Trials@uspto.gov
571.272.7822

Paper 72
Entered: November 5, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

WYETH LLC,
Patent Owner.

IPR2017-00380
Patent 8,562,999 B2

Before FRANCISCO C. PRATS, ERICA A. FRANKLIN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.[1]

FRANKLIN, *Administrative Patent Judge*.

JUDGMENT
Final Decision on Remand
Determining Claims 1–6, 10, 11, 14, 17, 19, and 20 Unpatentable
35 U.S.C. §§ 144, 318

[1] As explained in the Panel Change Order, Administrative Patent Judge Francisco C. Prats replaces Administrative Patent Judge Jacqueline T. Harlow, who is no longer with the Patent Trial and Appeal Board. *See* Paper 63.

I. INTRODUCTION

We address this case on remand after a decision by the U.S. Court of Appeals for the Federal Circuit in *Merck Sharp & Dohme Corp. v. Wyeth LLC*, 792 F. App'x 813 (Fed. Cir. 2019) ("*Merck*").

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

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

Petitioner and Patent Owner each filed a Motion to Exclude Evidence. Papers 34 and 38. Each party filed an Opposition to the other party's motion. Papers 43 and 47. Each party filed also a Reply to the other party's Opposition. Papers 50 and 55.[2] Patent Owner filed Motions for Observation on Cross-Examination Testimony. Papers 39 and 40. Petitioner filed a Response to each of Patent Owner's Motions for Observation. Paper 44 and 45.

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

On February 27, 2018, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 56 ("Tr."). We issued a Final Written Decision, in accordance with 37 C.F.R. § 42.73, on June 8, 2018. Paper 59 ("FWD"). In the Final Written Decision, we determined that Petitioner had shown by a preponderance of the evidence that claims 1–6, 10, 11, 14, 17, 19, and 20 are unpatentable. *See* 35 U.S.C. § 316(e). Additionally, we determined that Petitioner had not shown by a preponderance of the evidence that claim 18 is unpatentable. In the Final Written Decision, we also addressed the parties' Motions to Exclude Evidence, as set forth below in Section III. FWD 37–40.

Neither party requested a rehearing of any matter decided in the Final Written Decision. Petitioner, however, appealed the Final Written Decision to the United States Court of Appeals for the Federal Circuit, challenging only our determination that Petitioner had not shown by a preponderance of the evidence that claim 18 is unpatentable.

On November 26, 2019, the Federal Circuit issued a decision in Merck vacating and remanding the Final Written Decision for further proceedings. *Merck*, 792 F. App'x at 814. The Court entered the Mandate on January 2, 2020. Mandate, *Merck Sharp & Dohme Corp. v. Wyeth LLC*, No. 18-2133 (Fed. Cir. Jan. 2, 2020), ECF No. 71. The Court found that our findings were insufficient to support a determination that Petitioner failed to demonstrate a motivation or a reasonable expectation of success for modifying the prior art to yield the subject matter of dependent claim 18. *Merck*, 792 F. App'x at 817. In particular, the Federal Circuit explained that the Board "did not address the evidence as to whether someone skilled in the art would have been motivated to combine the 13 serotypes [disclosed in the

prior art and recited by claim 18] into a CRM_{197} conjugate or whether the potential loss of immunogenicity would have dissuaded someone skilled in the art from making such a combination." *Id.* at 818.

On January 24, 2020, we held a conference call with the parties to discuss their proposals for a procedure on remand, in view of the Board's Standard Operating Procedure 9 ("SOP 9"), App'x 2, "Guidance for Parties Regarding Remand Procedures." See Paper 66 (Conduct of the Proceeding Order). As a result, we authorized each party to file a table highlighting arguments and evidence of record previously asserted in this proceeding regarding the challenge to claim 18. Paper 66, 4. We explained that submission of the table was not an opportunity to incorporate by reference any additional evidence or arguments to their previous submissions regarding claim 18. Id. at 5. Thereafter, such briefing was completed. *See* Paper 67 (Patent Owner's Citation Table), Paper 68 (Petitioner's Citation Table).

Although the Federal Circuit vacated the Final Written Decision only with respect to "the Board's obviousness findings with respect to claim 18," this Decision on Remand includes: our previous, unappealed analysis on the patentability of challenged claims 1–6, 10, 11, 14, 17, 19, and 20; [3] our previous determination on the parties' Motions to Exclude Evidence, with

[3] Patent Owner's appeal was limited to claim 18 and did not challenge the findings or conclusions regarding claims 1–6, 10, 11, 14, 17, 19, and 20. Our original analysis of claims 1–6, 10, 11, 14, 17, 19, and 20 is included in this Decision on Remand only for completeness and we have not revisited those claims here.

revised remarks relating to Exhibit 1037; [4] and our further discussion regarding the challenges to claim 18. In other words, in this Decision on Remand, we revisit only the challenges to claim 18 and the Motion to Exclude Exhibit with respect to 1037.

A. Related Proceedings

We issued Final Written Decisions in two additional *inter partes* reviews challenging claims of the '999 patent in IPR2017-00378 and IPR2017-00390. Petitioner has appealed our Final Written Decision in IPR2017-00378 and the Federal Circuit has vacated and remanded that decision for the same reasons involved here. *Merck*, 792 F. App'x at 813–819. The Decision on Remand in that case is issued concurrently with the Decision on Remand in the instant case.

B. The '999 patent

In some aspects, the '999 patent relates to formulations comprising an immunogen in the form of a polysaccharide-protein conjugate, a pH buffered saline solution, and an aluminum salt. Ex. 1001, 2:62–64, 12:9–15. The Specification defines the term "polysaccharide" as including "any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including, but not limited to, a 'saccharide', an 'oligosaccharide', a 'polysaccharide', a 'liposaccharide', a 'lipo-oligosaccharide (LOS)', a 'lipopolysaccharide (LPS)', a 'glycosylate', a

[4] Petitioner submits Exhibit 1037 and identifies it as "Ireland EPA Memorandum regarding 'Application for IPC licence from AHP Manufacturing B.V. Trading as Wyeth Medica Ireland for the Wyeth BioPharma Campus at Grange Castle Reg. No. 652' (June 11, 2003)." Pet. viii.; Ex. 1037 ("Ireland EPA Memo").

