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Paper No. 9
Entered: June 13, 2017

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*.

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

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.").

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon consideration of the Petition and Preliminary Response, we determine Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–6, 10–11, 14, and 17–20. 35 U.S.C. § 314(a). Accordingly, we institute an *inter partes* review of those claims.

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. *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^{TM}80 significantly enhances the stability and inhibits precipitation of an immunogenic composition." *Id*. at 10:35–39.

The container means include, 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).

Thus, 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 Claim

Independent claim 1 and of the ’999 patent is 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.

Ex. 1001, 31:7–12.

Claims 2–6, 10–11, 14, and 17–19 depend directly from claim 1. Claim 20 depends directly from claim 19.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–6, 10–11, 14, and 17–20 of the ’999 patent on the following grounds:

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

Petitioner also relies on the Declarations of Dennis L. Kasper, M.D. (Ex. 1007) and Devendra Kalonia, Ph.D. (Ex. 1009).

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).

[1] Summary of Product Characteristics for Prevenar Suspension for injection: Pneumococcal saccharide conjugated vaccine, adsorbed, Annex 1:1–15 (2005). Ex. 1017 ("Prevenar").
[2] Patent Application Publication No. WO 03/009869 A1 by Mario Contorni et al., published February 6, 2003. Ex. 1011 ("Chiron").
[3] de la Peña et al., *Present and future of the pneumonia vaccination*, 24(4) PEDIATRIKA 47–55(2004) (English Translation). Ex. 1015 ("Peña").

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; 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. 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 '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. 12–13. 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 13. 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 13–14 (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 15. 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 15. 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 13.

At this stage in the proceeding, and based on the current record, we determine that the Specification set 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. 13. 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 15. 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 immunogenecity. Instead, the claims recite another

property of the formulation, i.e., inhibition of aggregation/precipitation[4] 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 comprise 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, so long as the formulation comprising that element 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 37 (citing Ex. 1009 ¶ 95). For example, Petitioner asserts that the plain language of the claim does not require that it is the aluminum salt that 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,"

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

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*. at 37.

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. 17. Patent Owner, however, asserts that "[t]he plain language of the claim 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 15–16. 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 16. 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 16. According to the Patent Owner, under that construction, "the claim 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 37. 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. 16 (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. 16, 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.[5]

[5] 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

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. in 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 disagrees 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. in

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the conjugate." *See* Prelim. Resp. 16–20.

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.

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. 1009, 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 over Prevenar and Chiron

Petitioner asserts that claims 1–6, 10–11, 14, and 17–20 are unpatentable over the combination of Chiron, Smith, and Elan. Pet. 38–58. Patent Owner disagrees. Prelim. Resp. 21–35.

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. 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 aluminium 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. 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.

3. Obviousness Analysis

Petitioner contends that Prevenar teaches two of the three ingredients recited in the formulations of the challenged claims. 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 aluminium phosphate. Pet. 39–43 (citing Ex. 1017, 11). Additionally Petitioner asserts that Prevenar discloses using sodium chloride. *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 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. *Id*. at 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, 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).

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

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. 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).

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 and Prevenar that have aluminum phosphate adjuvant. Pet. 45 (citing Ex. 1009 ¶ 142).

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 shown sufficiently that there is a reasonable likelihood that it would prevail in showing the

unpatentability of independent claim 1 over the combined references. Further, at this stage in the proceeding, for reasons discussed by Petitioner (*see* Pet. 46–58), we are satisfied that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of dependent claims 2–6, 10–11, 14, and 17–20.

Our remaining analysis in this Decision focuses on the deficiencies in Patent Owner's arguments in its Preliminary Response as to the challenged claims.

