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Paper 74
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

WYETH LLC,
Patent Owner.

IPR2017-00378
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 42 and 45. Each party also filed a Reply to the other party's Opposition. Papers 49 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 43 and 46.

[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 45–48.

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 69 (Patent Owner's Citation Table), Paper 70 (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 IPR2017-00380 and IPR2017-00390. Petitioner has appealed our Final Written Decision in IPR2017-00380 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^{TM}80 significantly enhances the stability and inhibits precipitation of an immunogenic composition." *Id*. at 10:35–39.

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

C. Illustrative Claims

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

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

Ex. 1001, 31:7–12, 32:24–44.

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

D. The 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)	Chiron,[5] Smith,[6] Elan[7]
17 and 18	103(a)	Chiron, Smith, Elan, Peña[8]

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

II. ANALYSIS

A. Claim Construction

For petitions filed before November 13, 2018—as here—the Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. §

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

42.100(b) (2017);[9] *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

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

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

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

[9] The amendment to this rule does not apply here because the Petition was filed before November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018).

in the Specification. PO Resp. 11.

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

> a conjugate resulting from reacting any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including but not limited to, a saccharide, an oligosaccharide, a polysaccharide, a liposaccharide, a lipooligosaccharide, a liposaccharide, a glycosylate, a glycoconjugate, and the like with a carrier protein, that is amenable to standard conjugation procedures, wherein the antigenic saccharide element retains antigenicity after conjugation.

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

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

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

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

Based on the record as a whole, we determine that the Specification sets forth with reasonable clarity, deliberateness, and precision the definition of the term "polysaccharide," as accurately represented by Petitioner, and acknowledged by Patent Owner. With respect to the phrase "polysaccharide-protein conjugates," the Specification does not provide a similarly precise definition. However, the Specification generally describes such conjugates in a manner that is consistent with the plain and ordinary meaning of the phrase. For example, the Specification explains that polysaccharides are "chemically activated (e.g., via reductive amination) to make the saccharides capable of reacting with the carrier protein." Ex. 1001, 17:35–37. The Specification also explains that "[c]arrier proteins should be amenable to standard conjugation procedures." *Id.* at 17:47–50. In particular, the Specification states, "[t]he chemical activation of the polysaccharides and subsequent conjugation to the carrier protein (i.e., a polysaccharide-protein conjugate) are achieved by conventional means." *Id.* at 17:43–45. Moreover, as Patent Owner asserts, the Specification describes the polysaccharide-protein conjugates as an example of an "immunogenic composition." Ex. 1001, 1:29–30.

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

procedures.

Although we recognize that the claimed invention is directed toward an immunogenic composition, we also note that the claims do not recite any specific level of immunogenicity for the composition. The Specification explains that the invention "broadly relates to novel formulations which stabilize and inhibit precipitation of immunogenic compositions." Ex. 1001, 2:53–55. The Specification describes aggregation as an indicator of physical/thermal stability of the immunogenic composition. *Id*. at 2:7–8. Breakdown of the composition to an undesired form (e.g., an aggregate) lowers the total concentration of the product. *Id*. at 1:43–46.

Insofar as Patent Owner asserts that the claims require "measuring antigenicity to determine the extent of the loss of antigenicity due to silicone-induced aggregation," as in Example 4 of the Specification, PO Resp. 14, we disagree. Although Example 4 discusses total antigenicity (and loss), the claims do not require the formulation to retain a particular degree of immunogenicity. Instead, the claims are directed to a formulation comprising a polysaccharide-protein conjugate, i.e., an "immunogen," *see, e.g.*, Ex. 1001, 14:19–23, wherein the formulation inhibits aggregation[10] 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

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

"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. 41 (citing Ex. 1008 ¶ 95). For example, Petitioner asserts that the plain language of the claim does not require that the aluminum salt inhibits silicone-induced aggregation. *Id*. (citing Ex. 1008 ¶ 97). According to Petitioner, because independent claim 1 recites a "formulation" followed by an open-ended term, "comprising," any element(s) comprised in the formulation may contribute the required inhibition, so long as the formulation as a whole "inhibits aggregation induced by the siliconized container means." *Id*.

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

Further, Patent Owner asserts that the "broadest reasonable interpretation of claim 1 should go no further than to read on embodiments that contain the three recited ingredients in a formulation that meets the functional property limitation." *Id*. at 19. According to Patent Owner, the functional requirement of inhibiting aggregation induced by the siliconized container means must be satisfied by "a formulation of the three specifically recited ingredients [buffered saline solution, aluminum salt, and polysaccharide-protein conjugate], without any un-recited ingredient(s)." *Id*.

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

specified in the claims); *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'").

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

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

B. Level of Ordinary Skill in the Art

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

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

formulating protein-based compositions, and would have had familiarity or experience with the general components of bacterial vaccines." Pet. 35–36 (citing Ex. 1008 ¶ 80).

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

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

in the art relating to silicone-induced interactions/aggregation in pharmaceuticals.