'glycoconjugate' and the like." *Id*. at 16:32–38.

In certain embodiments, the compositions further comprise a surfactant. *Id*. at 12:65–67. The Specification explains that a suitable surfactant is one that "stabilizes and inhibits aggregation of an immunogenic composition described herein." *Id*. at 13:9–12. According to the Specification, in one aspect, the "invention relates to the unexpected and surprising results that formulating an immunogenic composition with a surfactant such as Tween™80 significantly enhances the stability and inhibits precipitation of an immunogenic composition." *Id*. at 10:35–39.

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

C. Illustrative Claims

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

> 1. A formulation comprising (i) a pH buffered saline solution, wherein the buffer has a pKa of about 3.5 to about 7.5, (ii) an aluminum salt and (iii) one or more polysaccharide-protein conjugates, wherein the formulation is comprised in a siliconized container means and inhibits aggregation induced by the siliconized container means.
>
> 18. The formulation of claim 1, wherein the one or more polysaccharide-protein conjugate comprises an *S. pneumoniae* serotype 4 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6B polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 9V polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 14 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 18C polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 19F polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 23F polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 1 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 3 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 5 polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 6A polysaccharide conjugated to a CRM197 polypeptide, an *S. pneumoniae* serotype 7F polysaccharide conjugated to a CRM197 polypeptide and an *S. pneumoniae* serotype 19A polysaccharide conjugated to a CRM197 polypeptide.

Ex. 1001, 31:7–12, 32:24–44.

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

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of the claims as follows:

Claim(s) Challenged	35 U.S.C. §	References
1–6, 10, 11, 14, 17–20	103(a)	Prevenar[5], Chiron[6]
18	103(a)	Prevenar, Chiron, Peña[7]

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

II. ANALYSIS

A. Claim Construction

For petitions filed before November 13, 2018—as here—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

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

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

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

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

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

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

> a conjugate resulting from reacting any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including but not limited to, a saccharide, an oligosaccharide, a polysaccharide, a

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

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

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

Patent Owner draws our attention to the Specification discussion in the "Background of the Invention" section that "the immunogenic composition must be active throughout its 'expected' shelf life, wherein any breakdown of the immunogenic composition to an inactive or otherwise undesired form (e.g., an aggregate) lowers the total concentration of the product." *Id*. (quoting Ex. 1001, 1:41–46). According to Patent Owner and

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

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

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

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

In light of those Specification descriptions, we determine that the broadest reasonable construction of the claim phrase "polysaccharide-protein conjugates" refers to an immunogenic composition resulting from reacting any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including, but not limited to, a saccharide, an oligosaccharide, a polysaccharide, a liposaccharide, a lipo-oligosaccharide, a lipopolysaccharide, a glycosylate, a glycoconjugate, and the like with a carrier protein that is amenable to standard conjugation procedures.

Although we recognize that the claimed invention is directed toward an immunogenic composition, we also note that the claims do not recite any specific level of immunogenicity for the composition. The Specification explains that the invention "broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions." Ex. 1001, 2:53–55. The Specification describes aggregation as an indicator of physical/thermal stability of the immunogenic composition. *Id.* at 2:7–8.

Breakdown of the composition to an undesired form (e.g., an aggregate) lowers the total concentration of the product. *Id*. at 1:43–46.

Insofar as Patent Owner asserts that the claims require "measuring antigenicity to determine the extent of the loss of antigenicity due to silicone-induced aggregation," as in Example 4 of the Specification, PO Resp. 15, we disagree. Although Example 4 discusses total antigenicity (and loss), the claims do not require the formulation to retain a particular degree of immunogenicity. Instead, the claims are directed to a formulation comprising a polysaccharide-protein conjugate, i.e., an "immunogen," *see, e.g.*, Ex. 1001, 14:19–23, wherein the formulation inhibits aggregation[8] induced by the siliconized container means. The presence of a polysaccharide-protein conjugate confers the immunogenic element of the claim. While performing an immunoassay to measure loss of antigenicity, as in Example 4, may provide information regarding whether silicone-induced aggregation has occurred, such an assay is not required to meet the "protein-polysaccharide conjugate" element of the claim. Moreover, as explained in each example described in the Specification, the occurrence of aggregation/precipitation may be detected upon visual inspection. *See, e.g.*, Ex. 1001, 27:6–11 (discussing visual inspection for precipitation).

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

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

example, Petitioner asserts that the plain language of the claim does not require that the aluminum salt inhibits silicone-induced aggregation. *Id*. at 37–38 (citing Ex. 1009 ¶ 96). According to Petitioner, because independent claim 1 recites a "formulation" followed by an open-ended term, "comprising," any element(s) comprised in the formulation may contribute the required inhibition, so long as the formulation as a whole "inhibits aggregation induced by the siliconized container means." *Id*.

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

Further, Patent Owner asserts that the "broadest reasonable interpretation of claim 1 should go no further than to read on embodiments that contain the three recited ingredients in a formulation that meets the functional property limitation." *Id*. at 21. According to Patent Owner, the functional requirement of inhibiting aggregation induced by the siliconized container means must be satisfied by "a formulation of the three specifically recited ingredients [buffered saline solution, aluminum salt, and polysaccharide-protein conjugate], without any un-recited ingredient(s)." *Id*. at 20.

