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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

WYETH LLC,
Patent Owner.

Case IPR2017-00390
Patent 8,562,999 B2

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

HARLOW, *Administrative Patent Judge.*

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

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 7–9, 12, 13, 15, 16, 21, and 22 of U.S. Patent No. 8,562,999 B2 (Ex. 1001, "the '999 patent"). Paper 1 ("Pet."). Wyeth LLC ("Patent Owner") filed a Patent Owner's Preliminary Response. Paper 6 ("Prelim. Resp.").

On June 13, 2017, we instituted an *inter partes* review of all challenged claims. Paper 8 ("Dec. Inst."). On September 13, 2017, Patent Owner filed a Patent Owner Response to the Petition. Paper 15 ("PO Resp."). On December 13, 2017, Petitioner filed a Reply to the Patent Owner Response. Paper 27 ("Reply").

Petitioner and Patent Owner each filed a Motion to Exclude Evidence. Papers 33 and 37. Each party filed an Opposition to the other party's motion. Papers 42 and 46. Each party also filed a Reply to the other party's Opposition. Papers 48 and 59.[1] Patent Owner filed Motions for Observation on Cross-Examination Testimony. Papers 38 and 39. Petitioner filed a Response to each of Patent Owner's Motions for Observation. Paper 43 and 44.

On February 27, 2018, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 55 ("Tr.").

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

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a). and 37 C.F.R. § 42.73. Having considered the record before us, we determine that Petitioner has shown by a preponderance of the evidence that claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent are unpatentable. *See* 35 U.S.C. § 316(e). Additionally, the Motions to Exclude Evidence by Petitioner and Patent Owner have been decided below in Section III.

A. Related Proceedings

We have instituted two additional *inter partes* reviews of claims of the'999 patent in IPR2017-00378 and IPR2017-00380. Petitioner and Patent Owner explain that they are unaware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding. Pet. 3–4; Paper 4, 2. Paper 7, 2.

B. The '999 Patent

In some aspects, the '999 patent relates to formulations comprising an immunogen in the form of a polysaccharide-protein conjugate, a pH buffered saline solution, and an aluminum salt. Ex. 1001, 2:62–64, 12:9–15. The Specification defines the term "polysaccharide" as including "any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including, but not limited to, a 'saccharide', an 'oligosaccharide', a 'polysaccharide', a 'liposaccharide', a 'lipo-oligosaccharide (LOS)', a 'lipopolysaccharide (LPS)', a 'glycosylate', a 'glycoconjugate' and the like." *Id*. at 16:32–38.

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

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

C. Illustrative Claim

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

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

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

D. The Instituted Grounds of Unpatentability

Petitioner challenges the patentability of the claims as follows:

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

[2] Patent Application Publication No. WO 03/009869 A1 by Mario Contorni et al., published February 6, 2003. Ex. 1011 ("Chiron").
[3] *Smith et al., Technical Report No. 12: Siliconization of Parenteral Drug Packaging Components*, 42 (4S) J. PARENTERAL SCI. & TECH. S3–S13 (1988). Ex. 1012 ("Smith").
[4] Patent Application Publication No. WO 2004/071439 A2 by David Burke et al., published August 26, 2004. Ex. 1013 ("Elan").
[5] Summary of Product Characteristics for Prevenar Suspension for injection: Pneumococcal saccharide conjugated vaccine, adsorbed, Annex 1:1–15

Claims	Basis	References
13 and 16	pre-AIA § 103(a)	Merck[6] and the '787 patent[7]

Petitioner also relies on the Declarations of Dennis L. Kasper, M.D. (Ex. 1007), Devendra Kalonia, Ph.D. (Ex. 1010) Christopher Jones, Ph.D. (Ex. 1120), and Harm HogenEsch, D.V.M., Ph.D. (Ex. 1123).

Patent Owner relies on the Declarations of Paul Dalby, Ph.D. (Ex. 2117), Ali Fattom, Ph.D. (Ex. 2118), Lakshmi Khandke, Ph.D. (Ex. 2119), Garry Morefield, Ph.D. (Ex. 2122), and James W. Thomson, Ph.D. (Ex. 2125).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the

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(2005). Ex. 1017 ("Prevenar").

[6] Patent Application Publication No. WO 2011/100151 A1 by Michael J. Caulfield et al., published August 18, 2011.

[7] U.S. Patent No. 7,935,787 B2 by Lakshmi Khandke et al., issued May 3, 2011.

invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner and Patent Owner propose constructions for certain claims terms. Pet. 27–31; PO Resp. 12–21. As relevant to this Decision, we address the following claim terms.

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

Petitioner asserts that the broadest reasonable interpretation of the claim term "polysaccharide" is set forth in the Specification. Pet. 28–29. In particular, the Specification defines "polysaccharide" as including "any antigenic saccharide element (or antigenic unit) commonly used in the immunologic and bacterial vaccine arts, including, but not limited to, a 'saccharide', an 'oligosaccharide', a 'polysaccharide', a 'liposaccharide', a 'lipo-oligosaccharide (LOS)', a 'lipopolysaccharide (LPS)', a 'glycosylate', a 'glycoconjugate' and the like." Ex. 1001, 16:32–38. Patent Owner similarly acknowledges that the term "polysaccharide" is expressly defined in the Specification. PO Resp. 12.

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

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

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

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

Patent Owner asserts that "a purpose of the invention is to provide formulations that preserve the antigenicity of immunogenic formulations." PO Resp. 13. 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 14 (citing, e.g., Ex. 1001, 14:19–23) ("the immunogen (i.e., a polysaccharide-protein conjugate . . .)").

Patent Owner draws our attention to the Specification discussion in the "Background of the Invention" section that "the immunogenic composition must be active throughout its 'expected' shelf life, wherein any breakdown of the immunogenic composition to an inactive or otherwise undesired form (e.g., an aggregate) lowers the total concentration of the product." PO Resp. 14 (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. 2125 ¶ 39). Patent Owner asserts that "[f]or an immunogen to be capable of inducing an immune response in a body, the immunogen must be antigenic." *Id*. Patent Owner asserts that "[a]ntigenicity is a prerequisite for immunogenicity." *Id*. at 15. According to Patent Owner, although immunogenicity is not recited in the claims, it is related to a property recited in the claims, i.e., that the formulation "inhibits aggregation induced by the siliconized container means." *Id*. Patent Owner asserts that "silicone-induced aggregation is assessed by measuring antigenicity to determine the extent of the loss of antigenicity due to silicone-induced aggregation." *Id*. (citing Ex. 1001, Example 4).

Petitioner asserts that the Board should reject Patent Owner's proposed "antigenicity" limitation for the same reasons it rejected the importation of an "immunogenicity" requirement in the Institution Decision, because Patent Owner refers to "antigenicity" as a "prerequisite for immunogenicity." Reply at 2 (citing PO Resp. 15).

