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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES, INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2017-01008
Patent 9,085,619 B2

Before SUSAN L. C. MITCHELL, TINA E. HULSE, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges*.

ANKENBRAND, *Administrative Patent Judge*.

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

I. INTRODUCTION

Coherus Biosciences, Inc. ("Petitioner") requests an *inter partes* review of claims 16–19 and 24–30 of U.S. Patent No. 9,085,619 B2 ("the '619 patent," Ex. 1201). Paper 1 ("Pet."). AbbVie Biotechnology Ltd. ("Patent Owner") filed a Preliminary Response. Paper 10 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Applying that standard, and upon consideration of the information presented in the Petition and the Preliminary Response, we deny the Petition and do not institute an *inter partes* review.

II. BACKGROUND

A. Related Matters

The parties do not identify any litigation involving the '619 patent. *See* Pet. 4–7; Paper 4, 2. Petitioner, however, explains that it filed three additional petitions requesting an *inter partes* review of the '619 patent: IPR2017-00822, IPR2017-00823, and IPR2017-01009.[1] Pet. 4–6; *see* Paper 4, 1 (Patent Owner's listing of Office proceedings involving the '619 patent). Petitioner and Patent Owner also note that U.S. Patent No.

[1] Petitioner identifies two additional petitions it filed requesting an *inter partes* review of the '619 patent: IPR2017-00826 and IPR2017-00827. Pet. 5–6. The Board dismissed those petitions at Petitioner's request, so Petitioner could proceed with the petitions in the present proceeding and IPR2017-01008, which Petitioner represents are "substantively the same as, and intended to replace," the petitions filed in IPR2017-00826 and IPR2017-00827. Pet. 5–6; *see* IPR2017-00826, Paper 11; IPR2017-00827, Paper 11.

8,420,081, a patent claiming a common priority application with the ’619 patent, is the subject of U.S. Patent Interference No. 106,057, declared May 18, 2016. Pet. 6–7; Paper 4, 1. Patent Owner further identifies as related U.S. Patent Application No. 15/423,503, which claims priority to the application that matured into the ’619 patent, and is pending. Paper 4, 2.

B. The ’619 Patent

The ’619 patent, titled “Anti-TNF Antibody Formulations,” issued on July 21, 2015. Ex. 1201, [45], [54]. The ’619 patent relates to “methods and compositions for aqueous protein formulations” that “comprise water and a protein, where the protein is stable without the need for additional agents,” such as a buffer system. *Id.* at 3:34–37, 3:66–4:2. The specification explains that certain physical and chemical instabilities (e.g., aggregation and deamidation) “must be overcome” in order to make an efficacious and commercially viable pharmaceutical protein formulation. *Id.* at 1:24–37. The specification details a number of factors that contribute to the challenges in developing protein formulations, including the high concentrations at which some proteins have to be formulated for therapeutic efficacy and the processes related to long-term storage and lyophilization, which involve thawing and freezing cycles. *Id.* at 2:20–66.

With those factors in mind, the specification describes the field of pharmaceutical protein formulation as requiring a careful balance of ingredients and concentrations to enhance protein stability and therapeutic requirements while, at the same time, limiting negative side-effects. *Id.* at 3:8–11; *see id.* at 3:11–14 (“Biologic formulations should include stable protein, even at high concentrations, with specific amounts of excipients reducing potential therapeutic complications, storage issues, and overall

cost."). The specification explains that such a balance typically was achieved by including additives or excipients in the formulation that interact with the protein in solution to maintain the stability and solubility of the protein, as well as to keep the protein from aggregating. *Id.* at 1:38–44. The specification further states that "[t]he near universal prevalence of additives in all liquid commercial protein formulations indicates that protein solutions without such compounds may encounter challenges with degradation due to instabilities." *Id.* at 1:57–61.

Contrary to the specification's statement regarding the challenges of developing a protein formulation having no additives, the '619 patent discloses "an aqueous formulation comprising a protein and water" that provides "a number of advantages over conventional formulations in the art," including stability "without the requirement for additional excipients, increased concentrations of protein without the need for additional excipients to maintain solubility of the protein, and low osmolality." *Id.* at 28:43–49. According to the specification, the formulations do not rely on a buffering system and other excipients to keep the protein in the formulation "soluble and from aggregating." *Id.* at 30:5–7.