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

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

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

B. Level of Ordinary Skill in the Art

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

Petitioner asserts that a person of ordinary skill in the art at the time of the invention would have had either (a) "a Ph.D. degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least 2 years of work experience formulating protein-based compositions, and would have had familiarity or experience with the general components of bacterial vaccines," or (b) "a Master's degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least 4 years of work experience formulating protein-based compositions, and would have had familiarity or experience with the general components of bacterial vaccines." Pet. 32 (citing Ex. 1009 ¶ 80).

Patent Owner relies upon its definition of the level of ordinary skill in the art set forth in the Patent Owner Preliminary Response. PO Resp. 21. In that filing, Patent Owner disagreed with Petitioner's definition insofar as it suggests the field of invention involved protein-based formulations. Prelim. Resp. 10. According to Patent Owner, a person of ordinary skill in the art at

the time of the invention would have had either (a) "a Ph.D. degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least two years of work experience formulating polysaccharide-protein conjugate immunogenic compositions, and would have had familiarity or experience with the general components and formulation of bacterial vaccines," or (b) "a Master's degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least four years of work experience formulating polysaccharide-protein conjugate immunogenic compositions, and would have had familiarity or experience with the general components and formulation of bacterial vaccines." *Id*. at 10–11.

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

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

protein chemistry, at least four years of work experience involving researching silicone-induced interactions/aggregation in pharmaceuticals.

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

Petitioner does not challenge the expertise of any of Patent Owner's declarants. Patent Owner, however, asserts that Petitioner's declarants, Drs. Kalonia and Kasper, lack "experience in developing polysaccharide-protein conjugate formulations, and certainly not on a commercial scale." PO Resp. 21–22. Regarding Dr. Kalonia, Patent Owner asserts that his experience is "limited to the aggregation of proteins in formulations on a laboratory scale." *Id*. at 20. However, as described in Dr. Kalonia's declaration, such experience involves "significant research experience in protein-interface, protein-protein, and protein-excipient interactions, including interactions among protein, silicone oil and surfactants," as well as co-authoring a book chapter describing applications and concerns relating to silicone oil in biopharmaceutical containers. Ex. 1009 ¶ 7.

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

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

In support of its challenge of Dr. Kasper, Patent Owner directs us only to deposition testimony relating to Dr. Kasper's inexperience using siliconized containers with his vaccine formulations. PO Resp. 22–23 (citing Ex. 2035, 13:3–18, 35:20–23). However, as Petitioner has explained, Dr. Kasper's testimony is not offered to address silicone-induced aggregation in pharmaceuticals. Rather, Petitioner relies upon Dr. Kasper to provide testimony in his area of expertise, i.e., formulating polysaccharide-protein conjugate immunogenic compositions, and asserts that he would have had familiarity or experience with the general components and

formulation of bacterial vaccines. *See* Pet. 4 (describing Dr. Kasper as "a renowned researcher focusing on the development of human vaccines, including polysaccharide-protein conjugate vaccines").

C. Obviousness over Prevenar and Chiron

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

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

"An obviousness determination requires finding both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)).

1. Prevenar

Prevenar provides a summary of product characteristics for the Prevenar vaccine (marketed as "Prevnar"), a pneumococcal saccharide conjugated vaccine prepared as a suspension for injection. Ex. 1017, 1–2. The vaccine comprises *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, each conjugated to the CRM_{197} carrier protein and adsorbed on aluminum phosphate. *Id*. at 2. The composition also comprises sodium chloride as an excipient. *Id*. at 7. The suspension is provided in a vial with Type I glass and a grey butyl rubber stopper, either without syringe or needles, or with syringe and one needle for withdrawal and one needle for injection. *Id*.

2. Chiron

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

3. Obviousness Analysis

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

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

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

According to Petitioner, it would have been obvious to a person of ordinary skill in the art to use the histidine buffer of Chiron in the Prevenar vaccine because Chiron teaches that histidine enhances the stability of

vaccines which include aluminum salt adjuvants. Pet. 40 (citing Ex. 1009 ¶ 127; Ex. 1011, 1:31–2:3). Additionally, Petitioner asserts that Chiron teaches that "[t]he use of histidine in combination with an aluminum phosphate (particularly a hydroxyphosphate) is particularly advantageous for acidic antigens." *Id*. at 42 (quoting Ex. 1011, 5:3–4). According to Petitioner and Dr. Kasper, because Prevenar's vaccine comprises acidic antigens, a person of skill in the art would have understood from Chiron that the formulation would benefit from histidine buffer. *Id*. (citing Ex. 1007 ¶ 55). Further, Petitioner asserts that Chiron's histidine buffer is inherently within the scope of the claim limitation requiring the buffer to have a pKa of about 3.5 to about 7.5 because "the pKa with respect to the side group proton is approximately 6.0." *Id*. at 42 (citing Ex. 1009 ¶ 131; Ex. 1045,[9] 22).

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

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

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

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

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

Reason to Combine and Reasonable Expectation of Success

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

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

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

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

Each of those contentions by Patent Owner, however, are inadequately supported by the testimony of Drs. Morefield (Ex. 2121) and Thomson (Ex. 2124). The portions of the declarations of Drs. Morefield and Thomson relied upon by the Patent Owner do not refer to any evidence to support their opinions that a histidine buffer would not be a beneficial addition to the Prevenar formulation. Rather, those discussions sound of unsubstantiated theoretical concerns, and are speculative at best. At worst, certain of those theories has been refuted in the art. For example, Petitioner directs us to the testimony of one of its declarants, Dr. HogenEsch, who has a Ph.D. in Pathology and Immunology. Reply 13–16. Dr. HogenEsch explains persuasively that, contrary to the speculation of Drs. Morefield and Thomson, "histidine buffer had specifically been reported . . . not to interact with aluminum adjuvant through ligand exchange." Ex. 1122 ¶ 43. In support of this testimony, Dr. HogenEsch quotes a disclosure from US Patent No. 6,251,678 B1[10] explaining that, although phosphate-containing buffers are generally not preferred because they may interact with aluminum adjuvants, "the non interaction of histidine . . . buffers with aluminum adjuvant was demonstrated by zeta potential measurements of the surface charge of the aluminum adjuvant." *Id*. (quoting Ex. 1109, 3:24–30).