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

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

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

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

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

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

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

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

Petitioner asserts this claim phrase "recites a property of the formulation as a whole, without attributing inhibitory effect to any specific ingredient recited in the claim." Pet. 30 (citing Ex. 1010 ¶ 97). For example, Petitioner asserts that the plain language of the claim does not require that the aluminum salt inhibits silicone-induced aggregation. *Id*. at 30–31 (citing Ex. 1010 ¶¶ 98–102). According to Petitioner, because independent claim 1 recites a "formulation" followed by an open-ended term, "comprising," any element(s) comprised in the formulation may contribute the required inhibition, so long as the formulation as a whole "inhibits aggregation induced by the siliconized container means." *Id*.

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

Further, Patent Owner asserts that the "broadest reasonable interpretation of claim 1 should go no further than to read on embodiments that contain the three recited ingredients in a formulation that meets the

functional property limitation." *Id*. at 20–21. According to Patent Owner, the functional requirement of inhibiting aggregation induced by the siliconized container means must be satisfied by "a formulation of the three specifically recited ingredients [buffered saline solution, aluminum salt, and polysaccharide-protein conjugate], without any un-recited ingredient(s)." *Id.* at 20.

Having considered the arguments and evidence, we agree with Petitioner's rationale that claim 1 "recites a property of the formulation as a whole, without attributing inhibitory effect to any specific ingredient recited in the claim." Pet. 30 (citing Ex. 1010 ¶ 97). Further, we agree with Patent Owner that the claim element "the formulation . . . inhibits aggregation induced by the siliconized container means" may be interpreted to include an embodiment wherein the three specific ingredients recited in the claim, i.e., buffered saline solution, aluminum salt, and polysaccharide-protein conjugate, cause inhibition of aggregation induced by the siliconized container means. *See* PO Resp. 19–20. However, we do not agree with Patent Owner that the broadest reasonable interpretation ends there. Rather, we determine that by reciting the formulation using the open-ended term "comprising," along with attributing the aggregation inhibition property to "the formulation," the broadest reasonable construction also includes formulations comprising additional, unrecited ingredients, and such additional ingredient(s) may contribute to the required aggregation inhibition by the formulation. *See In re Baxter*, 656 F.2d 679, 686 (CCPA 1981) (use of the term "comprising" in a preamble of a claim permits inclusion of elements in addition to those specified in the claims); *CIAS, Inc. v. Alliance*

Gaming Corp., 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'").

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

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

B. Level of Ordinary Skill in the Art

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

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

bacterial vaccines," or (b) "a Master's degree in the pharmaceutical sciences, physical chemistry or protein chemistry, at least 4 years of work experience formulating protein-based compositions, and would have had familiarity or experience with the general components of bacterial vaccines." Pet. 27 (citing Ex. 1010 ¶ 82).

Patent Owner relies upon its definition of the level of ordinary skill in the art set forth in the Patent Owner Preliminary Response. PO Resp. 21. In that filing, Patent Owner disagreed with Petitioner's definition insofar as it suggests the field of invention involved protein-based formulations. Prelim. Resp. 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 11–12.

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. 14. Based on the record as a whole, we determine that a declarant having significant experience relating to protein-silicone oil interactions also

offers useful information relating to the subject matter of the challenged claims. Thus, we also recognize those having ordinary skill in the art relating to silicone-induced interactions/aggregation in pharmaceuticals.

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

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

Petitioner does not challenge the expertise of any of Patent Owner's declarants. Patent Owner, however, asserts that Petitioner's declarants, Drs. Kalonia and Kasper, lack "experience in developing polysaccharide-protein conjugate formulations, and certainly not on a commercial scale." PO Resp. 21. Regarding Dr. Kalonia, Patent Owner asserts that his experience is "limited to the aggregation of proteins in formulations on a laboratory scale." *Id*. at 21–22. 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. 1010 ¶ 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. 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. 1010 ¶¶ 18, 57, 89, 126, 165, 168.

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

focus" of his work is "the development of human vaccines, including polysaccharide-protein conjugate vaccines." Ex. 1007 ¶¶ 1, 5.

In support of its challenge of Dr. Kasper, Patent Owner directs us only to deposition testimony relating to Dr. Kasper's inexperience with using siliconized containers with his vaccine formulations. PO Resp. 22 (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.

C. Obviousness over Chiron, Smith, and Elan

Petitioner asserts that claims 7–9, 12, 13, 15, 16, 21, and 22 are unpatentable over the combination of Chiron, Smith, and Elan. Pet. 31–46. Patent Owner disagrees. PO Resp. 23–50.

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

the claim is unpatentable under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

1. Chiron

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

2. Smith

Smith is a Technical Report published in the Journal of Parenteral Science and Technology by The Parental Drug Association. Ex. 1012, 1. The report describes siliconization of parenteral drug packaging components. *Id*. Smith explains that "[m]ost parenteral packaging components require the use of some form of lubrication in order to improve their processability and functionality." *Id*. at 4. According to Smith,

silicone fluid is "[o]ne of the most commonly used lubricants for pharmaceutical packaging." *Id*. "Siliconization of packaging components such as glass, elastomeric closures, plastic, and metal, places an invisible water repellant film on the surface of the components" that "aid[s] in the free-draining characteristics, processing and machinability of vials and elastomeric closures." *Id*. Smith explains that "[s]ilicone fluid is commonly applied to plastic syringe barrels and glass cartridges used as plunger barrels to facilitate easy movement of the plunger within the barrel." *Id*. When applied to hypodermic needles, silicone oil reduces the frictional drag and pain associated with such drag as the coated needle passes through body tissue. *Id*.

3. Elan

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

reports that visual inspection confirmed that such precipitation was resolved by the addition of polysorbate 80. *Id*. at 17–18.

4. Obviousness Analysis

a. Claims 7–9 and 12

Petitioner contends that Chiron teaches or suggests every ingredient of the formulation recited in claim 1, from which each of challenged claims 7–9 and 12 depends. Pet. 32–38. 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 32–33 (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 33 (citing Ex. 1010 ¶ 138; Ex. 1045, 22). As for the saccharide antigen, Petitioner asserts that Chiron teaches that conjugation to a carrier protein is preferred. *Id*. at 33 (citing Ex. 1011, 3:20–21). Petitioner asserts that Chiron also teaches that its formulation comprises polysorbate 80. Pet. 36.

Focusing on challenged dependent claims 7–9, Petitioner contends that Chiron discloses a preferred pH range of between 6 and 7, the use of histidine as a buffer, and the use of a sodium salt, such as sodium phosphate or sodium chloride in the pH buffered saline solution of a vaccine formulation, as required by those claims. Pet. 38–39 (citing Ex. 1011, 5:15, 5:28, 6:7–8, 11:30–12:15, 14:3–17:4 (Examples 2, 7–9)).