The specification describes the methods for making the formulations. In particular, the formulations are made using ultrafiltration (UF), diafiltration (DF), or diafiltration/ultrafiltration (DF/UF) techniques. *See id.* at 3:37–42, 9:21–50 (defining "UF," "DF," and "DF/UF").[2] To prepare the

[2] UF utilizes a membrane to separate components of a solution based on molecular size (i.e., small molecules pass through, while macromolecules like proteins are retained), and also can be used to increase the concentration of the protein. *Id.* at 9:21–28, 22:44–47. DF utilizes a solvent to reduce the

compositions, the specification teaches that a first solution containing the protein of interest is diafiltered using water as the diafiltration medium, so that the concentration of excipients is significantly decreased in the final aqueous formulation (i.e., "95-99% less excipients" are retained in the formulation compared to the initial protein solution). *Id.* at 3:37–48, 25:12–18. The specification explains that "[d]espite the decrease in excipients, the protein remains soluble and retains its biological activity, even at high concentrations." *Id.* at 3:48–50.

The '619 patent includes examples of aqueous pharmaceutical formulations comprising various concentrations of adalimumab and water without a buffering system. *See id.* at 51:48–54:54, 60:47–63:67.

C. Illustrative Claim

Of the challenged claims, claim 16 is independent. Claim 16 is illustrative of the claimed subject matter and recites:

> 16. An aqueous pharmaceutical formulation comprising:
>
> (a) an anti-tumor necrosis factor alpha antibody comprising a light chain variable region (LCVR) having a CDR3[3] domain comprising the amino acid sequence of SEQ ID NO:3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO:5, and a CDRl domain comprising the amino acid sequence of SEQ ID NO: 7, and a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDRl domain comprising the amino acid

concentration of the membrane-permeable components of a solution. *Id.* at 9:29–46.

[3] CDR is short-hand for the phrase complementarity determining region. Claim 16 recites an antibody having the six CDR amino acid sequences of adalimumab. *See* Pet. 11, 17; Prelim. Resp. 14.

> sequence of SEQ ID NO:8, wherein the concentration of the antibody is 50 to 200 mg/ml; and
>
> (b) water;
>
> wherein the formulation does not comprise a buffering system.

Ex. 1201, 152:16–33.

Claims 17 and 18 further narrow the antibody of claim 16 to certain additional amino acid sequences that are present in adalimumab (claim 17) and to adalimumab (claim 18). *Id.* at 152:18–39. Claim 19 requires the formulation of claim 16 to further comprise "a non-ionizable excipient." *Id.* at 152:40–41. Claims 24–26 limit the pH range of the formulation of claim 16, and claims 27–30 limit the pH range of the formulation of claim 18. *Id.* at 152:52–65.

D. The Asserted Grounds of Unpatentability

Petitioner asserts that the challenged claims of the '619 patent are unpatentable based upon the following grounds:

References	Statutory Basis	Claims Challenged
2003 Humira Label,[4] Fransson,[5] and Gokarn '011[6]	§103	16–19, 24–30
Gokarn '011 and 2003 Humira Label	§103	16–19, 24–30

Petitioner supports its assertions with the testimony of Klaus-Peter Radtke, Ph.D. (Ex. 1202) and David D. Sherry, M.D. (Ex. 1207).

[4] Physicians' Desk Reference, Humira entry 470–474 (58th ed. 2004) (Ex. 1205).
[5] J. Fransson & A. Espander-Jansson, *Local Tolerance of Subcutaneous Injections*, 48 J. PHARM. PHARMACOL. 1012–1015 (1996) (Ex. 1219).
[6] US 2016/0319011 A1, published November 3, 2016 (Ex. 1203).

III. ANALYSIS

A. Level of Ordinary Skill in the Art

We consider each asserted ground of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends that, as of November 30, 2007, a person of ordinary skill in the art "would have had an advanced degree in biology, biochemistry, or chemistry (or related discipline)" and "at least two years of experience preparing formulations of proteins suitable for therapeutic use." Pet. 22 (citing Ex. 1202 ¶ 64).

At this stage of the proceeding, Patent Owner does not dispute Petitioner's proposed level of ordinary skill, which we adopt for purposes of this decision. *See* Prelim. Resp. 15 ("For the limited purpose of this Preliminary Response, Patent Owner does not contest Petitioner's proposed level of ordinary skill in the art."). We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect the appropriate level of ordinary skill in art).

B. Claim Construction

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms are given their ordinary and customary meaning in view of the specification, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions

for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner proposes that we construe the phrase "does not comprise a buffering system." Pet. 22–23. Although Patent Owner does not dispute Petitioner's proposed construction at this stage of the proceeding (*see* Prelim. Resp. 15), neither party identifies a dispute that turns on the meaning of the phrase "does not comprise a buffering system." *See generally* Pet.; Prelim. Resp. Thus, we determine that no claim term requires construction for purposes of this decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy").