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

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

Petitioner does not challenge the expertise of any of Patent Owner's declarants. Patent Owner, however, asserts that Petitioner's declarants, Drs. Kalonia and Kasper, lack "experience in developing polysaccharide-protein conjugate formulations, and certainly not on a commercial scale." PO Resp. 20. Regarding Dr. Kalonia, Patent Owner asserts that his experience is "limited to the aggregation of proteins in formulations on a laboratory scale." *Id*. However, as described in Dr. Kalonia's declaration, such experience involves "significant research experience in protein-interface, protein-protein, and protein-excipient interactions, including interactions among protein, silicone oil and surfactants," as well as co-authoring a book chapter describing applications and concerns relating to silicone oil in biopharmaceutical containers. Ex. 1008 ¶ 7.

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

Regarding Dr. Kasper, Patent Owner asserts that he "has no experience in the development of commercial scale vaccine products," and "is not knowledgeable about vaccine formulation issues such as stability and aggregation." PO Resp. 21. We disagree. As Dr. Kasper explains in his declaration, he is a professor of medicine and microbiology at Harvard

Medical School and runs his own research laboratory, wherein a "major focus" of his work is "the development of human vaccines, including polysaccharide-protein conjugate vaccines." Ex. 1007 ¶¶ 1, 5.

In support of its challenge of Dr. Kasper, Patent Owner directs us only to deposition testimony relating to Dr. Kasper's inexperience with using siliconized containers with his vaccine formulations. PO Resp. 21 (citing Ex. 2035, 13:3–18, 35:20–23). However, as Petitioner has explained, Dr. Kasper's testimony is not offered to address silicone-induced aggregation in pharmaceuticals. Rather, Petitioner relies upon Dr. Kasper to provide testimony in his area of expertise, i.e., formulating polysaccharide-protein conjugate immunogenic compositions, and asserts that he would have had familiarity or experience with the general components and formulation of bacterial vaccines. *See* Pet. 5 (describing Dr. Kasper as "a renowned researcher focusing on the development of human vaccines, including polysaccharide-protein conjugate vaccines").

C. Obviousness over Chiron, Smith, and Elan

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

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) where in evidence, so-called secondary considerations. *Graham*, 383 U.S. at 17–18. If the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a

person having ordinary skill in the art to which said subject matter pertains, the claim is unpatentable under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007).

"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. Chiron

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

2. Smith

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

3. Elan

Elan discloses stable pharmaceutical immunoglobulin formulations comprising a therapeutically effective amount of an antibody, polysorbate 80, and a buffer. Ex. 1013, Abstract, 3. Elan explains that developing stable formulations that can maintain a small volume even with an increased concentration of antibody "has been hindered by the proteins or the antibodies themselves, which have a high tendency to aggregate and precipitate." *Id*. at 2. Elan explains that silicone oil was introduced into the

product upon use of standard lubricated polypropylene syringes equipped with siliconized rubber stoppers. *Id*. at 15. Elan determined that the presence of the silicone oil was sufficient to cause discernible antibody precipitation in a formulation of antibody (natalizumab), histidine, and a buffer, upon gentle agitation and room temperature storage. *Id*. at 17. Elan reports that visual inspection confirmed that such precipitation was resolved by the addition of polysorbate 80. *Id*. at 17–18.

4. Obviousness Analysis

a) Claims 1–6, 10, 11, 14, 19, and 20

Petitioner contends that Chiron teaches or suggests every ingredient recited in the formulations of claims 1–6, 10, 11, 14, 19, and 20. Pet. 43–44. In particular, Petitioner asserts that Chiron teaches vaccine formulations comprising a bacterial saccharide antigen, histidine buffer, a sodium salt, e.g., sodium phosphate or sodium chloride, and an aluminum salt. *Id*. at 44–45 (citing, e.g., Ex. 1011, 1:6–7, 2:1, 5:6–7, 15, 28). Petitioner asserts that Chiron's histidine buffer is inherently within the scope of the claim limitation requiring the buffer to have a pKa of about 3.5 to about 7.5 because "the pKa with respect to the side group proton is approximately 6.0." *Id*. at 45 (citing Ex. 1008 ¶ 28; Ex. 1045, 22). As for the saccharide antigen, Petitioner asserts that Chiron teaches that conjugation to a carrier protein is preferred to enhance immunogenicity. *Id*. at 45 (citing Ex. 1011, 3:20–21). Petitioner asserts that Chiron also teaches that its formulation comprises polysorbate 80. Pet. 50. Regarding dependent claims 2–6, 10, 11, 14, 19, and 20, Petitioner also asserts that Chiron teaches or suggests the additional limitations set forth in those claims. *See* Pet. 50–57 and 62.

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

(1) Siliconized container means

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

Chiron's formulations in pre-filled syringes, as that was a common method of supplying vaccines, as evidence by the commercialized Chiron polysaccharide-protein vaccine, Vaxem Hib. *Id*. (citing Ex. 1008 ¶ 136; Ex. 1051; Ex. 1053).