To begin, Patent Owner asserts that the Petition fails "to identify any single reference" teaching the recited formulation "comprised in a siliconized container means." Prelim. Resp. 21. 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 21–22. According to Patent Owner, despite those assertions, "[t]he fact remains that the primary reference 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 22. 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. Petitioner asserts that a person of ordinary skill in the art that would have understood that those items were siliconized. Pet. 44 (citing Ex. 1009 ¶ 136). Based upon the current record, we determine that Petitioner has sufficiently established that assertion 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. Ex. 1009 ¶ 13.

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. 22. 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. 1009 ¶¶ 13, 34–41.

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." Pet. 22. 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. 44 (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 induced by siliconized container means." *Id*. at 24. According to Patent Owner, the Board's decision in *Sandoz Inc. v. EKR Therapeutics, LLC*, IPR2015-00007, Paper 20, is applicable here. *Id*. at 23–24. We disagree. 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. 44–46. Petitioner and Dr. Kalonia further explain that the 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. *Id*. at 20, 45; Ex. 1009 ¶¶ 138–140.

Patent Owner asserts that Chiron teaches away from using histidine buffer in the Prevenar formulation. Prelim. Resp. 25–26. According to Patent Owner, based upon Example 2 of Chiron, adding histidine to Prevenar's formulation would cause the conjugate to be only minimally adsorbed, leaving the remaining conjugate free to aggregate. *Id*. Even if true, the challenged claim requires a formulation that "*inhibits* aggretation 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. 42 (quoting Ex. 1011, 5:3–4).

As for the challenged dependent claims, Patent Owner specifically addresses claim 18. Prelim. Resp. 27. Patent Owner accurately characterizes claim 18, which depends directly from claim 1, as further requiring the one or more polysaccharide-protein conjugates to comprise "13 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." *Id*. Patent Owner asserts that Petitioner does not provide any reference disclosing the 13-valent conjugate formulation recited in claim 18. *Id*. Patent Owner acknowledges that a 7-valent conjugate was known in the art at the time of the invention, but asserts that a person of ordinary skill in the art would not have a reasonable expectation of success with Petitioner's asserted "natural progression" from the known 7-valent conjugate to the recited 13-valent conjugate. *Id*. at 34 (citing Pet. 60). According to Patent Owner, "others in the industry have not used a single carrier protein approach." *Id*. Patent Owner asserts that "given the variability of carrier proteins used in the industry and the unpredictability by which silicone oil interacted with protein and the different polysaccharides used in vaccines, a [person of ordinary skill in the art] would not have a reasonable basis to make the claimed 13-valent pneumococcal conjugate vaccine formulation of claim 18." *Id*. at 35.

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 claim 18 would have been obvious. Petitioner and Dr. Kasper explain that the 13 serotypes of claim 18 were known in the

art at the time of the invention. Pet. 55; Ex. 1007 ¶¶ 45–46 (discussing Peña, Ex. 1015). Patent Owner's assertion that "others in the industry have not used a single carrier protein approach," does not establish, on its own, that a person of skill in the art would not have had the skill or been motivated with a reasonable expectation of successfully doing so. Indeed, Patent Owner acknowledges the single carrier protein approach was known, and specifically, that the prior art disclosed a 7-valent vaccine conjugated to only to CRM_{197}. Prelim. Resp. 34. Further, Patent Owner has not explained persuasively how the asserted unpredictability by which silicone oil interacts with protein would have discouraged a person of ordinary skill in the art from making such a formulation that inhibits aggregation induced by the siliconized container means, wherein the protein carrier for each conjugate does not vary.

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 provides each of the ingredients recited for the formulation of independent claim 1, (b) that a person of ordinary skill in the art would have understood that Prevenar's pre-filled 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, Chiron, and the knowledge in the art would have taught or suggested the invention of independent claim 1 to a person of ordinary skill in the art. Moreover, for reasons discussed by

Petitioner (*see* Pet. 50–62), we are satisfied that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of dependent claims 2–6, 10–11, 14, and 17–20. Patent Owner's arguments in the Preliminary Response do not persuade us otherwise.