We find that the unsupported testimony offered by Patent Owner's declarants to be outweighed by rebuttal testimony from Dr. HogenEsch and the express disclosures by Chiron relied upon by Petitioner. Generally, as Petitioner and Dr. Kalonia note, Chiron teaches that buffers are a standard

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

component of vaccines. Pet. 40; Ex. 1009 ¶ 128 (citing Ex. 1011, 1:6–7). More specifically, as Petitioner asserts, Chiron teaches that adding histidine buffer to aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulations comprising a sodium salt is advantageously biocompatible and safe, and enhances pH and antigen stability. Pet. 40–41 (citing Ex. 1011, 1:6–7, 5:6–7, 15, 11:30–12:15, 14:3–17:4). Chiron teaches also that "[t]he use of histidine in combination with an aluminum phosphate (particularly a hydroxyphosphate) is particularly advantageous for acidic antigens." Ex. 1011, 6:3–4. Prevenar's formulation represents such an aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulation comprising a sodium salt, wherein the aluminum phosphate adjuvant is a hydroxyphosphate, as recognized by Dr. Morefield. *See* Ex. 2121 ¶ 37. Thus, on balance, we determine that the preponderance of the evidence supports Petitioner's contention that a person of ordinary skill in the art would have had a reason to add a histidine buffer to the Prevenar vaccine with a reasonable expectation of enhancing the stability of the product.

Inhibition of aggregation induced by the siliconized container means

Patent Owner asserts that Petitioner "fails to show that the formulation resulting from the combination of Prevenar [] and Chiron [] was known to inhibit silicone-induced aggregation." PO Resp. 25. Additionally, Patent Owner asserts that the stated mechanism of action of the claimed formulation's ability to inhibit such aggregation, i.e., via adsorption of polysaccharide-protein conjugate to the aluminum salt, was not known in the prior art. *Id*. at 26. According to Patent Owner, Petitioner has not adequately established that Prevenar's formulation, modified to include Chiron's histidine, inherently possessed the properties of the claimed

invention. *Id*. In support of that assertion, Patent Owner cites case law explaining that "[w]hat is important regarding properties that may be inherent, but unknown, is whether they are unexpected." *Id*. (quoting *Honeywell Int'l Inc. v. Mexichem Amanco Holding S. A.*, 865 F.3d 1348, 1355 (Fed. Cir. 2017).

To Patent Owner's point, we agree that an asserted inherent property in an obviousness challenge must be subjected to consideration of whether such property would have been unexpected. *See id*. Patent Owner, however, has not alleged, or provided any evidence demonstrating that the claimed formulations unexpectedly inhibit silicone-induced aggregation.[11]

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

Here, Petitioner asserts that Prevenar's formulation, modified to include Chiron's histidine buffer, comprises every recited ingredient of independent claim 1. Petitioner's inherency argument is not based upon probabilities or possibilities. Rather, Petitioner relies on the fact that

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

Prevenar's modified formulation is the formulation that is claimed, wherein the claims and the Specification of the '999 patent describe that the inhibition of silicone-induce aggregation is the natural result of the combination of elements disclosed in the prior art. Pet. 44–45; Ex. 1009 ¶ 137 (characterizing the '999 patent Specification as emphasizing that the adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation); *see PAR Pharm.*, 773 F.3d at 1196 (describing meeting high standard for inherency in an obviousness analysis when the claim limitation is the "natural result of the combination of elements explicitly disclosed by the prior art"). As Petitioner asserts, such adsorption is taught by Prevenar and Chiron. Pet. 45; Ex. 1017, 2 (polysaccharide-protein conjugates adsorbed on aluminum phosphate); Ex. 1011, 5:4 (antigen is preferably adsorbed to the aluminum salt). Thus, we determine that Petitioner has established persuasively that Prevenar's composition, as modified by the addition of Chiron's histidine, yields the formulation of claim 1, wherein the recited aggregation inhibition property of the formulation must be present, or is the natural result of the combination of elements disclosed by the prior art.

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

Claim 2 depends from claim 1 and further recites that the formulation "further comprises polysorbate 80, and wherein the final concentration of the polysorbate 80 in the formulation is at least 0.001% to 10% polysorbate 80 weight/volume of the formulation." Ex. 1001, 31:13–17. Petitioner asserts that a person of skill in the art would have had a reason to include Chiron's

polysorbate 80 (e.g., 0.005% Tween 80) in the Prevenar formulation because the skilled artisan would have known that (a) Chiron taught that adding a surfactant, such as polysorbate 80, advantageously minimized adsorption of proteins to containers, and (b) such surfactant also inhibits silicone-induced aggregation. Pet. 46–47 (citing Ex. 1011, 6:14–15 and Examples 7–9; Ex. 1009 ¶¶ 146–147(citing Ex. 1013 "Smith")). Further, in terms of a reasonable expectation of successfully adding a surfactant to Prevenar, Petitioner asserts that the skilled artisan would have known, and thus expected, that surfactants in low amounts were a safe and standard component of pharmaceuticals and had been included in other polysaccharide-protein conjugate vaccines. *Id*. at 47 (citing Ex. 1009 ¶147).

