 3:8–9. Thus, based on the current record, Patent Owner has not established persuasively that Elan teaches away from Chiron's combination of polysorbate 80 and histidine because such disclosure does not discredit, or otherwise discourage such use, but instead teaches it. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Patent Owner additionally asserts that the "Petition has failed to show any prior art reference meeting the limitation that the polysaccharide-protein conjugate formulation recited in the claim inhibits aggregation by a siliconized container means." Prelim. Resp. 29. In particular, Patent Owner contends that Elan's "showing that polysorbate 80 inhibits aggregation in the antibody formulation is insufficient to meet this element of the claim in particular because there is no teaching in Elan 2004 about retaining immunogenicity of the composition in which aggregation is inhibited." *Id*. at 27. That argument is not persuasive as we have determined on the current record that the claims do not require retaining any particular level of immunogenicity.

Patent Owner also asserts that Dr. Kalonia provides testimony that in proteins and polysaccharide-protein conjugates, "it is the protein component that drives aggregation" without providing any citation to references or data to support that opinion. *Id*. (citing Pet. 11; Ex. 1010 ¶ 51). According to

Patent Owner, "Dr. Kalonia fails to establish that in a conjugate, the protein would remain exposed to the solvent and thus, free to aggregate." *Id*.

At this stage in the proceeding, however, we consider Dr. Kalonia's testimony to be reasonable and based on the knowledge of a person of ordinary skill in the art. In particular, Dr. Kalonia's opinion that "the protein component drives aggregation (as opposed to the polysaccharide in the conjugate)" is supported with an explanation of how the protein structure of protein provides a polarity amenable to aggregation, unlike the polysaccharide molecules. Ex. 1010 ¶ 51. Moreover, Patent Owner seems to acknowledge that the protein component drives aggregation by stating in another portion of the Preliminary Response that, at the time of the invention, the prior art had determined that "the effect of silicone oil on proteins was considered unique to each protein." Prelim. Resp. 8. In any event, Patent Owner's postulation here that the protein in the conjugate may not be "free to aggregate" would seem to suggest that the conjugate itself contributes to the inhibition of aggregation and, thus, meets the claimed property of the formulation.

Turning to claims 21 and 22, Patent Owner asserts that "Petitioner fails to show where the prior art teaches the succinate buffer at the recited pH or concentration." Prelim. Resp. 29. As an initial matter, we observe that Patent Owner does not affirmatively dispute that an ordinarily skilled artisan would have recognized succinate buffer as an acceptable alternative to histidine buffer. Rather, Patent Owner takes issue with the sufficiency of Dr. Kalonia's testimony concerning the overlap in buffering ranges for succinate and histidine buffers and rationale for using succinate buffer in

place of histidine buffer. For purposes of this decision, however, we are satisfied that Dr. Kalonia's testimony is reasonable based on the knowledge of a person of ordinary skill in the art. In this regard, we observe that it is undisputed that succinate and histidine were both well-known buffers at the time of invention. *See* Ex. 1011 ¶ 170. We further observe the "pH range of use" for succinate disclosed by Akers,[11] the reference on which Patent Owner relies in challenging Dr. Kalonia's opinions (Prelim. Resp. 29), is consistent with the succinate buffering range described by Dr. Kalonia, and overlaps with both the pH range of use for histidine taught by Akers, and the histidine buffering range provided by Dr. Kalonia. Ex. 1045, 22. Thus, at this stage of the proceeding, we are satisfied that Dr. Kalonia's reasoning concerning why an ordinarily skilled artisan would have found it obvious to use succinate buffer in place of histidine buffer is sound.