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

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 7–9 and 12. Instead, 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.

i. Siliconized Container Means

Petitioner acknowledges that Chiron does not expressly teach that its formulations are comprised in a siliconized container means. *See* Pet. 34. 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 34–35(citing Ex. 1010 ¶¶ 144–147). 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 34–35 (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*. at 35 (citing Ex. 1010 ¶ 144). 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. 1010 ¶ 145; Ex. 1011, 8:37; 15:9–10). Similarly, Petitioner asserts that it would have been obvious to store Chiron's formulations in pre-filled syringes, as that that was a common method of supplying vaccines, as evidence by the commercialized Chiron polysaccharide-protein vaccine, Vaxem Hib. *Id*. (citing Ex. 1010 ¶¶ 146–147; Ex. 1051 and 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. 35 (citing Ex. 1010 ¶ 148). 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 34 (citing Ex. 1010 ¶ 143).

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*. at 24–25 (citing Ex. 2125 ¶ 55, Ex. 2122 ¶¶ 39–40, Ex. 2117 ¶¶ 75–78). Patent Owner asserts that although vials are used in Example 8 of Chiron, there is no teaching whether they were siliconized. *Id*. at 25. 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*. (citing Ex. 2122 ¶¶ 38, 40; Ex. 2117 ¶¶ 55, 5–78). Patent Owner notes that Chiron's Example 8 demonstrates that the 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 25–26 (citing Ex. 2122 ¶¶ 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." Pet. 26 (citing Ex. 2122 ¶¶ 45–46; 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*. 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*. at 26–27 (citing Ex. 2125 ¶¶ 55–56; Ex. 2122 ¶¶ 37–47; Ex. 2117 ¶¶ 45–50). 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 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. 1010 ¶ 148. 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. 21, Ex. 1010 ¶¶ 119–123, 148.

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. 25, 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?" *Id*. at 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. 1010 ¶¶ 102, 148. 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. 2122) and Thomson (Ex. 2125), 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. 25–26 (citing Ex. 2122 ¶¶ 39–42). 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, 15:3–6.

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. 2125 ¶ 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. 33–36.

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 5 (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*. (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*. at 6 (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 6, n.4 (citing 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. 26–27 and 29–30. 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.

ii. 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. 36 (citing Ex. 1011, 6:14–15; 14:3–17:4, Examples 7–9 with 0.0005% Tween ® 80). According to Petitioner, a person of ordinary skill in the art would have known that such a surfactant inhibits silicone-induced aggregation, as taught by Elan. *Id*. (citing Ex. 1010 ¶ 149; Ex. 1013, 16:13–15; 17:6–14). 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 37–38 (citing Ex. 1010 ¶¶ 153–154).

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 licensed conjugate vaccines similar to the formulations of Chiron . . . but without surfactant, e.g., Menactra®, did not exhibit from silicone-induced aggregation." *Id*. (citing Ex. 2122 ¶¶ 31, 33–36; Ex. 2117 ¶¶ 54–55, 57) (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. 36. 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.* (citing Ex. 2114 ¶¶ 32–35, 36–41, 80, 103; Ex. 2125 ¶ 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 50. 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 45 (citing Ex. 1013, 18:19–20; Ex. 2125 ¶¶ 68–74; Ex. 2117 ¶ 88. 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 48. 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 49.

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. 2122 ¶¶ 31–36).

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. 11 (citing Ex. 1010 ¶¶ 47–49). 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 (*id.*):

> 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.

Ex. 1001, 2:17-24; *see also* Ex. 1010 ¶ 49. 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. 22 (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. 36. 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 7–9 and 12, 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. 38–40. Patent Owner relies only on the arguments addressed above, and does not separately challenge Petitioner's assertions and evidence as they relate to these claims. Thus, we determine that Petitioner has shown by a preponderance of the evidence that claims 7–9 and 12 are unpatentable.

b. Claims 13, 15, and 16

Claims 13, 15, and 16 each depend from claim 1 and impose further limitations on the recited buffered saline solution, aluminum salt, and/or polysaccharide-protein conjugates. Each of claims 13, 15, and 16 requires that the buffer is histidine, the salt in the pH buffered saline solution is sodium chloride, and the aluminum salt is aluminum phosphate. Ex. 1001, 31:47–50, 32:1–10. Petitioner relies on the same disclosures by Chiron described above with regard to claim 12, and undisputed by Patent Owner,

as teaching the use of a histidine as a buffer, sodium chloride as the salt in the pH buffered saline solution, and aluminum phosphate as the aluminum salt. Pet. 39–40.

Claims 13 and 16 additionally require that the histidine buffer have a pH of 5.8. Ex. 1001, 31:47–48, 32:8–9. Petitioner asserts, relying on Dr. Kalonia, that "[t]he effective buffering range of histidine is approximately pH 5.0–7.0, and the choice of a specific pH within that range would have been a matter of routine optimization." *Id*. at 40–41 (citing Ex. 1010 ¶ 161). In this respect, Petitioner notes that the '999 patent neither expressly describes nor exemplifies a histidine buffer at pH 5.8; nor does the '999 patent suggest that such pH is critical to the invention or that it yields unexpectedly superior results. *Id*. Petitioner acknowledges that Chiron identifies a pH range for histidine buffer of pH 6–7 as preferred, but explains that an ordinarily skilled artisan "would have been motivated to choose histidine buffer with a pH below 6 to increase adsorption of acidic antigens (such as CRM_{197} and most bacterial polysaccharides) to aluminum phosphate adjuvant." *Id*. at 41 (citing Ex. 1010 ¶ 163). Petitioner also notes that the recited pH of 5.8 is close to the preferred range described by Chiron. *Id*. at 42.

Claims 15 and 16 further recite that the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides. Ex. 1001, 32:1–3, 32:6–8. Relying on Dr. Kalonia, Petitioner avers that "[i]t would have been obvious to use pneumococcal polysaccharide-protein conjugates in [the claimed] formulation, and that such formulations would still inhibit silicone-induced aggregation." *Id*. at 42 (citing Ex. 1010 ¶ 164).

Petitioner asserts that Chiron expressly discloses the use of pneumococcal polysaccharides as antigens. *Id*. (citing Ex. 1007 ¶¶ 32, 34, 42–46; Ex. 1010 ¶ 165; Ex. 1011, 2:15, 3:14, 6:32–35). Petitioner additionally states that an ordinarily skilled artisan "would have understood that the *protein* component of polysaccharide-protein conjugates (not the polysaccharide) is responsible for the claimed 'aggregation induced by the siliconized container means.'" *Id*. at 43 (citing Ex. 1010 ¶ 166).

Patent Owner responds that "none of the asserted references disclose histidine at pH 5.8," as required by claims 13 and 16. PO Resp. 31. Patent Owner additionally argues that an ordinarily skilled artisan "would have chosen a pH that is optimal for the conjugates included in the formulation" and asserts that Petitioner provides "no basis" for its assertion that histidine at pH 5.8 is optimal for the claimed formulation. *Id*. As for the recitation in claims 15 and 16 that the polysaccharide-protein conjugates comprise one or more pneumococcal polysaccharides, Patent Owner contends that "none of the asserted references disclose such conjugates." PO Resp. 32.