According to Petitioner and Dr. Kalonia, a person of ordinary skill in the art would have understood that standard pharmaceutical vial stoppers, syringe plungers, and syringe barrels were siliconized. Pet. 47 (citing Ex. 1008 ¶ 138). Additionally, Petitioner asserts that Smith teaches that "it was standard industry practice to lubricate the components of such containers (rubber vial stoppers, syringe plungers and the interiors of syringe barrels) with silicone oil." *Id*. at 46 (citing Ex. 1008 ¶ 133).

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

Patent Owner notes that Chiron's Example 8 demonstrates that the MenW135 and MenY conjugates were highly unstable by industry standards, thus, a person of ordinary skill in the art would have been unlikely to put the formulations in siliconized containers. *Id*. at 25 (citing Ex. 2120 ¶¶ 40–42).

As for Chiron Example 9, Patent Owner asserts that the disclosed lyophilized component was unstable in solution, and that even if the syringes containing the formulation were siliconized, "the [reconstituted] formulation would not have been in the syringe for a time period long enough for silicone-induced aggregation to occur." *Id*. (citing Ex. 2120 ¶¶ 43–44; Ex. 2036, 164:14–19, 172:7–17 (describing reconstitution at the time of administration)). Patent Owner asserts that Petitioner's reference to Chiron's Vaxem Hib, a haemophilus influenza b vaccine, marketed as a liquid formulation in prefilled syringes does not suggest that the meningococcal formulation disclosed in Chiron would be similarly marketed. *Id*. at 26.

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

Based upon our review of the record, as a whole, we determine that the preponderance of the evidence supports Petitioner's contention that a person of skill in the art would have found it obvious at the time of the invention to store Chiron's formulations in siliconized container means. As the parties acknowledge, Chiron disclosed placing the formulations in vials and storing them for at least one month. There is no dispute that a person of ordinary skill in the art would have had a reason to use a rubber stopper with such storage vials. Although Patent Owner asserts that a person of skill in the art would not have used rubber stoppers that were siliconized, persuasive evidence suggests otherwise. Dr. Kalonia provides testimony that, at the time of the invention, "it was well understood in the art that pharmaceutical containers required lubrication, and that the standard lubricant for that purpose was silicone oil." Ex. 1008 ¶ 138. The evidence reveals that such use of silicone oil as a lubricant was ubiquitous by that time. In particular, as Petitioner and Dr. Kalonia assert, Smith discloses that not only was lubrication common in parenteral packaging, "[m]ost parenteral packaging components require the use of some form of lubrication in order to improve their processability and functionality," wherein such lubrication is essentially all based upon the use of "silicone fluid." Ex. 1012, 4 and 8; Pet. 31; Ex. 1008 ¶¶ 118–120, 138.

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

plunger within the barrel." Ex. 1012, 4.

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

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

Ex. 2036, 87:12–88:13.

The first portion of the above discussion refers to the description in the '999 patent Specification relating to the use of Pyrex beakers when combining formulation ingredients. Ex. 1001, 20:1–3. When asked if the Pyrex beaker was siliconized or not, Dr. Kalonia confirmed that "there was a practice to siliconize" such containers. Ex. 2036:16–21. However, because some labs stopped using such containers in "some cases," Dr. Kalonia explained that "without any specific information," he could not know

whether the beakers described in the '999 patent were siliconized or not. After discussing the beakers, Dr. Kalonia was asked "if the text said a vial, are you saying you can't tell whether or not the vial is siliconized or not?" Ex. 2036, 88:4–7. Dr. Kalonia responded, "I would use it – unless the explicit language, I would be reluctant to use it." *Id*. at 88:11–13. That response is consistent with his declaration testimony that a person of skill in the art would have found it obvious to use a siliconized container for Chiron's formulation, at the time of the invention, because such container means were commonly lubricated with silicone oil. *See, e.g.*, Ex. 1008 ¶ 118. In other words, in view of that common practice, a skilled artisan would have had a reason to use such a siliconized container to store Chiron's formulations, and, absent some caution in Chiron that the storage container means should not be siliconized, the artisan would have had a reasonable expectation of successfully storing the formulations in that manner.

We credit Dr. Kalonia's testimony that a skilled artisan would have used a siliconized container to store Chiron's formulation with persuasive weight, as that testimony is supported by Smith's disclosure, as discussed above. On the other hand, we find that Patent Owner's assertions and the related opinions by its declarants, e.g., Drs. Morefield (Ex. 2120) and Thomson (Ex. 2123), that a person of ordinary skill would not have found it obvious to use siliconized containers to store Chiron's formulations are inadequately supported. For example, Patent Owner relies upon Dr. Morefield's testimony that a siliconized container would not have been used in Chiron's Example 8 because (a) the example involved a saccharide stability study, and introducing a siliconized container would have injected an unknown parameter into the experiment, and (b) the data demonstrates

that the formulation was highly unstable. PO Resp. 25 (citing Ex. 2120 ¶¶ 36–42). However, Dr. Morefield has not provided any evidence to suggest that a siliconized container represented an "unknown" parameter. Rather, as evidenced by Smith and Elan, it was a known parameter, with a known solution. Nor has Dr. Morefield accurately characterized the data disclosed in Chiron's Example 8 as demonstrating Chiron's formulation was "highly unstable." Chiron expressly concludes from the data in Example 8 that "[f]ree saccharide levels are thus stable for at least 1 month at 2–8°C, before and after packaging," and that stability issues arose for two formulations, MenW125 and Men Y, only "[u]nder thermal stress conditions." Ex. 1011, 16:3–6.