Patent Owner's contentions that the succinate buffer concentrations and pH required by claims 21 and 22 would not have been obvious are likewise unavailing. Chiron discloses that the concentration of histidine buffer "is preferably at least 1mM", more preferably "between 2mM and 10mM (*e.g.* between 5mM and 8mM) and, most preferably, it is about 5mM." Ex. 1011 6:8–13. Chiron additionally reports a six-fold increase in antigen adsorption in the presence of 5 mM histidine buffer as compared to a histidine buffer-free solution. *Id*. at 13:11–13. Thus, although Patent Owner

[11] Akers et al., *Formulation Development of Protein Dosage Forms*, in 14 *Development and Manufacture of Protein Pharmaceuticals*, PHARM. BIOTECH. 47–128 (2002) (EX. 1045).

is correct that Chiron discloses a further increase in adsorption at a histidine buffer concentration of 10mM, and that Chiron postulates that the positive charge of histidine might be able to mask the negative charge of an acidic antigen (Prelim. Resp. 30; Ex. 1011, 13:1–5, 13:11–13), such results are insufficient to establish a teaching away, particularly where, as here, a 5mM buffer concentration is expressly disclosed as most preferred.

For similar reasons, we are also unpersuaded by Patent Owner's arguments concerning the non-obviousness of the claimed succinate buffer pH range of 5.8 to 6.0. Patent Owner does not dispute Dr. Kalonia's testimony that the use of succinate buffer within the claimed pH range of pH 5.8 to pH 6.0 would have been obvious because the claimed pH range is close to the pKa of succinate and within the preferred pH range disclosed by Chiron (Ex. 1010 ¶ 171); testimony on which we rely in instituting review of claims 21 and 22. Instead, Patent Owner points to particularly embodiments described by Chiron. But Chiron cannot be said to teach away from "histidine at a pH lower than 7" (Prelim. Resp. 30) when it expressly discloses that "[t]he pH of the composition is preferably between 6 and 7" (Ex. 1011, 7:7).

Patent Owner asserts variations of the same arguments addressed above concerning the succinate buffer concentration and pH range in challenging the rationale for, and reasonable expectation of success in, combining the asserted references. Prelim. Resp. 33, 35. In particular, Patent Owner contends that an ordinarily skilled artisan would not have had reason to, or a reasonable expectation of success in making the proposed combination because Chiron focuses "on the benefits conferred by

histidine's positive charge on negatively charged acidic antigens", and "teaches that the advantage of histidine lies in a high concentration of 10 mM, at a basic pH (or at least, a non-acidic pH) that exceeds 7." *Id*. at 35; *see also id*. at 33. As explained above, however, Patent Owner's reading of Chiron is overly narrow. Chiron explicitly discloses a buffer concentration of 5 mM as most preferred (Ex. 1011, 6:12–13), and identifies a pH of 6 a preferred pH for the vaccine compositions (*id*. at 7:7). Accordingly, at this stage in the proceeding, Patent Owner's arguments do not persuade us that Petitioner has not established a reasonable likelihood of prevailing in showing that claims 21 and 22 would have been obvious.

Patent Owner asserts that "[t]he specification of the '999 patent shows that the three-ingredient formulation recited in claim 1 unexpectedly inhibits aggregation induced by siliconized containers while retaining the immunogenicity as measured by antigenicity of the composition." Prelim. Resp. 9. In support of that contention, Patent Owner discusses Examples 3 and 4 of the Specification. *Id*. That discussion, however, does not explain or establish that the results of the experiments conducted in those examples were unexpected compared to with the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Thus, at this stage in the proceeding, Patent Owner has not provided persuasive evidence of nonobviousness by referring to Examples 3 and 4 of the '999 patent.

Based on the current record, we note that the Petitioner in this proceeding has shown that (a) Chiron taught or suggested formulations comprising each of the ingredients recited in the challenged claims at the required concentration and pH, along with a surfactant, (b) a person of

ordinary skill in the art would have had a reason to store Chiron's formulation in a siliconized container means, in view of Smith, and (c) a person of skill in the art would have reasonably expected Chiron's formulation to inhibit aggregation induced by the siliconized container means based upon the knowledge in the art, in view of Elan. Thus, at this stage in the proceeding, based upon the current record and our preliminary claim constructions, we are persuaded that the combined teachings of Chiron, Smith and Elan would have suggested the invention of the challenged claims to a person of ordinary skill in the art. Patent Owner's arguments in the Preliminary Response do not persuade us otherwise.

Based on the foregoing, therefore, we determine that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent are unpatentable. Accordingly, we institute an *inter partes* review of those claims.