Patent Owner further argues that Petitioner fails to identify a rationale for changing the formulation disclosed in any of the cited references to include either a histidine buffer at pH 5.8 or pneumococcal polysaccharides, and fails to address whether formulations so modified would satisfy the claim 1 requirement for inhibiting aggregation induced by the siliconized container means. PO Resp. 30–31. 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).

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 1, for the reasons set forth, supra. 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 a histidine buffer at pH 5.8, as required by claims 13 and 16, and one or more pneumococcal polysaccharides, as required by claims 15 and 16.

With regard to the pH requirement of claims 13 and 16, the record shows that the effective buffering range of histidine buffer is from approximately pH 5.0 to 7.0 (Ex. 1010 ¶ 161), and the physiologically acceptable pH range for buffers in pharmaceuticals is from approximately pH 5.5 to 7.5 (*id.* at ¶ 58), each of which encompasses the claimed histidine buffer pH of 5.8. Ex. 1010 ¶ 161. Accordingly, we determine that an ordinarily skilled artisan would have had reason for, and a reasonable expectation of success in, using a histidine buffer within the physiologically acceptable pH range, including pH 5.8, with the vaccine formulations disclosed by Chiron. In this regard, we observe that the record does not indicate that, beyond the contours of histidine's effective buffering range, and the physiological acceptability of the formulation, histidine at a particular pH is critical to the invention claimed in the '999 patent, or that histidine at pH 5.8 provides unexpectedly beneficial results. Ex.1010, ¶161; *see ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345

(Fed. Cir. 2012) (finding invalidity over prior art where "there is no allegation of criticality or any evidence demonstrating any difference across the range [i.e., the broader range of the prior art]").

Moreover, we determine that a preponderance of the evidence demonstrates that an ordinarily skilled artisan would have been motivated to use histidine buffer at a pH slightly below the preferred range of pH 6 to 7 disclosed by Chiron in order to increase the adsorption of acidic antigens (such as CRM_{197} and most bacterial polysaccharides) to the aluminum phosphate adjuvant, and would have had a reasonable expectation that such a formulation would have worked for its intended purpose. Ex.1010, ¶¶ 162, 163; Ex. 1123 ¶¶ 29–31. In this regard, we note that Chiron exemplifies formulations in which the histidine buffer falls outside of the disclosed preferred pH range, discrediting the contention that the use of histidine buffer with a pH slightly outside of the preferred range would frustrate the purpose of the formulations disclosed. Ex. 1011, 15:3–16:6 (Examples 7 and 8). We also credit Dr. Kalonia's testimony that an ordinarily skilled artisan would have sought to reduce the pH of the histidine buffer to 5.8 in order to promote adsorption between acidic antigens and aluminum phosphate adjuvant, without any expectation that the slightly lowered pH would interfere with the purpose of the formulations disclosed by Chiron. Ex.1010, ¶ 162. We likewise find persuasive Dr. HogenEsch's testimony reiterating that histidine "is most effective as a buffer in the pH range of about 5 to 7," and confirming that "[u]sing histidine buffer, a POSITA could freely optimize the pH required for adsorption of CRM_{197} conjugates to aluminum phosphate." Ex. 1123 ¶ 31.

Concerning the requirement of claims 15 and 16 that the one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides, Chiron expressly discloses that its formulation may be prepared using a saccharide antigen from *S. pneumonia*, and specifically cites a reference in that discussion disclosing a vaccine comprising 7-valent polysaccharide-protein conjugate. Ex. 1011, 2–3 and 6 (citing Ex. 1073, 14).

Furthermore, 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 Dr. Kalonia persuasively explained, 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. Ex. 1010 ¶ 51; *see also* Pet. 11.

Accordingly, we determine that Petitioner has established by a preponderance of the evidence that claims 13, 15, and 16 are unpatentable over the combination of Chiron, Smith, and Elan.

c. Claims 21 and 22

Claim 21 depends indirectly from claim 1 and further requires that "is succinate at a final concentration of 1 mM to 10 mM and pH 5.8 to 6.0." Ex. 1001, 32:85–54. Claim 22 depends from claim 21 and additionally recites that "the succinate buffer is at a final concentration of 5 mM. *Id.* at 32:55–56.

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

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

Petitioner similarly contends that the 5 mM succinate buffer concentration required by claim 22 "is a matter of routine optimization and 5 mM is a standard one for buffers. *Id*. at 60 (citing Ex. 1010 ¶ 172; Ex. 1011, 5:12–13 ("most preferably, [concentration of histidine buffer] is about 5 mM").

Patent Owner responds that "none of the references in the asserted combination discloses a succinate buffer." Patent Owner additionally contends that an ordinarily skilled artisan "would understand that histidine in Chiron 2003 is not used as a buffer at all, but as a competitive ligand binding agent to phosphate, and therefore the use of other buffers would not have been expected to have the same effect as histidine." PO Resp. 33. Patent Owner further asserts that an ordinarily skilled artisan "would have recognized that the key disclosure relevant to the concentration of histidine in the formulation of Chiron 2003 is the molar ratio between histidine and free phosphate," and, thus, "would not have found it obvious to substitute succinate for histidine." *Id.*

Having considered the entirety of the record, 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 1, for the reasons set forth regarding the discussion of claim 1, supra. 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 a

succinate buffer at pH 5.8 to 6.0, and having a final succinate concentration of 1mM to 10mM (claim 21) or 5mM (claim 22).

In particular, we find persuasive Dr. Kalonia's testimony that an ordinarily skilled artisan would have had reason for, and a reasonable expectation of success in, substituting succinate buffer for histidine buffer in view of the overlap of the effective buffering range for succinate buffer with the effective buffering range for histidine buffer, and the physiologically acceptable pH range for vaccine formulations. Pet. 44–45 (citing Ex. 1010 ¶¶ 170, 171.

Furthermore, we do not find persuasive Patent Owner's argument that an ordinarily skilled artisan would have understood that Chiron uses histidine as a ligand binding agent, rather than a buffer, and, thus, would not have expected succinate to have the same effect as histidine in the formulations disclosed (PO Resp. 33). As explained in greater detail in Section II.D.2.a.i, below, we are persuaded by the testimony of Dr. HogenEsch that, contrary to the speculation of Patent Owner's declarants, Drs. Morefield and Thomson, "histidine buffer had specifically been reported . . . not to interact with aluminum adjuvant through ligand exchange." Ex. 1123 ¶ 43 (citing US Patent No. 6,251,678 B1[9]).

Based on the foregoing, therefore, we determine that Petitioner has established by a preponderance of the evidence that claims 21 and 22 are unpatentable over the combination of Chiron, Smith, and Elan.

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

D. Obviousness over Prevenar and Chiron

Petitioner asserts that claims 7–9, 12, 13, 15, 16, 21, and 22 are unpatentable under § 103(a) as obvious in view of Prevenar and Chiron. Pet. 46–60. Patent Owner disagrees. PO Resp. 51–62.