Similarly, Patent Owner relies upon Dr. Thomson's opinion that siliconized containers are "avoided in a research setting to minimize secondary effects while developing a formulation." Ex. 2123 ¶ 56. In line with this argument, Patent Owner asserts also that a person of ordinary skill in the art would not have combined the teachings of Smith with Chiron because Smith provided information concerning the use of lubrication on pharmaceutical packaging components whereas Chiron is directed to research stage formulations that are not commonly placed in siliconized containers. PO Resp. 31–34.

Here again, we determine that the preponderance of the evidence does not support Patent Owner's argument. As Petitioner explains, Chiron did not simply operate as a research laboratory, but instead as a major vaccine manufacturer, as confirmed by Dr. Thomson, a former Chiron scientist. Reply 9 (citing Ex. 1094, 72:8–16, 72:24–73:5). As Petitioner also explains, Dr. Thomson acknowledged that Chiron would have considered marketing

the disclosed formulations in siliconized pre-filled syringes. *Id*. at 10 (citing Ex. 1094, 74:20–25). Further, Petitioner directs us to Dr. Thomson's testimony that, in addition to Vaxem Hib, Chiron also marketed Menjugate, a meningococcal conjugate vaccine, in a vial with a siliconized stopper. *Id*. (citing Ex. 1094, 75:21–77:3). Dr. Thomson additionally confirmed that each of those products contains all the ingredients recited in claim 1. *Id*. at 10–11 (citing Ex. 1094, 43:11–15, 43:23–44:4, 44:9–12, 75:7–10, 75:21–76:8). Thus, we determine that a skilled artisan would have had a reason to use siliconized containers with Chiron's formulation because it had previously done so for other conjugate vaccines including similar ingredients. Moreover, the skilled artisan would have had a reason to consider the teachings of Smith, directed to parenteral drug packaging components, when formulating and storing Chiron's parenteral vaccine, as it would have been reasonable to expect that Chiron prepared the formulation not simply for research purposes, but instead with a goal of ultimately commercializing the formulation and distributing it in siliconized containers, consistent with industry standards at the time.

Most problematic with Patent Owner's position are its competing assertions that a person of skill in the art would have viewed Chiron's formulations "to be unsuited for storage in siliconized containers," and that a person of ordinary skill in the art "would have doubted that the formulation in Chiron [] would be susceptible to silicone-induced aggregation" of the meningococcal conjugate formulations in siliconized containers. PO Resp. 26, 30. When these apparently contradictory positions were addressed at the oral hearing, no clarity was provided. *See* Tr. 49:1–51:7 (explaining only that one skilled in the art would not use siliconized containers because

Chiron's formulations were allegedly unstable and partially in a lyophilized form). In any event, as discussed above, the preponderance of the evidence, involving teachings of the prior art, and testimony of each parties' experts, demonstrates persuasively that a person of ordinary skill in the art would have had reason to provide Chiron's formulation in a siliconized container means, and would have had a reasonable expectation of successfully doing so, as had been done with other Chiron conjugate vaccines.

(2) Inhibition of aggregation induced by the siliconized container means

Petitioner asserts that a person of ordinary skill in the art would have understood that Chiron's polysaccharide-protein conjugate formulations inhibit aggregation induced by the siliconized container means because Chiron's formulation contains a surfactant, such as polysorbate/Tween® 80. Pet. 48 (citing Ex. 1011, 6:14–15, 14:3–17:4, Examples 7–9 with 0.0005% Tween ® 80). According to Petitioner, a person of ordinary skill in the art would have known that such a surfactant inhibits silicone-induced aggregation, as taught by Elan. *Id*. (citing Ex. 1008 ¶ 139; Ex. 1013, 16:13–15, 17:6–14). Based on this knowledge, Petitioner asserts that a person of ordinary skill in the art would have been further motivated to provide Chiron's formulations in a siliconized container and would have had a reasonable expectation of successfully doing so, as Elan taught that a formulation including a surfactant, such as in Chiron, would successfully address silicone-induced protein aggregation. *Id*. at 49–50 (citing Ex. 1008 ¶¶ 143–144).

Patent Owner asserts that Chiron discloses using a surfactant, polysorbate 80, to minimize adsorption of antigens to containers, but contains no disclosure that the surfactant would inhibit silicone-induced

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

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

Patent Owner asserts also that a person of ordinary skill in the art "would not have had any reasonable expectation that polysorbate 80 would inhibit aggregation, let alone silicone-induced aggregation," in Chiron's

formulation, based upon Elan's disclosure. *Id*. at 48. According to Patent Owner, "[p]olysorbate's effects were unpredictable and its anti-aggregation effects were formulation and protein dependent." *Id*. Patent Owner asserts that a "vaccine formulator would not have added polysorbate to a formulation without a reason related to its known properties." *Id*.