D. Obviousness Ground of Unpatentability Based on Prevenar and Chiron

Petitioner asserts that claims 7–9, 12, 13, 15, 16, 21, and 22 are unpatentable under § 103(a) as obvious in view of Prevenar and Chiron. Pet. 46–60. Patent Owner disagrees. Prelim. Resp. 35–44.

1. Prevenar

Prevenar provides a summary of product characteristics for Prevenar, 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 1 needle for injection. *Id*.

2. Obviousness Analysis

Petitioner contends that Prevenar teaches two of the three ingredients recited in claim 1, from which each of the challenged claims ultimately depends. Pet. 25. 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. *Id*. at 50 (citing Ex. 1017, 11). Additionally Petitioner asserts that Prevenar discloses using sodium chloride as an excipient. *Id*. at 47 (citing Ex. 1017, 14[12]). Prevenar does not teach that its vaccine comprises a buffer. *Id*. at 25. 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 48 (citing Ex. 1010 ¶ 179; Ex. 1011, 1:6–7).

[12] In view of the concurrent citation to § 6.1, reference by the Petition to page 16 of Exhibit 1017, rather than page 14, appears to be an inadvertent typographical error.

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 47–48 (citing Ex. 1011, 1:27–2:3; 5:17–20, 5:28). Petitioner asserts that Chiron teaches that the addition of histidine is advantageously biocompatible and safe, and enhances pH and antigen stability. *Id*. at 48–49 (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 that include aluminum salt adjuvants. *Id*. at 48 (citing Ex. 1010 ¶ 178; 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 49 (quoting Ex. 1011, 5:3–4). According to Petitioner, because Prevenar's vaccine comprises acidic antigens, 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*. (citing Ex. 1010 ¶ 182; Ex. 1045, 22).

As for the siliconized container means, Petitioner asserts that an approved formulation of the Prevenar vaccine is provided in "'pre-filled syringe (Type I glass),' which was known to be siliconized." Pet. 50 (quoting Ex. 1010 ¶ 187 (quoting 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. 51 (citing Ex. 1010 ¶ 188). 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*. Petitioner asserts that such adsorption is taught by Prevenar and Chiron. *Id*. (citing Ex. 1017, 11; Ex. 1011, 4:5).

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 that include aluminum phosphate adjuvant, such as those disclosed by Chiron and Prevenar. Pet. 52–53 (citing Ex. 1010 ¶ 195).

Turning to the challenged dependent claims, with regard to claims 7–9, Petitioner relies on the same disclosures by Chiron described in conjunction with the asserted ground of unpatentability based on Chiron, Smith, and Elan, discussed in Part II.C.4, above. Petitioner additionally asserts that it would have been obvious to modify Prevenar to include histidine buffer, as required by claim 8, for the reasons set forth above with respect to claim 1. Pet. 53 (citing Ex. 1010 ¶ 200). Petitioner also contends that Prevenar's disclosure of sodium chloride as an excipient, in conjunction with Chiron's teachings concerning the inclusion of sodium salt in vaccine

formulations, renders claim 9 obvious. *Id*. at 54 (citing Ex. 1017, 14; Ex. 1011, 5:28).

With regard to claims 12, 13, 15, and 16, Petitioner reiterates its position that it would have been obvious to incorporate the histidine buffer of Chiron into the formulation of Prevenar, and further points out that each of Chiron and Prevenar discloses the use of sodium chloride and aluminum phosphate in vaccine formulations. Pet. 54–55 (citing Ex. 1017, 9, 14; Ex. 1011, 5:28, 11:30–12:15); *see also* supra, Part II.C.4.

Concerning the additional requirement of claims 13 and 16 that the histidine buffer have a pH of 5.8, relying on the same arguments detailed above in Part II.C.4, Petitioner asserts that arriving at the claimed pH would have been a matter of routine optimization. Pet. 55–56 (citing Ex. 1010 ¶¶ 209–211, 21) *id*. at 58 (citing Ex. 1010 ¶¶ 216–217).

As for the further requirement of claims 15 and 16 that the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, Petitioner contends that Prevenar discloses seven pneumococcal polysaccharides, each conjugated to the CRM_{197} carrier protein. Pet. 57 (citing Ex. 1010 ¶¶ 214–215; Ex. 1017, 9); *id*. at 58 (citing Ex. 1010 ¶¶ 216–217; Ex. 1017, 9).