C. Asserted Obviousness over the Combination of 2003 Humira Label, Fransson, and Gokarn '011

Petitioner asserts that claims 16–19 and 24–30 of the '619 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of 2003 Humira Label, Fransson, and Gokarn '011. Pet. 34–57.

1. 2003 Humira Label

2003 Humira Label provides a description of HUMIRA and the commercially available HUMIRA formulation. Specifically, 2003 Humira Label states that "HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF)" that "consists of 1330 amino acids." Ex. 1205, 470. HUMIRA is supplied in single-use 1 ml pre-filled glass syringes for subcutaneous injection. *Id.* The HUMIRA solution is "clear and colorless, with a pH of about 5.2." *Id.* Each syringe delivers 0.8 ml of drug product, which "contains 40 mg adalimumab,

4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and Water for Injection, USP." *Id.*

2003 Humira Label also discloses adverse reactions to HUMIRA, including injection site pain, which 12 percent of patients experienced during clinical trials. *Id.* at 472. According to 2003 Humira Label, "[m]ost injection site reactions [including pain] were described as mild and generally did not necessitate drug discontinuation" and "[t]he most common adverse events leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%)." *Id.*

2. Fransson

Fransson, titled "Local Tolerance of Subcutaneous Injections," describes a study assessing pain associated with subcutaneous injection of human insulin-like growth factor I (hIGF-I). Ex. 1219, Abstract. The study investigated local tolerance to injection of different formulations with or without hIGF-I. *Id.* Fransson discloses that the goal of the study was to evaluate how pH, buffer concentration, and hIGF-I "affect local tolerance to subcutaneous injection of the solution [i.e., each formulation]." *Id.* at 1012. In carrying out the study, the authors "hypothesized that [] injection pain could be reduced if a formulation with a lower buffer capacity was used for hIGF-I." *Id.*

The formulations were made with phosphate buffer "because citrate buffer causes pain." *Id.* The formulations ranged in pH from 6 to 7, with phosphate buffer concentrations of 5 to 50 mM. *Id.* at Abstract. According to Fransson, "the different formulations caused different amounts of

injection pain." *Id.* at 1014. In particular, "pH 6, 50 mM phosphate formulations clearly caused more injection pain than pH 6, 10 mM phosphate formulations." *Id.* Further reduction in buffer concentration to 5 mM phosphate, however, "did not reduce pain further." *Id.* Fransson concludes that "for subcutaneous injections at non-physiological pH, the buffer strength should be kept as low as possible to avoid pain upon injection." *Id.* at Abstract.

3. Gokarn '011

Before turning to the disclosures of Gokarn '011, a threshold issue is whether is whether Gokarn '011 is available as prior art. Petitioner asserts that Gokarn '011 qualifies as prior art under 35 U.S.C. § 102(e) because Gokarn '011 properly claims priority to, and incorporates by reference, U.S. Provisional Application No. 60/690,582 ("Gokarn Provisional"), filed June 14, 2005. Pet. 1. Patent Owner contends that Gokarn '011 does not qualify as prior art under § 102(e) because the Petitioner fails to show written description support for: (1) the subject matter it relies upon in Gokarn '011 (and Gokarn Provisional) to show the unpatentability of the challenged claims; or (2) any issued claim of Gokarn '011. Prelim. Resp. 16–27.

We find it unnecessary to resolve the parties' dispute regarding whether Gokarn '011 is entitled to the benefit of priority of the Gokarn Provisional because, even assuming that Gokarn '011 is entitled to Gokarn Provisional's filing date, we find that Petitioner fails to show a reasonable likelihood of prevailing on its asserted ground, as explained below. Thus, for purposes of this decision, we assume that Gokarn '011 is entitled to the

June 14, 2005 filing date of Gokarn Provisional and turn to the disclosures of Gokarn Provisional (as incorporated by reference into Gokarn '011).[7]

Gokarn Provisional, titled "Bufferless Protein Formulation," relates to "liquid formulations and methods of formulating protein pharmaceuticals wherein the active protein compound in the pharmaceutical formulation is the primary source of the pH control." Ex. 1204, 1:9–13. According to Gokarn Provisional, "one or more types of polypeptides act as the buffering agent for the pharmaceutically active compound," and in the preferred embodiment, "the pharmaceutically active compound is the buffering agent." *Id.* at 1:13–17.