Further, according to Patent Owner, Elan teaches away from combining polysorbate 80 with the histidine buffer disclosed in Chiron by teaching that impurities arose from degradation of polysorbate 80 through an oxidation reaction involving metal ions and histidine. *Id*. at 42 (citing Ex. 1013, 18:19–20; Ex. 2123 ¶¶ 68–74; Ex. 2115 ¶ 83). Patent Owner asserts that, in view of Elan, "[h]istidine may be included only where a phosphate buffer is also present to inhibit auto-oxidation. . . ." *Id*. at 46. Further, Patent Owner asserts that "there would have been no motivation to use histidine as a buffer because Chiron [] teaches that histidine's effects on stability are tied to its actions as a non-buffering excipient on the adjuvant." *Id*. According to Patent Owner, Chiron teaches away from inclusion of phosphate ions while Elan depends on it, thus dissuading a person of ordinary skill in the art from "combining . . . their opposite teachings regarding the critical role of a phosphate buffer." *Id*. at 47.

Based upon our review of the record, as a whole, we determine that the preponderance of the evidence supports Petitioner's contention that a person of ordinary skill in the art would have appreciated that Chiron's formulation inhibits aggregation induced by a siliconized container means. To begin, we address Patent Owner's assertion that Petitioner's position, i.e., that a person of ordinary skill in the art would have understood that the polysorbate 80 in Chiron's formulations inhibits silicone-induced

aggregation, requires the artisan to have expected that the formulation would undergo such aggregation in the absence of polysorbate 80. PO Resp. 28. Based upon that rationale, Patent Owner asserts that a person of skill in the art would not have expected such formulations without polysorbate 80 to be susceptible to silicone-induced aggregation. *Id*. Patent Owner supports that assertion by referring to Dr. Morefield's testimony that Menactra, another Chiron product having a similar formulation as disclosed in Chiron, but without polysorbate 80 or any surfactant, was packaged in siliconized vials without any reports of recalls due to aggregation. *Id*. at 28–30 (citing Ex. 2120 ¶¶ 31–34).

We note that Patent Owner and Dr. Morefield do not address whether a person of ordinary skill in the art would have attributed the lack of such aggregation in Menactra to the formulation's ability to inhibit silicone-induced aggregation, in the absence of polysorbate 80. Based upon our claim construction, the required inhibition of such aggregation may be attributable to any component, or combination of components, making up the formulation. Thus, Chiron's formulation may read on the functional claim requirement if one or more of the formulation ingredients contributes to the formulation's ability to inhibit silicone-induced aggregation.

Insofar as Patent Owner argues that Chiron's formulation does not inhibit silicone-induced aggregation because Petitioner has not established that it would have been subject to such aggregation, we do not find that argument supported by the evidence. Petitioner provides persuasive evidence that, at the time of the invention, it was well-known in the pharmaceutical industry that silicone oil lubricant in contact with pharmaceutical formulations, including vaccines, could lead to protein

aggregation. Pet. 16 (citing Ex. 1008 ¶¶ 46–48). In addition to Dr. Kalonia's testimony describing the knowledge in the art at the time of the invention regarding silicone-induced aggregation, Petitioner also directs us to the following statement in the "Background of the Invention" section of the '999 patent describing what was known in the art at the time of the invention regarding silicone-induced aggregation:

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

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

Based upon the foregoing, we are persuaded that Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have reasonably expected that (a) a formulation comprising a

polysaccharide-protein conjugate may be subject to silicone-induced aggregation, and (b) any such aggregation would successfully be inhibited by polysorbate 80. *See In re O'Farrell*, 853 F.2d 894, 903–904 (Fed. Cir. 1988) (a proper obviousness inquiry focuses on *reasonable* expectations, as opposed to absolute certainty, that a skilled artisan would gain from the knowledge in the art, along with the teachings or suggestions of the combined prior art).

Moreover, in view of the above mentioned statements by Patent Owner during the prosecution of the '999 patent, we are not persuaded that a person of skill in the art would not have combined the teachings of Chiron and Elan because Elan addresses inhibiting aggregation in proteins and "simply affecting the protein moiety would be insufficient to inhibit the overall aggregation of the conjugate" in Chiron, as Patent Owner asserts here. PO Resp. 34. Further, we find Patent Owner's arguments that Elan teaches away from combining polysorbate 80 with a histidine buffer, and that a vaccine formulator would not have added polysorbate to a formulation without a reason related to its known properties are misplaced, as Chiron's formulation already combines both of those elements successfully, wherein polysorbate 80 serves to "minimize adsorption of antigens to the containers." Ex. 1011, 2–4 and 7.

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

preponderance of the evidence that claims 2–6, 10, 11, 14, 19, and 20 are unpatentable.

b) Claim 17

Claim 17 depends from claim 1 and further requires that the "one or more polysaccharide-protein conjugate" comprises seven conjugates, with each having a different polysaccharide from a specific *S. pneumoniae* serotype (4, 6B, 9V, 14, 18C, 19F, 23F) conjugated to a CRM_{197} polypeptide.