With respect to claims 21 and 22, which require the use of succinate as a buffer, and further specify buffer concentration and pH, Petitioner relies on the same arguments detailed in Part II.C.4 to support its contention that the use of succinate buffer in place of histidine buffer at the recited concentration and pH would have been a matter of routine optimization. Pet. 59–60 (citing Ex. 1010 ¶¶ 218–221; Ex. 1011, 5:12–13).

Based upon our review of the current record, we discern no deficiency in Petitioner's characterization of the cited references and the knowledge in the art, or in Petitioner's assertions as to the reasonable inferences an ordinary artisan would make from those references. Thus, based on the information presented at this stage of the proceeding, and in light of our preliminary claim constructions, Petitioner has demonstrated sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of independent claims 7–9, 12, 13, 15, 16, 21, and 22 over the combined references.

Patent Owner focuses its arguments predominantly on sole independent claim 1; dependent claims 21 and 22 are the only challenged claims directly addressed. Patent Owner asserts that the Petition fails "to identify any single reference" teaching the recited formulation "comprised in a siliconized container means." Prelim. Resp. 35. Patent Owner acknowledges that the Petitioner explains that "Prevenar 2005 shows prefilled syringes, a second reference (EX1076) shows use of butyl for the syringe tip cap and stopper, and a third reference (EX1045) and a fourth reference (EX1047) show that siliconization is required so the plunger can slide smoothly through the syringe." *Id*. at 35–36. According to Patent Owner, despite those assertions, "[t]he fact remains that Prevenar 2005 nowhere states that the syringe is siliconized and certainly does not recognize the problem that silicone oil can induce aggregation of the polysaccharide protein conjugate formulation." *Id*. at 36. Further, Patent Owner asserts that the Petition fails to show an appropriate rationale why a person of ordinary skill in the art would have combined the cited references

to arrive at the conclusion Prevenar's syringes were necessarily siliconized. *Id*.

Although we agree with Patent Owner that the Petition does not show that Prevenar expressly teaches that its prefilled syringes, butyl rubber stopper, and syringe tip cap are siliconized, such a showing is not required in an obviousness analysis. Instead, Petitioner has asserted that a person of ordinary skill in the art that would have understood that those items were inherently siliconized. Based upon the current record, we determine that Petitioner has sufficient established such inherency by showing that Prevenar vaccine was provided in prefilled syringes and providing, at this time, uncontroverted declaration testimony that it was standard industry practice to lubricate components of syringes with silicone oil and that "there were no suitable alternatives to silicone oil for lubricating the glass barrel interiors of pre-filled syringes" at the time of the invention. Pet. 9–10; Ex. 1010 ¶¶ 13, 35–42.

On the current record, we are also unpersuaded by Patent Owner's assertion that Petitioner did not provide a rationale for combining references describing the siliconization of pharmaceutical containers with Prevenar. Prelim. Resp. 36. Such references were relied upon to show the general knowledge of a person of ordinary skill in the art with respect to the use of silicone oil to lubricate container means, such as those disclosed in Prevenar. Moreover, those references were identified by Petitioner's Declarant, Dr. Kalonia, in support of testimony as to the siliconization of syringe components at the time of the invention. *See, e.g.*, Ex. 1010 ¶¶ 13, 35–42.

Patent Owner also asserts that the Petition fails "to show any reference recognizing the problem of silicone induced aggregation or showing a formulation with the claimed ingredients that inhibits aggregation induced by a siliconized container." Prelim. Resp. 36. However, as Petitioner correctly asserts, a showing of obviousness does not require evidence that the prior art appreciated an inherent property recited in a claim for a known composition. Pet. 51, n.13 (citing *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009); *In re Spada*, 911 F.2d 705, 708–09 (Fed. Cir. 1990)). According to Patent Owner, Petitioner's inherency argument is not supported with "evidence, either from the prior art or testing data, that Prevenar 2005's formulation inhibited aggregation." *Id*. at 37. According to Patent Owner, the Board's decision in *Sandoz Inc. v. EKR Therapeutics, LLC*, IPR2015-00007, Paper 20, is applicable here. *Id*. at 37.