1. Prevenar

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

2. Obviousness Analysis

a. Claims 7–9, 12, and 15

Petitioner contends that Prevenar teaches two of the three ingredients recited in claim 1, from which each of the challenged claims ultimately depends. Pet. 25. In particular, Petitioner asserts that Prevenar teaches vaccine formulations comprising seven pneumococcal polysaccharides (from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) each conjugated to the CRM_{197} carrier protein and adsorbed on aluminum phosphate. *Id*. at 50 (citing Ex. 1017, 11). Additionally Petitioner asserts that Prevenar discloses

using sodium chloride as an excipient. *Id*. at 47 (citing Ex. 1017, 14[10]). Prevenar does not teach that its vaccine comprises a buffer. *Id*. at 25. Petitioner asserts, however, that "[b]uffer (used to resist change in pH) is a standard component of many protein-based pharmaceuticals, including polysaccharide-protein conjugate vaccines (*e.g.*, Vaxem Hib and ProHIBiT)." *Id*. at 48 (citing Ex. 1010 ¶ 179; Ex. 1011, 1:6–7).

Moreover, Petitioner asserts Chiron similarly discloses aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulations comprising a sodium salt such as sodium chloride and a histidine buffer. *Id*. at 47–48 (citing Ex. 1011, 1:27–2:3; 5:17–20, 5:28). Petitioner asserts that Chiron teaches that the addition of histidine buffer is advantageously biocompatible and safe, and enhances pH and antigen stability. *Id*. at 48–49 (citing Ex. 1011, 1:6–7; 5:6–7, 15; 11:30–12:15; 14:3–17:4).

According to Petitioner, it would have been obvious to a person of ordinary skill in the art to use the histidine buffer of Chiron in the Prevenar vaccine because Chiron teaches that histidine enhances the stability of vaccines which include aluminum salt adjuvants. *Id*. at 48 (citing Ex. 1010 ¶ 178; Ex. 1011, 1:31–2:3). Additionally, Petitioner asserts that Chiron teaches that "[t]he use of histidine in combination with an aluminum phosphate (particularly a hydroxyphosphate) is particularly advantageous for acidic antigens." *Id*. at 49 (quoting Ex. 1011, 5:3–4). According to

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

Petitioner and Dr. Kasper, because Prevenar's vaccine comprises acidic antigens, a person of skill in the art would have understood from Chiron that the formulation would benefit from histidine buffer. *Id*. (citing Ex. 1007 ¶ 55). Further, Petitioner asserts that Chiron's histidine buffer is inherently within the scope of the claim limitation requiring the buffer to have a pKa of about 3.5 to about 7.5 because "the pKa with respect to the side group proton is approximately 6.0." *Id*. (citing Ex. 1010 ¶ 182; Ex. 1045,[11] 22).

As for the siliconized container means, Petitioner asserts that an approved formulation of the Prevenar vaccine is provided in "'pre-filled syringe (Type I glass),' which was known to be siliconized." Pet. 50 (quoting Ex. 1010 ¶ 187 (quoting Ex. 1017, 14, Ex. 1076, 7).

Petitioner asserts that Prevenar's formulation, modified to include Chiron's histidine buffer, inherently inhibits silicone-induced aggregation in siliconized containers. Pet. 51 (citing Ex. 1010 ¶ 188). According to Petitioner, Patent Owner conveys in the Specification of the '999 patent and during prosecution that adsorption of polysaccharide-protein conjugates to aluminum phosphate adjuvant inhibits silicone-induced aggregation. *Id*. Petitioner asserts that such adsorption is taught by Prevenar and Chiron. *Id*. (citing Ex. 1017, 11; Ex. 1011, 4:5).

Further, Petitioner asserts that a person of ordinary skill in the art would have had a reasonable expectation of successfully combining the

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

teachings of Prevenar and Chiron to arrive at the claimed formulation because buffer was a common component of vaccines and Chiron teaches that histidine buffer confers pH and antigen stability to pneumococcal conjugate formulations such as Prevenar that have aluminum phosphate adjuvant. Pet. 52–53 (citing Ex. 1010 ¶ 195).

Turning to the challenged dependent claims, with regard to claims 7–9, Petitioner relies on the same disclosures by Chiron described in conjunction with the asserted ground of unpatentability based on Chiron, Smith, and Elan, discussed in Section II.C.4.a., above. Petitioner additionally asserts that it would have been obvious to modify Prevenar to include histidine buffer, as required by claim 8, for the reasons set forth above with respect to claim 1. Pet. 53 (citing Ex. 1010 ¶ 200). Petitioner also contends that Prevenar's disclosure of sodium chloride as an excipient, in conjunction with Chiron's teachings concerning the inclusion of sodium salt in vaccine formulations, renders claim 9 obvious. *Id*. at 54 (citing Ex. 1017, 14; Ex. 1011, 5:28).

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

As for the additional requirement of claim 15 that the "one or more polysaccharide-protein conjugate comprises one or more pneumococcal polysaccharides" (Ex. 1001, 32:1–3), Petitioner asserts that Prevenar

expressly discloses a formulation including 7 pneumococcal polysaccharides, sodium chloride, and aluminum phosphate. Pet. 57. Petitioner further contends that, for the same reasons identified above with regard to claim 1, it would have been obvious to modify Prevenar in view of Chiron to include histidine buffer. *Id.*

Patent Owner does not dispute that the only difference between the ingredients recited in challenged claims 7–9, 12, and 15 and Prevenar's formulation is that Prevenar does include a histidine buffer. Patent Owner also does not dispute Petitioner's contention that one of skill in the art would have understood that the Prevenar vaccine was provided in a siliconized container means because its approved formulation was distributed in a type of pre-filled syringe known to be siliconized. The parties' disputes instead center upon whether Petitioner has established by a preponderance of the evidence that (a) a person of ordinary skill in the art would have had a reason to combine Chiron's histidine buffer with the Prevenar vaccine with a reasonable expectation of success, and (b) the combined formula inherently inhibits silicone-induced aggregation.

i. Reason to Combine and Reasonable Expectation of Success

Patent Owner asserts that Petitioner fails to provide a reason to combine to Chiron's buffer to Prevenar's formulation, and that such combination is proposed only to reach the claimed invention and is, thus, based on hindsight. PO Resp. 56–57.

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

Prevenar's formulation. PO Resp. 57 (citing Ex. 2122 ¶¶ 49–73; Ex. 2125 ¶¶ 76–87). Patent Owner asserts that Prevenar's formulation was known to be stable, without a buffer, such that there would have been no reason to add one. *Id*.