The pharmaceutical proteins that can be formulated according to Gokarn Provisional's method include large and small proteins, different antibodies, and naturally or non-naturally occurring peptides and proteins, such as peptibodies, maxibodies, and interbodies. *Id.* at 2:10–15. Gokarn Provisional explains that it is not the function or structure of the protein that determines whether it can be the primary source of pH control, but rather, it is the presence of enough charged amino acid residues "that in high enough levels can provide pH control and obviate the need for a separate buffering agent." *Id.* at 2:15–23.

[7] Although Petitioner's ground is based on Gokarn '011, Petitioner's unpatentability arguments are based on the disclosure of Gokarn Provisional, which is incorporated by reference in its entirety into Gokarn '011. Ex. 1203 ¶ 1 ("This application [Gokarn '011] . . . claims fully priority benefit of U.S. Provisional Application Ser. No. 60/690,582 [Gokarn Provisional] filed 14 Jun. 2005, which is incorporated herein by reference in its entirety"). Accordingly, we refer to the disclosures of Gokarn Provisional in our overview of the asserted reference.

Gokarn Provisional further explains that the buffering ability of an antibody in the pH range of 4.0–7.5 arises mainly from its solvent-accessible, polar-charged amino acid residues (i.e., glutamic acid, aspartic acid, and histidine.). *Id.* at 2:27–31. Such buffering capacity depends on the total number of charged amino acid residues in the sequence (or "n") and the total concentration of the protein (or "C"). *Id.* at 2:31–3:4. Gokarn Provisional describes the relationship as follows: "the total buffering capacity of the antibody . . . is approximately proportional to the product n x C." *Id.* at 3:4–6. According to Gokarn Provisional, "[s]ince 'n' remains a constant for a given antibody (and relatively constant for a given class of monoclonal antibodies), the buffering capacity of the antibody will increase with increasing antibody concentration." *Id.* at 3:6–10. Gokarn Provisional also teaches that there will be a crossover concentration at which the antibody formulation will not require the addition of an extraneous buffer to maintain pH over its shelf-life, once its pH is adjusted to the desired value in the 4.0–7.5 pH range. *Id.* at 3:10–15.

Gokarn Provisional discloses data regarding the effect of EMAB concentration on buffer capacity in acidic (pH 4.5–5.0) and basic (pH 5.0–5.5) pH ranges. *Id.* at 8–9. Regarding the data in the acidic pH range, Gokarn Provisional states that "EMAB formulations possess increasing buffer capacity with increasing Ab [antibody] concentration," "EMAB alone has significant buffering capacity," and approximately 25–30 mg/mL of EMAB has a buffer capacity that is equivalent to 10 mM acetate. *Id.* at 8. Gokarn Provisional discloses similar findings in the basic pH range, explaining that "EMAB formulations possess increasing buffer capacity with

increasing Ab concentration" and approximately 50 mg/mL EMAB has a buffer capacity that is equivalent to 10 mM acetate. *Id.* at 9.

Gokarn Provisional concludes that EMAB exhibits significant buffer capacity at concentrations of greater than 30 mg/mL in pH 4.5 to 5.5 range, with crossover concentrations of approximately 30 mg/mL EMAB in the 4.5 to 5.0 pH range, and approximately 50 mg/mL EMAB in the 5.0 to 5.5 pH range. *Id.* at 13. Gokarn Provisional explains that "[a] more accurate estimate of the buffer capacity from EMAB alone will have to be obtained from bufferless high concentration EMAB solutions." *Id.* Gokarn Provisional describes that investigation as "on-going." *Id.*

4. Analysis

Petitioner asserts that the only difference between 2003 Humira Label and the challenged claims is the presence of a buffer system (i.e., a citrate-phosphate buffer system) in the formulation disclosed in 2003 Humira Label ("the 2003 HUMIRA formulation"). Pet. 35–36 (citing Ex. 1202 ¶ 98; Ex. 1205, 470 (setting forth the components of the 2003 HUMIRA formulation)). Petitioner asserts that Gokarn '011 accounts for that difference because Gokarn '011 (through its incorporation of Gokarn Provisional) teaches "[r]emoving the buffer altogether" from an antibody formulation. *Id.* at 36–37 (citing Ex. 1204, 1:5–8).