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

Patent Owner asserts also that "polysorbates were associated with numerous risks that would have dissuaded a POSA to add polysorbate to an approved formulation such as Prevenar []." PO Resp. 28. In particular, Patent Owner asserts that ether linkages in polysorbates "can spontaneously and rapidly oxidize in aqueous solution to protein-damaging peroxides,

epoxy acids, and reactive aldehydes, including formaldehyde and acetaldehyde," *id*. (citing Ex. 2124 ¶ 67); polysorbates oxidize histidine in a protein formulation that may cause a decrease in potency of the formulation, *id*. (citing Ex. 2124 ¶ 68); and polysorbates could cause aggregation, *id*. (citing Ex. 2124 ¶ 68).

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

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

would have viewed the referenced teaching to be applicable to a polysaccharide-protein conjugate formulation comprising polysorbate, histidine and an aluminum salt, such as Chiron's.

Similarly, Dr. Thomson has not explained why a person of skill in the art would have viewed a journal article describing polysorbate 20 has enhancing aggregation in solutions comprising high concentrations of PEG-GCSF, PEG-MGDF, or OP-GFc protein stored in a quiescent shelf-life setting, or would have viewed a journal article describing Tween 80 and 0.1% HAS as having no stabilizing effect on an aqueous solution comprising interleukin-1 β, NaCl, and a citrate buffer applicable to Chiron's polysaccharide-protein conjugate formulation. *See* Ex. 2124 ¶ 68 (citing Ex. 2069, 3 and Ex. 2070, 2).

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

Thus, on balance, we determine that the inadequately supported testimony offered by Patent Owner's declarants, Drs. Thomson and Khandke, is outweighed by the express disclosures by Chiron relied upon by

Petitioner. In other words, we determine that the preponderance of the evidence supports Petitioner's position that a person of skill in the art would have had a reason to add polysorbate 80 to the modified Prevenar formulation comprising histidine based upon Chiron's disclosure that adding a surfactant, such as polysorbate 80, advantageously minimized adsorption of proteins to containers, and such a surfactant may be successfully combined with histidine in a polysaccharide-protein conjugate vaccine. Pet. 46–47 (citing Ex. 1011, 6:14–15 and Examples 7–9; Ex. 1009 ¶¶ 146–147).

Moreover, Dr. Kalonia has explained persuasively that such surfactant was known in the art to inhibit silicone-induced aggregation, as evidence by Smith. *Id*. (citing Ex. 1009 ¶¶ 145–147(citing Smith)). Similarly, on balance, we determine that Petitioner has established by a preponderance of the evidence that, based upon those teachings of Chiron and Dr. Kalonia's testimony regarding the knowledge in the art, *see*, *e.g*. Ex. 1009 ¶147, a person of skill in the art would have had a reasonable expectation of successfully adding a surfactant to the modified Prevenar.

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

b) Claim 18

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

(1) Petitioner's Contentions

Petitioner asserts that the thirteen pneumococcal serotypes recited in claim 18 were well known in the art. Pet. 55 (citing Ex. 1007 ¶ 44). According to Petitioner, "[t]here is a natural progression in the development of multivalent vaccines." *Id*. (citing Ex. 1007 ¶ 45). Petitioner asserts that the 7-valent pneumococcal vaccine was expanded to a 9-valent vaccine, and subsequently to an 11-valent vaccine, wherein each polysaccharide is conjugated solely to CRM_{197}. *Id*. (citing Ex. 1007 ¶¶ 38, 45 (citing Ex. 1015, 7, 10; Ex. 1034,[12] 2; Ex. 1035,[13] 4; Ex. 1036,[14] 5; Ex. 1037, 4)). According to Petitioner, a person of skill in the art "would have understood that a further step in the natural progression included the 13 serotypes of claim 18 (which were well-known), conjugated only to CRM_{197}." *Id*. (citing

[12] Obaro et al., Safety and immunogenicity of pneumococcal conjugate vaccine in combination with diphtheria, tetanus toxoid, pertussis and *Haemophilus influenzaue type b conjugate vaccine*, 21(10) PEDIATRIC INFECT. DIS. J. 940–946 (2002). Ex. 1034 ("Obaro").

[13] Overturf, *Pneumococcal Vaccination of Children*, 13(3) SEMIN. PEDIATRIC INFEC. DIS. 155–164 (2002). Ex. 1035 ("Overturf").

[14] O'Brien et al., *Potential Impact of Conjugate Pneumococcal Vaccines on Pediatric Pneumococcal Diseases*, 159(7) AM. J. EPIDEMIOL. 634–644 (2004). Ex. 1036 ("O'Brien").

Ex. 1007 ¶¶ 44–46).

Petitioner asserts that a skilled artisan would not have been discouraged from following such a natural progression to conjugate 13 polysaccharides to the same carrier protein based upon alleged concerns that too much carrier protein could diminish immunogenicity because "claim 18 does not recite any particular level of required immunogenicity or amount of CRM_{197}," and there was no definitive teaching of such immune interference. *Id*. at 56–57 (citing Ex. 1007 ¶¶ 48–49; Ex. 1009 ¶ 173).

(2) Patent Owner's Contentions

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

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

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

(3) Discussion

The Federal Circuit vacated the Board's previous obviousness findings with respect to claim 18, and remanded the case "for further consideration of the parties' arguments and evidence as to (1) motivation to combine and (2) reasonable expectation of success and, if the Board finds a sufficient motivation to combine and reasonable expectation of success, other issues such as secondary considerations." *Merck*, 792 F. App'x at 818–819. The Federal Circuit explained that "[o]n this record, Merck established that it was obvious to combine the 13 serotypes into a single vaccine," and explained that "the question [is] whether it was obvious to conjugate the 13 serotypes to the CRM_{197} protein in a single vaccine." *Id.* at 817.