Additionally, Patent Owner asserts, a person of skill in the art would have understood that histidine competes with at least serotypes 6B, 19F, and 23F in the Prevenar vaccine for binding positions on the aluminum phosphate adjuvant. PO Resp. 58 (citing Ex. 2122 ¶¶ 49–51; Ex. 2125 ¶¶ 77, 87). According to Patent Owner, the skilled artisan would have avoided adding histidine because it would "disrupt antigen binding to the aluminum adjuvant, rendering the formulation inferior to the Prevenar [] vaccine without histidine." *Id*. at 60. Additionally, Patent Owner asserts that "histidine could also disrupt the electrostatic attraction mechanism of antigen adsorption to aluminum phosphate." *Id*. (citing Ex. 2122 ¶ 62).

Further, Patent Owner asserts that Petitioner fails to address whether histidine would meet the optimal pH for the Prevenar vaccine. PO Resp. 61–62. According to Patent Owner, without knowing the optimal pH of the Prevenar vaccine, a person of skill in the art would have been dissuaded from combining histidine with Prevenar. *Id*. at 62 (citing Ex. 2125 ¶¶ 76–87; Ex. 2122 ¶¶ 49–73).

Each of those contentions by Patent Owner, however, are inadequately supported by the testimony of Drs. Morefield (Ex. 2122) and Thomson (Ex. 2125). The portions of the declarations of Drs. Morefield and Thomson relied upon by the Patent Owner do not refer to any evidence to support their opinions that a histidine buffer would not be a beneficial

addition to the Prevenar formulation. Rather, those discussions sound of unsubstantiated theoretical concerns, and are speculative at best. At worst, certain of those theories has been refuted in the art. For example, Petitioner directs us to the testimony of one of its declarants, Dr. HogenEsch, who has a Ph.D. in Pathology and Immunology. Reply 18–20. Dr. HogenEsch explains persuasively that, contrary to the speculation of Drs. Morefield and Thomson, "histidine buffer had specifically been reported . . . not to interact with aluminum adjuvant through ligand exchange." Ex. 1123 ¶ 43. In support of this testimony, Dr. HogenEsch quotes a disclosure from US Patent No. 6,251,678 B1[12] explaining that, although phosphate-containing buffers are generally not preferred because they may interact with aluminum adjuvants, "the non interaction of histidine . . . buffers with aluminum adjuvant was demonstrated by zeta potential measurements of the surface charge of the aluminum adjuvant." *Id*. (quoting Ex. 1109).

We find that the unsupported testimony offered by Patent Owner's declarants to be outweighed by rebuttal testimony from Dr. HogenEsch and the express disclosures by Chiron relied upon by Petitioner. Generally, as Petitioner and Dr. Kalonia note, Chiron teaches that buffers are a standard component of vaccines. Pet. 48; Ex. 1010 ¶¶ 179 (citing Ex. 1011, 1:6–7). More specifically, as Petitioner asserts, Chiron teaches that adding histidine buffer to aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulations comprising a sodium salt is advantageously biocompatible and

[12] US Patent 6,251,678 B1 issued to David B. Volkin et al., June 26, 2001.

safe, and enhances pH and antigen stability. *Id*. at 48–49 (citing Ex. 1011, 1:6–7; 5:6–7, 15; 11:30–12:15; 14:3–17:4). Chiron teaches also that "[t]he use of histidine in combination with an aluminum phosphate (particularly a hydroxyphosphate) is particularly advantageous for acidic antigens." Ex. 1011, 5:3–4. Prevenar's formulation represents such an aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulation comprising a sodium salt, wherein the aluminum phosphate adjuvant is a hydroxyphosphate, as recognized by Dr. Morefield. *See* Ex. 2122 ¶ 59. Thus, on balance, we determine that the preponderance of the evidence supports Petitioner's contention that a person of ordinary skill in the art would have a reason to add a histidine buffer to the Prevenar vaccine with a reasonable expectation of enhancing the stability of the product.

ii. Inhibition of Aggregation Induced By the Siliconized Container Means

Patent Owner asserts that Petitioner "fails to show that the formulation resulting from the combination of Prevenar [] and Chiron [] was known to inhibit silicone-induced aggregation." PO Resp. 52. Additionally, Patent Owner asserts that the stated mechanism of action of the claimed formulation's ability to inhibit such aggregation, i.e., via adsorption of polysaccharide-protein conjugate to the aluminum salt, was not known in the prior art. *Id*. at 53. According to Patent Owner, Petitioner has not adequately established that Prevenar's formulation modified to include Chiron's histidine inherently possessed the properties of the claimed invention. *Id*. at 53–54. In support of that assertion, Patent Owner cites case law explaining that "[w]hat is important regarding properties that may be

inherent, but unknown, is whether they are unexpected." *Id*. (quoting *Honeywell Int'l Inc. v. Mexichem Amanco Holding S. A.*, 865 F.3d 1348, 1355 (Fed. Cir. Aug. 1, 2017).

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

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

Here, Petitioner asserts that Prevenar's formulation, modified to include Chiron's histidine buffer, comprises every recited ingredient of claim 1, from which each of the challenged claims depends. Petitioner's inherency argument is not based upon probabilities or possibilities. Rather, Petitioner relies on the fact that Prevenar's modified formulation is the formulation that is claimed, wherein the claims and the Specification of the '999 patent describe that the inhibition of silicone-induce aggregation is the natural result of the combination of elements disclosed in the prior art. Pet. 51–52; Ex. 1010 ¶¶ 188, 189 (characterizing the '999 patent Specification as emphasizing that the adsorption of polysaccharide-protein conjugates to

aluminum phosphate adjuvant inhibits silicone-induced aggregation); *see PAR Pharm.*, 773 F.3d at 1196 (describing meeting high standard for inherency in an obviousness analysis when the claim limitation is the "natural result of the combination of elements explicitly disclosed by the prior art"). As Petitioner asserts, such adsorption is taught by Prevenar and Chiron. Pet. 51; Ex. 1017, 2 (polysaccharide-protein conjugates adsorbed on aluminum phosphate); Ex. 1011, 4:5 (antigen is preferably adsorbed to the aluminum salt). Thus, we determine that Petitioner has established persuasively that Prevenar's composition, as modified by the addition of Chiron's histidine, yields the formulation of claim 1, wherein the recited aggregation inhibition property of the formulation must be present, or is the natural result of the combination of elements disclosed by the prior art.

Patent Owner does not separately address Petitioner's related challenges to dependent claims 7–9, 12, and 15, but relies, instead, solely on its arguments as to the patentability of claim 1. Based upon our review of Petitioner's contentions regarding the additional limitations of those claims, therefore, Pet. 46–54, and 57–58, we determine that Petitioner has shown by a preponderance of the evidence that each of those dependent claims would have been obvious over the combination of Prevenar and Chiron.

b. Claims 13 and 16

Petitioner relies on the same disclosures described above as suggesting the use of a histidine buffer, as taught by Chiron, in the vaccine formulation of Prevenar to satisfy the histidine buffer requirement of claims 13 and 16, and the pneumococcal polysaccharide requirement of

claim 16. Pet. 55–56, 58. With regard to the further recitation of those claims that the histidine buffer have a pH of 5.8 (Ex. 1001, 31:47–48, 32:8–9), Petitioner reasserts its position, detailed in Section II.C.4.b., above, that "[t]he effective buffering range of histidine is approximately pH 5.0–7.0, and the choice of a specific pH within that range would have been a matter of routine optimization." Pet. 55 (citing Ex. 1010 ¶ 209).