Petitioner further asserts that the person of ordinary skill in the art would have had a reason to remove the 2003 HUMIRA formulation's buffer system; namely, doing so would reduce injection site pain that was known to be caused by the citrate-phosphate buffer system used in the formulation. *Id.* at 37–41. In particular, Petitioner asserts, and Dr. Sherry and Dr. Radtke testify, that a skilled artisan would have been prompted to remove the

citrate-phosphate buffer system from the 2003 HUMIRA formulation in view of 2003 Humira Label's disclosure that "12% of patients reported injection site pain as an adverse event during clinical trials" (Pet. 37–39; Ex. 1207 ¶¶ 22, 23, 26, 27), as well as Fransson's teachings that "citrate buffer causes pain" and a high-concentration phosphate buffer system causes injection site pain when administered at non-physiological pH (Pet. 38–40). *See also* Ex. 1202 ¶ 100 ("A person of ordinary skill in the art would have been motivated to remove the buffer from Humira® in view of Fransson."). Petitioner also points to Fransson's conclusion that "for subcutaneous injection at non-physiological pH, the buffer should be kept as low as possible to avoid pain upon injection" to support its argument that the skilled artisan would have eliminated the buffer system from the 2003 HUMIRA formulation. Pet. 40 (quoting Ex. 1219, 1012).

According to Petitioner, in view of Fransson's teachings, a skilled artisan "[a]t most" had only two predictable solutions available to reduce the injection site pain caused by the 2003 HUMIRA formulation: "(i) identify a different extrinsic buffer system," or (ii) eliminate the extrinsic buffer and rely on the high (50 mg/mL or more) concentration of antibody to provide the formulation's buffer capacity." *Id.* at 41 (citing Ex. 1202 ¶¶ 103–108). Petitioner further contends that, given those two choices, a skilled artisan would have eliminated the buffer system altogether, in order to avoid unnecessary excipients in the pharmaceutical formulation and simplify manufacturing and quality control processes. *Id.* at 42–43 (citing Ex. 1202 ¶¶ 54–55, 104–105; Ex. 1204, 1:5–8, 2:22–23; Ex. 1217, 294–295, 297; Ex. 1246, 2; Ex. 1270, 2).

Petitioner also asserts that a skilled artisan would have had a reasonable expectation of success in achieving an aqueous, buffer-free pharmaceutical formulation comprising 50 to 200 mg/ml of adalimumab and water (i.e., eliminating the buffer system from the 2003 HUMIRA formulation) "based on the [above-described] teachings of Gokarn Provisional, which are carried forward into Gokarn '011." Pet. 44–48. Specifically, Petitioner asserts that a person of ordinary skill in the art "would have understood from the Gokarn Provisional that, at least for antibodies in the IgG class (such as adalimumab), approximately 50 mg/mL of antibody 'possess[es] adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation.'" *Id.* at 44 (citing Ex. 1204, 1:5–8; Ex. 1202 ¶¶ 109–116); *see also id.* at 45–54 (setting forth additional arguments regarding reasonable expectation of success in preparing a buffer-free formulation of adalimumab).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

Here, even assuming, as Petitioner asserts, that 2003 Humira Label and Gokarn '011 (through its incorporation of Gokarn Provisional) disclose all of the limitations of the challenged claims, we are not persuaded on this

record that a skilled artisan would have been prompted from the disclosures of Fransson to eliminate the buffer system from the 2003 HUMIRA formulation. Nor are we persuaded on this record that Petitioner shows sufficiently that an ordinarily skilled artisan would have had a reasonable expectation of success in achieving an aqueous, buffer-free pharmaceutical formulation comprising 50 to 200 mg/ml of adalimumab and water.

a. Reason for eliminating the 2003 HUMIRA formulation buffer system

Turning first to Petitioner's rationale for removing or eliminating the buffer system of the 2003 HUMIRA formulation based on Fransson's teachings, we find that Fransson neither discloses nor suggests removing the buffer system from a formulation. To the contrary, as Patent Owner points out, Fransson describes all of its formulations as including a buffer. Prelim. Resp. 33–34. Specifically, Fransson states that the tested formulations "were prepared by mixing disodium phosphate, monosodium phosphate, and sodium chloride in water for injection to give isotonic solutions of different pH and buffer concentration. hIGF-I was added to some of the solutions by ultrafiltration." Ex. 1219, 1012–13. Petitioner does not explain adequately how that express teaching of buffered formulations, with no disclosure of any tested formulations without a buffer, would have led the ordinary artisan to eliminate buffer from the 2003 HUMIRA formulation.