Having considered the record, as a whole, we determine Petitioner has not established by a preponderance of the evidence that a person of skill in the art would have found it obvious to further modify Prevenar's formulation by conjugating each of the 13 serotypes recited in claim 18 to a CRM_{197} polypeptide as required by claim 18. Petitioner's showing is deficient for two reasons. First, Petitioner has not provided a persuasive reason why a person of skill in the art would have modified Chiron's formulation to comprise the recited 13-valent conjugate. Second, Petitioner has not established persuasively that the skilled artisan would have had a reasonable expectation of success in combining the references to yield the recited 13-valent conjugate. In lieu of specifically articulating each of those required rationales, *see CRFD Research*, 876 F.3d at 1340, Petitioner addresses

obviousness in a more generalized manner by basing its challenge of claim 18 upon a so-called "natural progression" theory. Pet. 55.

Petitioner's evidentiary showing regarding claim 18 differs from that asserted for claim 17 in at least one significant aspect. For claim 17, Petitioner relied on Prevenar's disclosure of a pneumococcal conjugate vaccine comprising each of the same seven serotypes recited by claim 17 conjugated to CRM_{197} carrier protein. Pet. 54 (citing Ex. 1017, 9). Additionally, for claim 17, Petitioner relied on Chiron's teaching not only that its formulation may be prepared using a saccharide antigen from *S. pneumoniae* and that CRM_{197} is a particularly preferred carrier protein, but also that Chiron specifically cites to Rubin as an example for such a preparation. *Id.*; Ex. 1011, 3 (citing reference 23 ("Rubin") [15]). Rubin discloses pneumococcal conjugate vaccines comprising the seven serotypes recited by claim 17 conjugated to the same carrier protein, CRM_{197}, recited by claim 17. Ex. 1073, 14 (Table 4). The table in Rubin disclosing those vaccines indicates that each vaccine is in Phase III Efficacy Trials. *Id.* Of the three seven-valent conjugate vaccines listed, one was identified as having a "Completed" status. *Id.*

Petitioner's reliance on Prevenar and Chiron's incorporation of Rubin's disclosure served as a foundation for our conclusion regarding the obviousness of claim 17.

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

Here, for claim 18, Petitioner does not allege or demonstrate that Prevenar discloses a pneumococcal conjugate vaccine comprising the 13 serotypes recited by claim 18 conjugated to CRM_{197}. Nor does Petitioner allege or demonstrate that Rubin discloses a pneumococcal conjugate vaccine comprising the 13 serotypes recited by claim 18 conjugated to the CRM_{197}. Neither of those references suggest nor even mention those 13 serotypes. Indeed, Petitioner has not identified any teaching or suggestion in Prevenar or Chiron to incorporate the specific serotypes recited in claim 18 into its formulation using CRM_{197} as the sole carrier protein. Thus, key teachings in Prevenar and Chiron that support the obviousness of claim 17 do not exist for claim 18.

We acknowledge that Petitioner's declarant, Dr. Kasper, provides evidence that the 13 pneumococcal serotypes recited in claim 18 were known in the art. Pet. 55 (citing Ex. 1007 ¶ 44; Ex. 1033, 7;[16] Ex. 1015, 7). Specifically, Petitioner and Dr. Kasper refer to Hausdorff and Peña to support that assertion. *Id.* Neither of those references, however, describes conjugating those 13 serotypes with CRM_{197}. Indeed, Petitioner and Dr. Kasper do not allege as much. *See, e.g.*, Ex. 1007 ¶ 45 (acknowledging that Peña "does not explicitly state that the conjugates of the 11- and 13-valent vaccines are conjugated to CRM_{197}"). Rather, Petitioner and Dr. Kasper note that Peña discloses that CRM_{197} is used as the sole carrier in the 7-valent vaccine and refers to a journal article describing a 9-valent version of the vaccine also using CRM_{197} as the sole carrier protein. Pet. 55;

[16] Hausdorff et al., *Multinational study of pneumococcal serotypes causing acute otitis media in children*, 21(11) PEDIATRIC INFECT. DIS. J. 1008-1016 (2002). Ex. 1033 ("Hausdorff").

Ex. 1007 ¶ 45. Petitioner and Dr. Kasper assert also that it had been reported in the literature that an 11-valent conjugate vaccine used only CRM_{197} as a carrier protein. *Id.*

We agree with Petitioner that 7-valent, 9-valent, and 11-valent pneumococcal vaccines using only CRM_{197} as the carrier protein were known in the art. *See, e.g.*, Ex. 1034, 2 (disclosing a 9-valent pneumococcal conjugate vaccine using only CRM_{197} as the protein carrier); Ex. 1035, Table 4 (disclosing a 9-valent and an 11-valent pneumococcal conjugate vaccine using only CRM_{197} as the protein carrier); Ex. 1036, Table 3 (disclosing a 7-valent, 9-valent, and 11-valent pneumococcal conjugate vaccine using only CRM_{197} as the protein carrier). Petitioner and Dr. Kasper, however, have not identified any discussion in Peña or the other cited literature describing the rationale for selecting and using CRM_{197} as the sole carrier protein in the 7-valent, 9-valent and 11-valent vaccines. More specifically, they have not directed us to any discussion in those references describing the use of CRM_{197} in 9-valent or 11-valent vaccines as a "natural progression" from such use in the 7-valent vaccine. Further, those references do not address expanding the use of CRM_{197} as a sole carrier protein in a pneumococcal vaccine that has greater than 11 serotypes. Thus, we do not find adequate support on this record for Dr. Kasper's testimony that a skilled artisan would have used CRM_{197} as the only carrier protein in a pneumococcal conjugate vaccine comprising 13 serotypes based upon a "natural progression" principle. Accordingly, we do not give that testimony persuasive weight.