Patent Owner relies on the same arguments addressed above in Section II.C.4.b. as to the patentability of claims 13 and 16. PO Resp. 55 ("For the same reasons outlined in Section V.A.3.a[13] above, the asserted combination fails to disclose the additional limitations of claims 13 and 16.").

For the reasons previously provided, 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 modify Prevenar's vaccine formulation to included Chiron's histidine to arrive at the formulation of claim 1. Furthermore, based on the record as a whole, for the reasons set forth in Section II.C.4.b., 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 include that histidine buffer at pH 5.8, as required by claims 13 and 16, and one or more pneumococcal polysaccharides, as required by claim 16.

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[13] Patent Owner's reference to Section V.A.3.a appears to be an inadvertent typographical error, as no such section exists. We understand Patent Owner to reference Section VI.A.3.a.

c. Claims 21 and 22

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

Patent Owner reiterates the arguments addressed above in Section II.C.4.c. as to the patentability of claims 21 and 22. PO Resp. 55 ("For the same reasons outlined in Section V.A.3.a[14] above, the asserted combination fails to disclose the additional limitations of claims 21 and 22."). For the reasons previously explained, we do not find these arguments persuasive.

Patent Owner additionally contends that an ordinarily skilled artisan would not interpret Chiron's "disclosure of a preferred pH of 6–7 as the preferred pH for vaccine compositions in general." PO Resp. 55. In this regard, Patent Owner asserts that an ordinarily skilled artisan "would have understood that conjugates varied considerably and unpredictably in their stability and aggregation profile," and that it would, therefore, be necessary to empirically determine the preferred pH for a given conjugate. PO Resp. 55–56.

[14] Patent Owner's reference to Section V.A.3.a appears to be an inadvertent typographical error, as no such section exists. We understand Patent Owner to reference Section VI.A.3.a.

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 modify the composition of Prevenar to include the histidine buffer of Chiron in a manner that meets each limitation of claim 1, for the reasons set forth regarding the discussion of claim 1, supra. Further, based on the entirety of the record, 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 this formulation comprising a succinate buffer at pH 5.8 to 6.0, and having a final succinate concentration of 1mM to 10mM (claim 21) or 5mM (claim 22).

Chiron explicitly teaches that the pH of the disclosed aluminum-adjuvanted pneumococcal CRM_{197} conjugate formulation "is preferably between 6 and 7 (e.g. between 6.3 and 7.0). The pH may be maintained by the use of a buffer." Ex. 1011, 7:7–8. Notably, the pH range disclosed by Chiron falls within the physiologically acceptable pH range for pharmaceuticals of from approximately pH 5.5 to 7.5, and overlaps significantly with the effective buffering ranges of histidine and succinate buffers. Ex. 1010 ¶ 58. In addition to teaching the use of a buffer to maintain pH, Chiron specifically discloses that "histidine preferably acts as a buffer. Histidine buffers are well known to the skilled person." Ex. 1011, 6:15. Moreover, Patent Owner does not dispute that succinate and histidine are both well-known buffers, or that it would have required no more than routine optimization to arrive at the claimed concentration and pH of the succinate buffer.

Rather, Patent Owner resorts again to the inadequately supported testimony of one of its declarants, Dr. Dalby (Ex. 2117). However, Dr. Dalby's speculation regarding the role of histidine in Chiron (Ex. 2117 ¶¶ 120–125) conflicts directly with Chiron's explicit teachings that the pH of the disclosed formulations "may be maintained by the use of a buffer" (Ex. 1011, 7:7–8), and that "histidine preferably acts as a buffer (*id.* at 6:15). We are likewise unpersuaded by Dr. Dalby's discussion of the potential for variation in conjugate stability and aggregation profiles, as it is not addressed to the conjugates described in the asserted references, and does not identify adequate support for the contention that an ordinarily skilled artisan would not have recognized Chiron's disclosure of a preferred pH range of 6–7 as the preferred pH range for the formulation disclosed by Prevenar, in view of the similarities between the formulations disclosed by those references. *See* Ex. 2117 ¶¶ 124, 125 (speculating as to the preferred pH for vaccines "in general," without regard to the particular formulations at issue). Accordingly, we find that the unsupported testimony offered by Dr. Dalby is outweighed by the express disclosures of Chiron, as well as the testimony of Dr. Kalonia, relied upon by Petitioner.

We, therefore, determine that Petitioner has established by a preponderance of the evidence that claims 21 and 22 are unpatentable over the combination of Prevenar and Chiron.

E. Obviousness over Merck and the '787 patent

Subsequent to the Supreme Court's decision in *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018), we issued an order instituting review of claims 13 and 16 as obvious in view of Merck and the '787 patent. Paper 57. On May 14, 2018, pursuant to our authorization, the parties filed a Joint Motion to Limit the Petition. Paper 58. By that Motion,

> [t]he parties agree to withdraw from consideration, and jointly request withdrawal of, newly-instituted Ground 3 (*i.e.*, that "Claims 13 and 16 are unpatentable as obvious under pre-AIA 35 U.S.C. § 103(a) over Merck 2011 (Ex. 1018) in view of the '787 Patent (Ex. 1004) and the general knowledge of a POSITA").

Id. at 1. On June 5, 2018, we issued an Order granting the Joint Motion to Limit the Petition in the manner sought by the parties. Paper 61. Accordingly, because it has been removed from the proceeding, we do not address the alleged unpatentability of claims 13 and 16 as obvious in view of Merck and the '787 patent.

III. MOTIONS TO EXCLUDE

Petitioner and Patent Owner have each filed a motion to exclude evidence. Papers 33 and 37.

A. Petitioner's Motion

Petitioner moves to exclude Patent Owner's Exhibits 2033, 2113, 2114, 2150–2159, and portions of Exhibits 2125 (¶¶ 94–95) and 2119 (¶¶ 9, 12–17, 25, and 27–28). Paper 33. Patent Owner opposes the motion.

Paper 46. 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 2125 (¶¶ 94–95) as they relate to Patent Owner's assertion of commercial success with respect to claim 18. Paper 34, 2. Although claim 18 is at issue in two related cases, IPR2017-00378 and IPR2017-00380, it is not at issue here. Accordingly, because 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 33, 2 (citing Federal Rules of Evidence "FRE" 702 and 703). In this *inter partes* review proceeding, we find that such matters go to the probative weight of 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 33, 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, 1108, 1109, and 1123. Paper 37. 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 1123 is the Declaration of Harm HogenEsch, D.V.M., Ph.D., submitted in support of Petitioner's Reply (Paper 27). Patent Owner contends that "at least paragraphs 42 and 43 of Exhibit 1123, citing new Exhibits 1084 and 1109" should be excluded as beyond the proper scope of Petitioner's Reply. Paper 37, 14–15. According to Patent Owner, Petitioner's "inclusion of new arguments and evidence in Reply that could

have been included in the Petition is highly prejudicial to Patent Owner, and the prejudice substantially outweighs any relevance the evidence or arguments may have." *Id.* at 15.