Moreover, in summarizing the results of its study, Fransson explains that although an intermediate phosphate buffer concentration of 10 mM resulted in less injection pain than a higher buffer concentration of 50 mM, further reducing the phosphate buffer concentration to 5 mM "did not reduce pain further." Ex. 1219, 1014. In other words, Fransson teaches that reducing the buffer concentration below a particular threshold concentration

provides no additional pain reducing benefit. That disclosure fails to support Petitioner's assertion, and Dr. Radtke's testimony (Ex. 1202 ¶ 100), that Fransson would have led the skilled artisan to eliminate Humira's buffer system to reduce injection site pain.

Although we acknowledge Fransson teaches that "for subcutaneous injection at non-physiological pH [i.e., like the pH of the 2003 HUMIRA formulation], the buffer should be kept as low as possible to avoid pain upon injection" (Ex. 1219, Abstract), Petitioner does not explain sufficiently how Fransson's teaching of using a *low* buffer concentration to reduce pain would have led a skilled artisan to *eliminate* the buffer system from the 2003 HUMIRA formulation, particularly in light of Fransson's teaching that the low concentration 5 mM phosphate buffered formulation did not provide additional pain reducing benefit over the 10 mM phosphate buffered formulation. Petitioner also does not explain why such teachings would have led an ordinary artisan to eliminate the buffer system altogether, as opposed to lowering the concentration of the buffer system (as Fransson suggests), or removing the citrate buffer, but maintaining the phosphate buffer (as Fransson also suggests). *See* Ex. 1219, 1013 (substituting a phosphate buffer "because citrate buffer causes pain"), 1014 (describing the effect of different phosphate buffer concentrations on injection pain); *see also* Ex. 1207 ¶ 34 (Dr. Sherry's testimony that Fransson "concluded that injection site pain corresponded with higher concentrations of buffer" and "lower buffer strength generally was desirable to minimize pain in injection"); Ex. 1283, 4:6–10 (substituting a phosphate buffer system for a citrate buffer system to minimize patient discomfort).

Petitioner, therefore, fails to provide adequate reasoning why the teachings of Fransson would have prompted a person of ordinary skill in the art to remove or eliminate the buffer system from the 2003 HUMIRA formulation to reduce injection site pain.

b. Reasonable expectation of success

We also find, on the present record, that Petitioner fails to show sufficiently that an ordinarily skilled artisan would have had a reasonable expectation of success in achieving an aqueous, buffer-free pharmaceutical formulation comprising 50 to 200 mg/ml of adalimumab and water, given the state of the art at the time.

Petitioner focuses on Gokarn Provisional's disclosure that the antibody EMAB has sufficient buffer capacity at high concentrations to be formulated without a buffer. Pet. 44–48. Petitioner also points to the crossover concentration of EMAB (i.e., the concentration where the EMAB formulation did not require extraneous buffer to maintain pH), which Gokarn Provisional explains is about 50 mg/mL in the pH 5.0–5.5 range. *Id.* at 46–47 (citing Ex. 1204, 3:10–13, 13). Petitioner further relies on Gokarn Provisional's general statement that the number of amino acids contributing ionizable groups is "relatively constant for a given class of monoclonal antibodies." *Id.* at 45 (citing Ex. 1204, 3:1–10). Petitioner contends that an ordinary artisan would have understood such teachings to apply to any IgG1 antibody generally, and adalimumab in particular, because all IgG1 antibodies have the same constant regions, similar tertiary structures, and similar numbers of aspartic acid, glutamic acid, and histidine residues, which Gokarn Provisional describes as contributing to buffer control in the pH range of 4–7.5. *Id.* at 47 (citing Ex. 1202 ¶¶ 109–118, 125). Dr. Radtke's

testimony mirrors Petitioner's arguments, but also is broader in certain respects, as Dr. Radtke opines that a skilled artisan "would have expected that the teachings of the Gokarn Provisional would be generally applicable to formulating antibodies." Ex. 1202 ¶ 109.

We find that Petitioner's arguments and Dr. Radtke's testimony disregard the known challenges and unpredictability in the field of antibody formulation. Specifically, it was known in the 2006–2007 timeframe (i.e., after the filing date of Gokarn Provisional), and thereafter, that a successful formulation for one antibody would not necessarily work for another antibody, even if the two antibodies shared similar structures. *See* Ex. 1286, 5; Ex. 2021, 690. For example, a 2007 review article by Wang[8] explains that developing a commercially viable antibody pharmaceutical is complex "because the behavior of antibodies seems to vary, even though they have similar structures." Ex. 1286, 5; *see id.* at 14, 21.