Accordingly, we determine that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1–6, 10–11, 14, and 17–20 of the '999 patent are unpatentable. Accordingly, we institute an *inter partes* review of those claims.

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. Prelim. Resp. 21–35.

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.

2. Obvious Analysis

Claim 18 depends directly from independent claim 1. Petitioner relies on it argument raised with respect to independent claim 1 that the combined teachings of Prevenar and Chiron render the limitations of the independent claim obvious. Pet. 58. As discussed with respect to ground 1, we have determined on the current record that Petitioner has established a reasonable likelihood of prevailing in showing that the combined Prevenar and Chiron teach or suggest each of the limitations of independent claim 1. To address the additional limitations raised in claim 18, Petitioner relies upon Peña to show that the 13-valent conjugates recited by those dependent claims were known to one of ordinary skill in the art at the time of the invention. *Id*.

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 or 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 asserts that a person of ordinary skill in the art would not have considered Peña as teaching a natural progression in the development of higher-valent vaccines that would be immunogenic because Peña did not disclose any specific such formulation. Prelim. Resp. 31–32. Petitioner, however, has provided a reasonable explanation why a person of skill in the art would have understood Peña's conjugates to have included the same CRM_{197} carrier and that use of such carrier would have inhibited aggregation induced by a siliconized container. Pet. 59. Patent Owner does

not persuade us otherwise by asserting Peña did not expressly disclose the claimed formulation.

Further Patent Owner asserts that Peña "teaches away from liquid formulations in single-use syringes for higher-valent vaccines." Prelim. Resp. 32. In support of that position, Patent Owner asserts that Peña disclosed a 9-valent pneumococcal vaccine in a lyophilized formulation. *Id*. (citing Ex. 1015, 8; Ex. 2014, 1). According to Patent Owner, "[a] lyophilized formulation, because of its very nature, could not have been dispensed in a liquid formulation in a siliconized container means." *Id*. Thus, Patent Owner asserts that "Pena 2004 would not have motivated a person of ordinary skill to formulate a higher-valent vaccine in the liquid formulation of Prevenar 2005 and Chiron 2003." *Id*.

Without more, that argument is unpersuasive. Patent Owner has not explained, or provided evidence, that the referenced lyophilized formulation was not simply a preferred formulation, as opposed to a necessary one. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). In other words, Patent Owner has not shown that Peña or knowledge in the art taught away from Petitioner's proposed modification of the combined Prevenar-Chiron formulation by merely referring to a higher-valent vaccine that was prepared as a lyophilized formulation.

Patent Owner asserts also that a person of ordinary skill in the art would not have had a reasonable expectation of successfully using a common carrier to prepare a 13-valent conjugate vaccine. Prelim. Resp. 33–35. According to Patent Owner, others in the industry tried to do so and "ultimately required a three-carrier approach for a stable formulation . . . ." *Id*. at 42 (citing Ex. 2005, 14). Upon review of the those examples cited by

Patent Owner, we do not find any discussion supporting Patent Owner's assertion that a person of skill in the art would have been discouraged from using a common carrier in the Prevenar-Chiron formulation. In particular, Patent Owner has not referred us to any discussion in those exhibits explaining that a three carrier approach was selected out of a necessity, and that such necessity would have discouraged a person of skill in the art from using a common carrier in Petitioner's modified Prevenar-Chiron formulation.

Accordingly, we determine that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claim 18 of the '999 patent is unpatentable and that Patent Owner's arguments do not persuade us otherwise. Accordingly, we institute an *inter partes* review of those claims.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1–6, 10–11, 14, and 17–20 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.

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 1–6, 10–11, 14, and 17–20 of the '999 patent on the following grounds of unpatentability:

A. Claims 1–6, 10–11, 14, and 17–20 under 35 U.S.C. § 103(a) as obvious over Prevenar and Chiron; and

B. Claim 18 under 35 U.S.C. § 103(a) as obvious over Prevenar, Chiron, and Peña; 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.

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