We disagree with Patent Owner. In *Sandoz*, the challenged claims were directed to methods for making certain pharmaceutical compositions comprising the steps of providing a solution containing an active ingredient, adjusting the pH of the composition to be within a certain range, diluting the composition to achieve a final active ingredient concentration within a specific range, and filling pharmaceutically acceptable containers with the premixed composition. *Id*. at Paper 20, 3. The claims further required the solution, when stored in a container for at least one year at room temperature, to exhibit less than a 10% decrease in the concentration of the active ingredient, and a total impurity formation of less than about 3%. *Id*. The panel judges in that case determined that the petitioner did not present sufficient evidence to show that the methods of the cited prior art provide a

composition having the required final active ingredient concentration, or a reasonable basis for believing that the impurity-formation limitation is necessarily present in, or is the natural result of the combined teachings of the cited prior art. *Id*. at Paper 20, 10–11.

Unlike in *Sandoz*, the challenged claims at issue here are not directed to methods of making a composition, or to achieving any specific concentration of active or percentage of impurity formation. Rather, the challenged claims are directed to formulations comprised in a siliconized container means, wherein the formulation inhibits aggregation induced by the container means. Thus, in the instant case, Petitioner does not rely on inherency, as in *Sandoz*, to supply any specific stability or concentration requirements, as the claims do not recite any such specific limitations. Instead, Petitioner and Dr. Kalonia have explained persuasively, on the current record, that because Prevenar's composition, as modified by the addition of Chiron's histidine, yields a formulation including each of the ingredients recited by claim 1, the recited property of the formulation must be present, or the natural result of the combination of elements disclosed by the prior art. Pet. 51; Ex. 1010 ¶ 188. Petitioner and Dr. Kalonia further explain that Specification describes the recited benefit of that formulation in inhibiting silicone-induced aggregation is simply due to the interaction of two ingredients of the combined prior art, i.e., adsorption of antigens onto aluminum phosphate adjuvants. Pet. 15, 51; Ex. 1010 ¶ 188.

Patent Owner asserts that Chiron teaches away from using histidine buffer in the Prevenar formulation. Prelim. Resp. 38–39. According to Patent Owner, based upon Example 2 of Chiron, adding histidine to

Prevenar's formulation would cause the conjugate to be only minimally absorbed, leaving the remaining conjugate free to aggregate. *Id.* Even if true, the challenged claim requires a formulation that "*inhibits* aggregation by the siliconized container means." Ex. 1001, 31:10–12 (emphasis added). Patent Owner has not explained why a formulation comprising a conjugate that inhibits 50% of such aggregation does not meet the claim limitation. As Petitioner has explained, Chiron teaches that histidine enhances the stability of such vaccines by explaining that "[t]he use of histidine in combination with an aluminum phosphate (particularly a hydroxyphosphate) is particularly advantageous for acidic antigens." Pet. 49 (quoting Ex. 1011, 5:3–4).

Patent Owner similarly asserts that an ordinarily skilled artisan would not have had reason to, or a reasonable expectation of success in modifying Prevenar to incorporate a buffer as taught by Chiron. Prelim. Resp. 40–43. In particular, although Patent Owner acknowledges that "Chiron 2003 suggests that histidine will improve adsorption of antigen to aluminum versus a formulation containing no buffer," it nevertheless contends that the level of adsorption shown by Chiron is "not improved enough to rise to the level of a motivation to combine." Prelim. Resp. 41. Patent Owner further argues that because Prevenar 7 was licensed for use in the United States without histidine, a skilled artisan would not have been inclined to add histidine to the already licensed formulation. *Id.*

We do not agree. On the current record, we are persuaded by Dr. Kalonia's testimony that an ordinarily skilled artisan would have optimized the formulation of Prevenar with buffer, and had a reasonable

expectation of success in so doing, because "[b]uffer was a common component of vaccines, and Chiron 2003 teaches that histidine buffer confers pH- and antigen-stability to a pneumococcal conjugate formulation with aluminum phosphate adjuvant (as in Prevenar 2005), as well as enhanced adsorption to the aluminum phosphate adjuvant." Ex. 1010 ¶ 195. Accordingly, because we determine, based on the current record, that Chiron teaches the benefits of including histidine in its formulation, *i.e.*, improving pH- and antigen-stability, we do not find Patent Owner's contentions persuasive.