Petitioner contends that the challenges Wang 2007 describes would not have been a concern in achieving an aqueous, buffer-free adalimumab formulation because adalimumab already "had been successfully formulated as an aqueous, 50 mg/ml pharmaceutical composition." Pet. 52; *see id.* at 49; Ex. 1202 ¶¶ 121–124 (Dr. Radtke's testimony that Wang 2007's teachings are "largely irrelevant" for adalimumab). That commercial formulation, however, included a buffer system, and we are not persuaded on this record that the availability of one stable, commercially available antibody formulation dictates the stability or commercial viability of a different formulation of the same antibody (i.e., one lacking a buffer

[8] Wei Wang et al., *Antibody Structure, Instability, & Formulation*, 96 J. PHARM. SCI. 1–26 (2007) (Ex. 1286).

system). Rather, we agree with Patent Owner that "removing a buffer system from a protein formulation could change the chemistry, stability, and physical characteristics of the overall formulation." Prelim. Resp. 54; *see, e.g.*, Ex. 2033, 9691 ("Phosphate ions increase the stability of all Prot L mutants included in this study."); Ex. 2035, E2–E3 (explaining that buffer species "play a significant role" in retaining the stability of disulfide bridges in alpha interferons); Ex. 2036, Abstract (listing citrate as a protein stabilizing molecule).

Moreover, a 2006 article by Daugherty[9] points out that the variable regions of IgG1 antibodies "are dramatically different from one another." Ex. 2021, 690. Daugherty continues:

> one might assume that by finding a stable formulation for one of these antibody drugs, that such a formulation would be good for most if not all, similar antibodies. If this were borne out by experience, there would be no need for a review such as this. Instead, each antibody seems to have a unique personality related to its requirements for stability; a phenomenon that derives from the fact that the small differences between these antibodies are focused on surface-exposed amino acid differences that stipulate antigen specificity. Thus, the interfacial surface of each antibody drug is unique and thus requires specific formulation components to provide maximal stability and retention of activity.

Id. Daugherty, therefore, indicates that the variable region of an antibody plays a significant role in antibody formulation, and that there is no one-size-fits-all approach to antibody formulation. Petitioner and Dr. Radtke, however, do not account for the differences in the variable regions of EMAB

[9] Ann L. Daugherty & Randall J. Mrsny, *Formulation & delivery issues for monoclonal antibody therapeutics*, 58 ADVANCED DRUG DELIVERY REV. 687–706 (2006) (Ex. 2021).

and adalimumab. Rather, both Petitioner and Dr. Radtke focus on the similarity of the constant regions and tertiary structure in IgG1 antibodies. Pet. 44–53; *see, e.g.*, Ex. 1202 ¶¶ 33–37, 112–113.

In addition, Gokarn '011 discloses that the micro environment around a given amino acid side chain in a protein typically is affected by a number of factors, which "can influence the pK_a of a given amino acid ionization in a protein. The pK_as for specific residues in a given protein, thus, can vary dramatically from that of a free amino acid." Ex. 1203 ¶ 209. And a 2008 publication by Gokarn[10] acknowledges that predicting the buffering capacity of an antibody (or of any protein) remained a "nontrivial" task, even after the earliest effective filing date of the '619 patent. Ex. 2041, 3062; *see In re Hogan*, 559 F.2d 595, 605 (CCPA 1977) ("This court has approved use of later publications as evidence of the state of the art existing on the filing date of an application.").

The same reference explains that an accurate predictive model of antibody buffering capacity requires knowledge of three important parameters: "(i) the abundance of the three contributing amino acids [i.e., aspartic acid (Asp), glutamic acid (Glu), and histidine (His)], the determination of which is relatively straightforward, (ii) the number of solvent exposed Asp, Glu, and His residues," which requires "a fair degree of detailed structural knowledge, and most importantly (iii) the actual pK_as of the Asp, Glu, and His side-chains in the IgG or protein structure, which can be expected to vary significantly from their 'free-state' values depending upon their local conformational environment in the molecule." Ex. 2041,

[10] Yatin R. Gokarn et al., *Self-Buffering Antibody Formulations*, 97 J. PHARM. SCI. 3051–3066 (2008) (Ex. 2041).

3062. Petitioner and Dr. Radtke do not direct us to any teaching of the total number of Asp, Glu, and His residues in EMAB or adalimumab, or to the number of those residues that are solvent exposed in EMAB or adalimumab. *See generally* Pet.; Ex. 1202.