Petitioner responds that "Dr. HogenEsch's testimony was directly responsive to Patent Owner's argument (POR at 58–60) that the histidine buffer of Chiron 2003 interacts with aluminum adjuvant through ligand exchange, and therefore, histidine buffer would have interfered with adsorption of the conjugates of Prevenar 2005 to aluminum phosphate adjuvant." Paper 42, 14. Petitioner additionally asserts that "Patent Owner also was not prejudiced by Dr. HogenEsch's testimony, as Patent Owner had the opportunity to cross-examine Dr. HogenEsch." *Id.*

Having considered the evidence and the arguments, we agree with Petitioner that Dr. HogenEsch's declaration is directly responsive to arguments made by Patent Owner in the Response, and that the admission of that exhibit presents no undue prejudice. With particular regard to paragraphs 42 and 43, Dr. HogenEsch's testimony that histidine had been used successfully as a buffer in aluminum-adjuvanted vaccines, and that histidine buffer had been found not to interact with aluminum adjuvant through ligand exchange responds directly to the argument in the Patent Owner Response that the histidine buffer and aluminum adjuvant of Chiron interact through ligand exchange. Patent Owner does not identify any aspect of Dr. HogenEsch's testimony that sets forth a new line of reasoning regarding unpatentability. Rather, Patent Owner appears to argue that Dr. HogenEsch's testimony should be excluded because Petitioner should have anticipated Patent Owner's ligand exchange argument, and, thus,

should have included Dr. HogenEsch's testimony with the Petition. But that is not the standard for a motion to exclude. Because Dr. HogenEsch's testimony properly responds to arguments raised in the Patent Owner Response, Patent Owner's Motion to Exclude Exhibit 1123 is *denied*.

Patent Owner also seeks to exclude Exhibit 1084 and Exhibit 1109, on which Dr. HogenEsch relies in his testimony. Exhibit 1084 is the 2007 Physicians' Desk Reference entry for the Gardasil vaccine. Exhibit 1109 is a patent relating to the Gardasil vaccine formulation. Patent Owner moves to exclude Exhibit 1084 as legally irrelevant because Petitioner did not establish that it was publicly accessible before the priority date of the '999 patent. Paper 37, 7. Patent Owner additionally argues that each of Exhibits 1084 and 1109 should be excluded because the vaccines described in those references are not polysaccharide-protein conjugate drugs. Paper 37, 7, 14. Patent Owner further asserts that these exhibits exceed the proper scope of the Reply, for the same reasons described above concerning Exhibit 1123. *Id.* at 8–9, 13–14.

Petitioner counters that Exhibits 1084 and 1109 "each disclose an aluminum-adjuvanted vaccine formulation that includes both histidine buffer and polysorbate 80," and are directly responsive to the argument, set forth in Patent Owner's Response, that "'the combination of histidine and polysorbates was known to be unstable' as of April 26, 2006." Paper 42, 11. Petitioner further argues that the challenged exhibits demonstrate the compatibility of histidine buffer and polysorbate 80, and indicate what an ordinarily skilled artisan would have understood regarding that compatibility before the priority date of the '999 patent. *Id.* at 12. Petitioner also notes

that Patent Owner does not challenge the admissibility of Exhibit 1109 in IPR2017-00380, even though it is an exhibit in that proceeding. Paper 42, n.8.

For the same reasons set forth above with regard to Dr. HogenEsch's testimony, we are unpersuaded by Patent Owner's assertion that Exhibit 1109 exceeds the proper scope of the Reply. To the contrary, as set forth above, evidence concerning the combinability of histidine buffer and polysorbate 80 in vaccine formulations is probative of the issues at trial, and directly responsive to arguments made in the Patent Owner Response. We are likewise unpersuaded by Patent Owner's contention that Exhibit 1109 should be excluded as legally irrelevant because it does not describe a polysaccharide-protein conjugate drug. As previously explained, in contrast to a lay jury, by design, the Board is composed of individuals with competent scientific ability (35 U.S.C. § 6), and is capable of evaluating such evidence. Accordingly, the danger of prejudice in this proceeding is considerably lower than in a conventional district court trial. Finally, we observe that, irrespective of its admissibility, Dr. HogenEsch's reliance on Exhibit 1109—which Patent Owner does not challenge—is permissible because Exhibit 1109 is the type of information on which an expert would rely in forming an opinion on the subject matter at hand. *See* FRE 703. Accordingly, Patent Owner's Motion is *denied* with respect to Exhibit 1109.

Turning to Exhibit 1084, as an initial matter, we do not rely on that exhibit in this Final Written Decision. Patent Owner's Motion is, therefore, *dismissed* as moot regarding Exhibit 1084. Furthermore, although Patent Owner does not contest it, we observe that, to the extent Dr. HogenEsch

refers to Exhibit 1084 in his testimony, such reference is proper because Exhibit 1084 is the kind of information on which an expert would rely in formulating an opinion on the subject matter at issue. *See* FRE 703.

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 37, 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 43, 5.

Having considered the evidence and the arguments, we agree with Patent Owner that Petitioner has not established that Exhibit 1065 is relevant regarding the knowledge of those skilled in the art at the time of the invention. Based upon our review, Dr. Kalonia refers to the book chapter submitted as Exhibit 1065 in his declaration discussion of his credentials. Ex. 1010 ¶ 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. 10 (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 regarding Exhibit 1065.

We also have not relied upon Exhibits 1037, 1083, 1085, 1092, 1093, and 1108 in this Final Written Decision, as they were cumulative to previously submitted evidence, or related to issues disposed upon other bases. Accordingly, we *dismiss* Patent Owner's Motion to Exclude these exhibits as moot.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has shown by a preponderance of the evidence that claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent are unpatentable.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent are unpatentable under 35 U.S.C. § 103 as obvious over Chiron, Smith, and Elan;

FURTHER ORDERED that claims 7–9, 12, 13, 15, 16, 21, and 22 of the '999 patent are unpatentable under 35 U.S.C. § 103 as obvious over Prevenar and Chiron;

FURTHER ORDERED that Petitioner's Motion to Exclude is *dismissed* as moot with regard to Exhibits 2033, 2113, 2114, 2150–2159, and the designated portions of Exhibit 2125 (¶¶ 94–95), 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 with regard to Exhibits 1037, 1065, 1083–1085, 1092, 1093, and 1108, and *denied* with regard to Exhibit 1109, and the designated portions of Exhibit 1123 (¶¶ 42–43); and

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

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