(1) Petitioner's Contentions

Petitioner asserts that it would have been obvious from the disclosure in Chiron for a person of ordinary skill in the art to have prepared Chiron's formulation wherein the conjugate comprises the recited seven valent conjugate. Pet. 57. In particular, Petitioner asserts that Chiron teaches that its formulation may comprise one or more bacterial antigens, including a saccharide antigen from *S. pneumoniae*. *Id*. at 57–58 (citing Ex. 1011, 2–3 and 6). Petitioner and Dr. Kalonia assert also that Rubin 2000,[11] referenced in Chiron, expressly discloses a vaccine comprising the same seven valent polysaccharide-protein conjugate recited in the claim. Pet. 57; Ex. 1008 ¶ 158; Ex. 1011, 3 (citing Ex. 1073, 14).

According to Petitioner and Dr. Kalonia, a person of skill in the art would have known that a commercially available vaccine, Prevnar, already comprised this seven valent conjugate (without the histidine buffer and surfactant of Chiron). Pet. 58–59; Ex. 1008 ¶ 158; Ex. 1058, 42. Petitioner

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

and Dr. Kalonia assert that a person of skill in the art would have understood that modifying Chiron's formulation to include this disclosed seven valent conjugate would not change the aggregation characteristic of the formulation, as that characteristic is a function of the protein component and not the polysaccharide. Pet. 58; Ex. 1008 ¶ 157.

(2) Patent Owner's Contentions

Patent Owner asserts that Petitioner's cited references do not disclose the conjugate recited in claim 17. PO Resp. 30. Patent Owner asserts also that Petitioner has not provided a reason for a person of skill in the art to modify the formulation disclosed in any of the asserted references to include the recited conjugates. *Id*. Additionally, Patent Owner asserts that Petitioner has failed to show that the modified formulation meets the limitations of independent claim 1, from which claim 17 depends, namely, that it "inhibits aggregation induced by the siliconized container means." *Id*. at 31. According to Patent Owner, Petitioner's declarants, Drs. Kalonia and Kasper, agree that modifying the polysaccharide-protein conjugate would alter its behavior in the presence of silicone oil. *Id*. (citing Ex. 2036, 124:4–10; Ex. 2035, 32:4–25).

(3) Discussion

Having considered the record, as a whole, we determine that the preponderance of the evidence supports Petitioner's position that a person of ordinary skill in the art would have found it obvious to prepare Chiron's formulation in a manner that meets each limitation of claim 17. As previously discussed in Section II.C.4.b., Petitioner has shown by a preponderance of the evidence that a person of skill in the art would have found it obvious to prepare Chiron's formulation comprising a pH buffered

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

Insofar as Patent Owner asserts that Drs. Kalonia and Kasper agree that modifying the polysaccharide-protein conjugate would alter its behavior in the presence of silicone oil, we are not persuaded that any such modified response would cause a person of skill in the art to no longer reasonably expect the polysorbate 80 component of the formulation would inhibit any aggregation induced by a siliconized container means. To the contrary, as Petitioner asserts, Dr. Kalonia explained persuasively that a person of ordinary skill in the art "would have expected that the hydrophilic polysaccharide molecules would not have affected a surfactant's inhibition of silicone-induced protein aggregation," as the protein component is responsible for such aggregation. Reply 24–25 (quoting Ex. 1008 ¶ 50).

c) Claim 18

Claim 18 depends from claim 1 and further requires the "one or more polysaccharide-protein conjugate" comprises 13 conjugates, with each having a different polysaccharide from a specific *S. pneumoniae* serotype (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A) conjugated to a CRM_{197} polypeptide.

(1) Petitioner's Contentions

Petitioner asserts that it would have been obvious from the disclosures in Chiron for a person of ordinary skill in the art to have modified Chiron's formulation to include the 13-valent conjugate recited by claim 18 for the same reasons asserted regarding claim 17. Pet. 59. According to Petitioner, "[t]he only difference between claims 17 and 18 is that claim 18 adds six more required pneumococcal polysaccharide-protein conjugates (*i.e.*, claim 18 requires at least 13 conjugates." *Id.* Petitioner asserts that "[t]hose additional recited conjugates do not impact the obviousness analysis, especially when the 13 claimed pneumococcal serotypes were well known in the art." *Id.* (citing Ex. 1007 ¶ 44 (citing Ex. 1033,[12] 7 and Ex. 1015, 7)). Petitioner asserts further that using 13 conjugates would not have impacted the required "aggregation induced by the siliconized container means" because it is the protein component of the formulation that is responsible for that function and not the polysaccharide. *Id.* at 60 (citing Ex. 1008 ¶ 160).

[12] 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").