Focusing on claims 21 and 22, Patent Owner reasserts its arguments, addressed in Part II.C.4. above that "[n]one of Chiron 2003's disclosures meets the claim 21 and 22's requirements of a buffer at pH 5.8–6.0 and 5 mM concentration." Prelim. Resp. 40. Patent Owner likewise reiterates its position that an ordinarily skilled artisan would not have had reason to, or a reasonable expectation of success in combining Prevenar and Chiron to arrive at the inventions of claims 21 and 22. *Id*. at 42–44. For the reasons detailed in Part II.C.4 above, however, we do not agree. Accordingly, at this stage in the proceeding, Patent Owner's arguments do not persuade us that Petitioner has not established a reasonable likelihood of prevailing in showing that claims 21 and 22 would have been obvious.

Based on the current record, we note that the Petitioner in this proceeding has shown that (a) a person of ordinary skill in the art would have had a reason to combine Chiron's histidine buffer with Prevenar's vaccine formulation, and that doing so would have yielded formulations comprising each of the ingredients recited in the challenged claims at the

required concentration and pH, (b) that a person of ordinary skill in the art would have understood that Prevenar's prefilled syringes had siliconized components, and (c) Prevenar's modified formulation inherently inhibits aggregation induced by the siliconized container means. Thus, at this stage in the proceeding, based upon the current record and our preliminary claim constructions, we are persuaded that the combined teachings of Prevenar and Chiron would have suggested the invention of the challenged claims to a person of ordinary skill in the art. Patent Owner's arguments in the Preliminary Response do not persuade us otherwise.

Based on the foregoing, therefore, we determine that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent are unpatentable. Accordingly, we institute an *inter partes* review of those claims.

E. Obviousness Ground of Unpatentability Based on Merck and the '787 patent

Petitioner asserts that claims 13 and 16 are unpatentable under § 103(a) as obvious in view of Merck and the '787 patent. Pet. 60–65. Patent Owner disagrees. Prelim. Resp. 44–47.

This asserted ground of unpatentability addresses two claims—claims 13 and 16—for which, as set forth above, we institute review on two separate grounds—obviousness based on the combined teachings of Chiron, Smith, and Elan, and obviousness based on the combined teachings of Prevenar and Chiron. Accordingly, on this record, for reasons of

administrative efficiency and to ensure timely completion of this proceeding, we exercise our discretion to not institute *inter partes* review of claims 13 and 16 for obviousness based on Merck and the '787 patent. 37 C.F.R. § 42.108(a) ("the Board may authorize the review to proceed . . . on all or some of the grounds of unpatentability asserted for each claim"); *see also* 35 U.S.C. § 314(a) (authorizing institution of an inter partes review under particular circumstances, but not requiring institution under any circumstances); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1368 (Fed. Cir. 2016) ("[U]nder [37 C.F.R. § 42.108], it is clear that the Board may choose to institute some grounds and not institute others as part of its comprehensive institution decision.").

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent are unpatentable. Accordingly, we institute an *inter partes* review of those claims.

At this stage in the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an inter partes review is instituted as to claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent on the following grounds of unpatentability:

A. Claims 7–9, 12, 13, 15, 16, 21, and 22 under 35 U.S.C. § 103(a) as obvious over Chiron, Smith, and Elan; and

B. Claims 7–9, 12, 13, 15, 16, 21, and 22 under 35 U.S.C. § 103(a) as obvious over Prevenar and Chiron; and

FURTHER ORDERED that no other ground of unpatentability asserted in the Petition is authorized for this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision.

PETITIONER:

Arlene L. Chow
Ernest Yakob
HOGAN LOVELLS US LLP
arlene.chow@hoganlovells.com
ernest.yakob@hoganlovells.com

PATENT OWNER:

John Scheibeler
Dimitrios T. Drivas
WHITE & CASE LLP
jscheibeler@whitecase.com
ddrivas@whitecase.com