Moreover, we do not find that Petitioner and Dr. Kasper have properly relied upon the Ireland EPA Memo to support their contentions. The Ireland EPA Memo is directed to the manufacture of 7, 9, and 13 valent

pneumococcal conjugate vaccines. Ex. 1037, 4 ("Prevenar can be manufactured as 7, 9, or 13 valent Pneumo Conjugate vaccine."). Petitioner relies on the Ireland Memo for Dr. Kasper's testimony that "when Wyeth applied for a facility license to produce the 13-valent conjugate vaccine in around 2003, the Ireland EPA noted that *CRM_{197} would be the only carrier protein for the 7-, 9- and 13-valent versions* of the vaccine." Ex. 1007 ¶ 45 (emphasis added). To support that testimony, Dr. Kasper quotes the following portion of the Ireland EPA memo:

> The Strep-Pnemo vaccine (Prevenar) will be imported from Wyeth USA in the form of bulk carrier protein (CRM) and purified serotypes. The process operations for the Strep-Pnemo Vaccine will initiate with conjugation in the Pnemo-Conjugation suite of the Drug Production Facility prior to formulation and filling in the Strep Pneumo suite. Prevenar can be manufactured as 7, 9 or 13 valent Pnemo Conjugate vaccine.

Id. (quoting Ex. 1037, 4). That quoted portion of the Ireland EPA memo lacks the details that Dr. Kasper attributes to it. In particular, the Ireland EPA memo does not specifically mention CRM_{197}. Rather, it generally refers to "bulk carrier protein (CRM)." *Id.* Neither Dr. Kasper nor Petitioner address that difference. We note also that Petitioner and Dr. Kasper do not explain why a person having ordinary skill in the art at the time of the invention would have looked to or relied upon the Ireland EPA memo to modify Chiron's formulation.

Thus, we do not find that Petitioner has established persuasively that a skilled artisan would have understood the Ireland EPA Memo to teach that conjugating the 13 serotypes recited in claim 18 to CRM_{197} would have been a natural progression from the prior art 7-valent vaccine. *See* Pet. 55 (citing Ex. 1007 ¶¶ 45–46).

For the foregoing reasons, we determine that Petitioner's obviousness rationale based upon a "natural progression" from a seven valent conjugate formulation taught by Prevenar and Chiron to the 13-valent conjugate recited in claim 18 is not supported by teachings of the prior art or knowledge in the art.[17] Because Petitioner has not relied on or shown any other reason that would have prompted a person of ordinary skill in the relevant field to combine the elements of the prior art in the way that claim 18 does, we find that Petitioner has failed to demonstrate that a skilled artisan would have been motivated to modify the cited prior art in the manner proposed. *See KSR*, 550 U.S. at 418 (emphasizing the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.").[18]

---

[17] Petitioner's obviousness rationale based upon a "natural progression" from a known seven valent conjugate to the specific thirteen valent conjugate recited in claim 18 resembles a contention guided impermissibly by hindsight reasoning. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1343, 1368 (Fed. Cir. 2012) (care must be taken to avoid hindsight reasoning to reach the claimed invention without any explanation as to how or why the cited references would be combined). Dr. Kasper's testimony that his "natural progression" rationale extends only to formulating the Prevenar-Chiron combination to include the 13 serotypes of *S. pneumoniae* disclosed by Peña and not further to the 23 serotypes of *S. pneumoniae* disclosed by Peña, noting only that the '999 patent does not describe any formulation comprising more than 13 serotypes, also suggests the impermissible role of hindsight with that rationale. *See* Ex. 2035, 50:6–52:25.

[18] Petitioner asserts that a person having ordinary skill in the art would not have been discouraged from modifying Chiron's formulation to provide the 13-valent formulation recited in claim 18 based upon concerns that too much carrier protein could diminish immunogenicity of the conjugate vaccine.

In addition to not supplying a persuasive reason for a skilled artisan to modify Prevenar's pneumococcal conjugate vaccine to comprise each of the 13 serotypes recited in claim 18 conjugated with CRM_{197}, Petitioner has also failed to demonstrate that a skilled artisan would have had a reasonable expectation of successfully doing so. Petitioner does not squarely address that issue. To the extent that Petitioner relies upon its natural progression rationale in this regard, we do not find it persuasive for the reasons discussed above, i.e., the cited prior art does not teach or suggest applying the concept of natural progression to continue the use of CRM_{197} as the only carrier protein as you increase the valency when formulating pneumococcal conjugate vaccines. Petitioner has not identified any information in the cited art from which a person of ordinary skill in the art could have formed a reasonable expectation of successfully using CRM_{197} as the sole carrier in a 13-valent vaccine. The cited prior art is silent regarding a method of formulating that specific vaccine. Thus, we find that Petitioner has failed to demonstrate a reasonable expectation of success for its proposed modification of Chiron. *See Amgen Inc. v. F. Hoffman–La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.").

Pet. 56–57. Even if true, that assertion does not supply a motivation to combining the teachings of the prior art to yield the claimed invention as proposed by Petitioner. In other words, even if the potential loss of immunogenicity would not have dissuaded someone skilled in the art from making such a combination, the Petition remains deficient for failing to establish a persuasive reason to make the combination in the first place.

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

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

D. Obviousness over Prevenar, Chiron, and Peña

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

1. Peña

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

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

2. Obviousness Analysis

As discussed with respect to the obviousness challenge over the combination of Prevenar and Chiron, we have determined that Petitioner has established by a preponderance of the evidence that the combined teachings of those references teach or suggest each limitation of independent claim 1. Petitioner adds Peña to the combination to further demonstrate that it would have been obvious to modify the combined formulation of Prevenar and Chiron by using the 13-valent conjugate disclosed by Peña. Pet. 58–59. In particular, Petitioner asserts that Peña discloses a 13-valent pneumococcal conjugate vaccine with the same serotypes recited by claim 18. *Id*. at 59; Ex. 1015, 7. According to Petitioner, a person of ordinary skill in the art would have understood that each of those serotypes in Peña's conjugate vaccine used CRM_{197} as the sole carrier protein, "based on the published progression from 7-valent Prevnar®, to 9- and 11- valent iterations; each version contained CRM_{197} as the sole carrier protein." *Id*. (citing Ex. 1007 ¶¶ 45–46).