Additionally, Petitioner asserts that "the 13 conjugates in claim 18 are a natural progression from Patent Owner's prior art 7-valent vaccine." *Id.* (citing Ex. 1007 ¶ 45). In support of that contention, Petitioner states that "[t]he earliest version of multivalent vaccines utilizes the most prevalent polysaccharide serotypes. *Id.* (citing Ex. 1007 ¶ 36). "Over time, later versions of the vaccines will incorporate additional clinically-relevant serotypes for broader protection." *Id.* For pneumococcal CRM_{197}-conjugated vaccines, Petitioner asserts that such progression occurred with the 7-valent vaccine being expanded to the 9-valent vaccine, and then further to an 11-valent vaccine, each conjugated only to CRM_{197}. *Id.* (citing Ex. 1007 ¶¶ 38, 45 (citing Ex. 1015, 7, 10; Ex. 1034, [13] 2; Ex. 1035, [14] 4; Ex. 1036, [15] 5; Ex. 1037, 4)). According to Petitioner, a person of ordinary skill in the art would have understood that a further step in the natural progression included the 13 serotypes of claim 18 conjugated to only CRM_{197}. *Id.* (citing Ex. 1007 ¶¶ 45–46).

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

[13] 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").

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

[15] 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").

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 60–61(citing Ex. 1007 ¶¶ 48–49; Ex. 1008 ¶ 161).

(2) Patent Owner's Contentions

Patent Owner asserts that Petitioner's cited references do not disclose the conjugate recited in claim 18. PO Resp. 30. Patent Owner asserts also that Petitioner has not provided a reason that a person of skill in the art would have modified the formulation disclosed in any of the asserted references to include the recited conjugates. *Id*. Further, Patent Owner asserts that concerns relating to immune interference with multivalent conjugates would have prompted the skilled artisan to use more than one carrier protein for such vaccines. *Id.* at 5–6 (citing Ex. 2118 ¶¶ 22, 24, 26–27). Additionally, Patent Owner asserts that Petitioner has failed to show that the modified formulation meets the limitations of independent claim 1, from which claim 18 depends, namely, that it "inhibits aggregation induced by the siliconized container means." *Id*. at 31. Further, according to Patent Owner, Petitioner's reliance on a "natural progression" from the seven valent to the recited 13-valent conjugate formulation represents impermissible hindsight, as it is requires using the inventor's disclosure as a blueprint to piece together prior art. *Id*. at 31, 51–52 (citing *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)).

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

(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 modify Chiron'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. 60.

As noted above, Petitioner begins its challenge of claim 18 by asserting that the claim would have been obvious for the same reasons as claim 17. Pet. 59. In at least one significant aspect, however, Petitioner's evidentiary showing regarding claim 17 does not apply to claim 18. For claim 17, Petitioner demonstrated not only that Chiron teaches 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 one of three examples for such a preparation. Ex. 1011, 3 (citing reference 23 (Rubin)). 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.* Chiron's incorporation of Rubin's disclosure was a foundation for our conclusion regarding the obviousness of claim 17.

Rubin does not disclose a pneumococcal conjugate vaccine comprising the 13 serotypes recited by claim 18 conjugated to the CRM_{197}. Nor does Rubin suggest or even mention those 13 serotypes. Indeed, Petitioner has not identified any teaching or suggestion in Chiron to incorporate the specific serotypes recited in claim 18 into its formulation

using CRM_{197} as the sole carrier protein. Thus, a key teaching in Chiron that supports the obviousness of claim 17 does not exist for claim 18.[16]

We acknowledge Petitioner's assertion and evidence that the 13 serotypes recited in claim 18 were well known in the art. Pet. 59 (citing Ex. 1007 ¶ 44; Ex. 1033, 7; 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. 60; 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

[16] Petitioner does not rely on the teachings of Smith or Elan to demonstrate that a skilled artisan would have found it obvious to prepare Chiron's formulation by combining the recited thirteen serotypes with CRM_{197}.

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. In one aspect, Petitioner relies on the Ireland EPA Memo for its assertion that "literature subsequently disclosed a further progression to an 11-valent vaccine, again conjugated solely to CRM_{197}." Pet. 60 (citing Ex. 1034, 2; Ex. 1035, 4; Ex. 1036, 5; Ex. 1037, 4). Although we have acknowledged that at least one of the other cited references discloses an 11-valent vaccine conjugated to CRM_{197} as the only protein carrier, Petitioner has not identified that disclosure in the Ireland EPA Memo. 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 also 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. 60 (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 Chiron to the 13-valent conjugate recited in claim 18 is not supported by teachings of the prior art or knowledge in the art. 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 Chiron 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.").[17]

In addition to not supplying a persuasive reason for a skilled artisan to modify Chiron'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

[17] 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. Pet. 60–61. Even if true, that assertion does not supply a motivation to modify Chiron's formulation 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.

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.").

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 Chiron, Smith and Elan. Petitioner, however, has not established by a preponderance of the evidence that claim 18 is unpatentable over the combined prior art.