Given the foregoing, we are not persuaded by Petitioner's argument that Gokarn Provisional's disclosure of empirical data for one exemplary and allegedly buffer-free antibody formulation (i.e., EMAB), or its broader generic disclosure regarding the theoretical buffering capacity of antibodies, adds up to a reasonable expectation of success in achieving an aqueous, buffer-free adalimumab formulation. Accordingly, we are not persuaded the record before us establishes a reasonable likelihood that Petitioner will prevail in showing that the subject matter of claims 16–19 and 24–30 would have been obvious over the combination of 2003 Humira Label, Fransson, and Gokarn '011.

D. Asserted Obviousness over the Combination of 2003 Humira Label and Gokarn '011

Petitioner asserts that claims 16–19 and 24–30 of the '619 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of 2003 Humira Label and Gokarn '011. Pet. 57–61. Petitioner relies on the same teachings of 2003 Humira Label and Gokarn '011 for this asserted ground that are set forth above for Petitioner's first asserted ground. *See supra* Section III.C.4.

Petitioner argues that Gokarn '011 would have provided a skilled artisan with an express reason to eliminate the buffer system from the 2003 HUMIRA formulation because Gokarn '011 (through its incorporation of the Gokarn Provisional) "teaches that IgG antibodies 'at sufficiently high concentrations' can 'provide pH control for a liquid formulation' without the

need for traditional buffering agents." Pet. 57 (citing Ex. 1204, 1:5–8). In particular, Petitioner argues that Gokarn '011 teaches that, "for an IgG1 antibody, a 'sufficiently high concentration is about 30-50 mg/mL in the pH range of 4.5-5.5, and specifically 50 mg/mL in the 5.0-5.5 pH range," and at such concentrations "a separate buffering agent is unnecessary and can be removed." *Id.* (citing Ex. 1204, 13; Ex. 1202 ¶¶ 136–138). Petitioner points to the approximately 50 mg/mL EMAB antibody formulation exemplified in Gokarn Provisional, which Petitioner contends provides effective buffering in the pH 5.0–5.5 range, and argues that the skilled artisan would have a reason to make a similar formulation using adalimumab because it is also an IgG1 antibody that was available commercially in a high concentration (50 mg/mL and at a pH of 5.2 (i.e., within the pH range disclosed in Gokarn Provisional)). *Id.*

Petitioner also asserts that an ordinary artisan would have had a reasonable expectation of success in formulating adalimumab at 50 mg/mL without a buffer system. Pet. 59 (citing Ex. 1202 ¶¶ 109–120). Petitioner's arguments in that regard are substantively the same as the arguments Petitioner provides in connection with its first asserted ground. *See id.* ("A [person of ordinary skill in the art] would have had a reasonable expectation of success . . . for all the same reasons discussed in Section X.A.4 above."). In particular, Petitioner contends that the skilled artisan "would have understood that 50 mg/mL adalimumab would have about the same buffering capacity as 50 mg/mL epratuzumab [EMAB], because both are IgG1 antibodies and . . . share very similar amino acid sequences and tertiary structure." *Id.* (citing, *e.g.*, Ex. 1202 ¶¶ 37, 114). Petitioner further contends that a skilled artisan would have expected a stable, buffer-free formulation

because the formulation would maintain the same pH as the already existing commercial formulation. *Id.* (citing Ex. 1202 ¶¶ 118–125). According to Petitioner, the 2003 HUMIRA formulation "was a 'piece of prior art ready for the improvement'" disclosed in Gokarn Provisional and carried forward into Gokarn '011. *Id.*

After having considered the arguments and evidence before us, we find that Petitioner does not show sufficiently that the subject matter of the challenged claims would have been obvious over the cited prior art. Here, even assuming that the disclosures of Gokarn Provisional (as incorporated by reference into Gokarn '011) would have led the person of ordinary skill in the art to eliminate the buffer system from the 2003 HUMIRA formulation, we are not persuaded on this record that a skilled artisan would have had a reasonable expectation of success in achieving an aqueous, buffer-free pharmaceutical formulation comprising 50 to 200 mg/ml of adalimumab and water for the same reasons set forth above in connection with Petitioner's first asserted ground. *See supra* Section III.C.4. Accordingly, we are not persuaded the record before us establishes a reasonable likelihood that Petitioner will prevail in showing that the subject matter of claims 16–19 and 24–30 would have been obvious over the combination of 2003 Humira Label and Gokarn '011.

IV. CONCLUSION

Taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner fails to demonstrate a reasonable likelihood of prevailing at trial as to any challenged claim. Accordingly, the Petition is *denied*, and no trial is instituted.

V. ORDER

It is hereby

ORDERED that the Petition is *denied* as to all challenged claims of the ’619 patent, and no trial is instituted.

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