Patent Owner's arguments mirror those raised regarding the challenge of claim 18 over the combination of Prevenar and Chiron.[19] In view of those arguments and for similar reasons discussed regarding that ground, we

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

determine here that Petitioner has not demonstrated by a preponderance of the evidence that a person of ordinary skill in the art would have found it obvious to further modify the combined formulation of Prevenar and Chiron to comprise the thirteen valent conjugate recited in claim 18.

For similar reasons discussed in Section II.C.3.b. regarding the previous ground challenging claim 18, we determine here also that Petitioner has not demonstrated by a preponderance of the evidence that a person of ordinary skill in the art would have found it obvious to prepare the combined formulation of Prevenar and Chiron by conjugating each of the 13 serotypes recited in claim 18 to a CRM_{197} polypeptide as required by claim 18.

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

To the extent that Petitioner relies on a so-called "natural progression" from a seven valent conjugate to the thirteen valent conjugate recited in claim 18, we remain unpersuaded, as Petitioner has not directed us to any discussion in the cited prior art describing the use of CRM_{197} in 9-valent or 11-valent vaccines as a "natural progression" from such use in the 7-valent vaccine. Further, the cited prior art does not address expanding the use of CRM_{197} as a sole carrier protein in a pneumococcal vaccine that has greater than 11 serotypes. Thus, we do not find adequate support on this record for Dr. Kasper's testimony that a skilled artisan would have used CRM_{197} as the only carrier protein in a pneumococcal conjugate vaccine comprising 13 serotypes based upon a "natural progression" principle.[20] Accordingly, we do not give that testimony persuasive weight.

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

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

[20] As discussed above in Section II.C.3.b., we find that Dr. Kasper's natural progression rationale appears to impermissibly rely upon hindsight.

III. MOTIONS TO EXCLUDE

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

A. Petitioner's Motion

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

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

Petitioner challenges Exhibit 2119 (¶¶ 9, 12–17, 25, and 27–28) as allegedly "unreliable and unsupported testimony" by Patent Owner's declarant, Dr. Khandke, regarding the state of the art of conjugate vaccine formulation at the time of the invention. Paper 34, 2 (citing Federal Rules of Evidence "FRE" 702 and 703). In this *inter partes* review proceeding, we find that such matters go to the probative weight of her testimony, as opposed to its admissibility. *See, e.g.*, Office Patent Trial Practice Guide, 77 Fed. Reg. at 48,763 ("Opinions expressed without disclosing underlying facts or data may be given little or no weight."). Although we acknowledge Petitioner's reference to FRE 702 and 703 in seeking to exclude Dr.

Khandke's testimony, generally, unlike a lay jury, by design, the Board is composed of individuals with "competent scientific ability" (35 U.S.C. § 6), and is thus capable of evaluating such testimony. Accordingly, the danger of prejudice in this proceeding is considerably lower than in a conventional district court trial. Accordingly, we deny Petitioner's Motion to Exclude the designated portions of Exhibit 2119.

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

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

B. Patent Owner's Motion

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

Exhibit 1065 is a copy of a book chapter included in the "Concise Encyclopedia of High Performance Silicones," titled "Silicone Oil in Biopharmaceutical Containers: Applications and Recent Concerns." Patent

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

Having considered the evidence and the arguments, we agree with Patent Owner that Petitioner has not established that Exhibit 1065 is relevant regarding the knowledge of those skilled in the art at the time of the invention. Based upon our review, Dr. Kalonia refers to the book chapter submitted as Exhibit 1065 in his declaration discussion of his credentials. Ex. 1009 ¶ 7. Additionally, Petitioner and Dr. Kalonia refer to Exhibit 1065 when discussing certain arguments relating to the state of the art at the time of the invention. *See, e.g.*, Pet. 12 (referring to Exhibit 1065). We note that in such instances, those contentions are equally supported by other references. Insofar as Exhibit 1065 is relied upon to demonstrate Dr. Kalonia's expertise regarding silicone oil in biopharmaceutical containers, we find such use permissible, and do not interpret Patent Owner's motion to seek to exclude use of Exhibit 1065 in that context. In the Final Written Decision, we have considered Exhibit 1065 only to assess Dr. Kalonia's qualifications to offer testimony regarding the ordinary skill in the art. The exhibit, however, is not available to establish what was known in the art at the time of the invention. Indeed, we have not relied on Exhibit

1065 in the Final Written Decision with respect to any patentability challenge. Accordingly, Patent Owner's motion is dismissed as moot.

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

As for Exhibit 1037, we have considered this exhibit, as discussed above in Section II.C.3.b, pursuant to the Federal Circuit's express instruction to do so. *See Merck*, 792 F. App'x at 819 n.4 ("The Board in its decision did not consider the Ireland Environmental Protection Agency memorandum. On remand, the Board should consider these documents and their probative value."). Accordingly, we dismiss Patent Owner's Motion to Exclude Exhibit 1037.

IV. CONCLUSION[21]

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

ORDER

In consideration of the foregoing, it is hereby:

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

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

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

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

FURTHER ORDERED that any party to the proceeding seeking judicial review of this FINAL WRITTEN DECISION on REMAND must comply with the notice and service requirements of 37 C.F.R. § 90.2.

[21] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April

In summary:

Claims	35 U.S.C. §	References	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–6, 10, 11, 14, 17–20	103(a)	Prevenar, Chiron	1–6, 10, 11, 14, 17, 19, 20	18
18	103(a)	Prevenar, Chiron, Peña		18
Overall Outcome			1–6, 10, 11, 14, 17, 19, 20	18

2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

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
Sebastian Zonte
WHITE & CASE LLP
jscheibeler@whitecase.com
ddrivas@whitecase.com
sebastian.zonte@whitecase.com