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

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

1. Peña

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

2. Obviousness Analysis

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

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

a) Claim 17

Petitioner asserts that Peña expressly discloses the 7 conjugates recited by the claim. *Id*. (citing Ex. 1015, 3). According to Petitioner, a person of ordinary skill in the art would have been motivated to include the 7 conjugates disclosed by Peña in Chiron's formulation because Chiron (a) explains that the invention is directed to the "prevention and/or treatment of bacterial meningitis," including from pneumococcus, (b) teaches that its formulation may include "a saccharide antigen from *Streptococcus pneumonia*," (c) states that "[t]he composition may comprise one or more of these bacterial . . . antigens," and (d) refers to a journal article that discloses the 7-pneumococcal CRM_{197}-conjugate of claim 17. *Id*. at 64 (citing Ex. 1011, 6:32–35, 2:15, 3:14; Ex. 1073, 14).

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

Patent Owner asserts that the Petition only addresses the additional limitations of dependent claim 17, without addressing the limitations of independent claim 1 from which it depends. We disagree, as Petitioner expressly relies upon its assertions in Ground 1 as demonstrating how the combination of Chiron, Smith, and Elan teaches or suggests each limitation of independent claim 1. Pet. 63. Patent Owner's remaining arguments mirror those raised regarding the challenge of claim 17 over the combination of Chiron, Smith and Elan.

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

b) Claim 18

Petitioner asserts that Peña discloses a 13-valent pneumococcal conjugate vaccine with the same serotypes recited by claim 18. Pet. 65 (citing Ex. 1015, 7). According to Petitioner, a person of ordinary skill in the art would have understood that those conjugates each contain the CRM_{197} protein carrier, "based on the published progression from 7-valent

Prevnar®, to 9- and 11- valent iterations; each version contained CRM_{197} as the sole carrier protein." *Id*. (citing Ex. 1007 ¶¶ 45–46). Petitioner asserts that combining Peña's 13 conjugates with CRM_{197} as the only carrier protein would not have impacted the required "aggregation induced by the siliconized container means" because it is the protein component of the formulation that is responsible for that function and not the polysaccharide. *Id*. at 65 (citing Ex. 1008 ¶ 168).

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 65–66 (citing Ex. 1007 ¶ 48–49; Ex. 1008 ¶ 169). Petitioner's arguments mirror those raised in its challenge of claim 18 over the combination of Chiron, Smith and Elan, as Petitioner relies on Chiron and Peña in a similar manner for each ground.

Patent Owner's arguments also mirror those raised regarding the challenge of claim 18 over the combination of Chiron, Smith and Elan. PO Resp. 49–56. As in that ground, Patent Owner also asserts objective evidence of non-obviousness for claim 18. *Id*. at 56–63.

For similar reasons discussed in Section II.C.4.c. 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 Chiron's formulation 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 Chiron's 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 that is described as being in an "advanced phase of study." Pet. 59 (citing Ex. 1015, 2). Petitioner does not direct us to any disclosure in Peña, or other evidence of record, further characterizing the vaccine or the study, nor do we see such disclosures in the reference. Without such information, we are unable to assess whether the study involved a formulation comprising each of the 13 known serotypes conjugated to a CRM_{197} polypeptide, 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 modify Chiron's formulation to yield a 13-valent pneumococcal conjugate vaccine with the same serotypes as in Peña would have had a reasonable expectation of successfully doing so.

To the extent that Petitioner relies on a so-called "natural progression" from a seven valent conjugate to the 13-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. 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 established by a preponderance of the evidence that claim 17 of the '999 patent is unpatentable over the combination of Chiron, Smith, Elan and Peña. Petitioner, however, has not established by a preponderance of the evidence that claim 18 is unpatentable over the combined prior art.

III. MOTIONS TO EXCLUDE

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

A. Petitioner's Motion

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

Petitioner challenges Exhibits 2033, 2113, 2114, and portions of Exhibit 2123 (¶¶ 78–79) as they relate to Patent Owner's assertion of commercial success with respect to claim 18. Paper 34, 2. As we have not reached the merits of Patent Owner's evidence of secondary considerations of nonobviousness, we dismiss Petitioner's Motion to Exclude regarding

those exhibits as moot.

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

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

not refer to them in the Patent Owner Response. Accordingly, we dismiss Petitioner's Motion to Exclude those exhibits as moot.

B. Patent Owner's Motion

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

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

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

Having considered the evidence and the arguments, we agree with Patent Owner that Petitioner has not established that Exhibit 1065 is relevant regarding the knowledge of those skilled in the art at the time of the invention. Based upon our review, Dr. Kalonia refers to the book chapter submitted as Exhibit 1065 in his declaration discussion of his credentials. Ex. 1008 ¶ 7. Additionally, Petitioner and Dr. Kalonia refer to Exhibit 1065

when discussing certain arguments relating to the state of the art at the time of the invention. *See, e.g.*, Pet. 12 (referring to Exhibit 1065). We note that in such instances, those contentions are equally supported by other references, e.g., Smith.

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

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

As for Exhibit 1037, we have considered this exhibit, as discussed above in Section II.C.4.c, 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[18]

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 Chiron, Smith, and Elan;

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

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

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

FURTHER ORDERED that 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.

[18] 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)	Chiron, Smith, Elan	1–6, 10, 11, 14, 17, 19, 20	18
17, 18	103(a)	Chiron, Smith, Elan, 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).

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