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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 IPR2017-01009
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. 5–7; 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 IPR2017-01008.[1] Pet. 5–6; *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. 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, 3.

B. The ’619 Patent

The ’619 patent, titled “Anti-TNF Antibody Formulations,” issued on July 21, 2015. Ex. 1301, [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, 18; 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 Ground of Unpatentability

Petitioner asserts that claims 16–19 and 24–30 of the '619 patent are unpatentable under 35 U.S.C. § 103 over the combination of 2003 Humira Label,[4] Fransson,[5] and Gamimune Label.[6] Petitioner supports its assertions with the testimony of Klaus-Peter Radtke, Ph.D (Ex. 1302) and David D. Sherry, M.D. (Ex. 1303).

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

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[4] Physicians' Desk Reference, Humira entry 470–474 (58th ed. 2004) (Ex. 1305).
[5] J. Fransson & A. Espander-Jansson, *Local Tolerance of Subcutaneous Injections*, 48 J. PHARM. PHARMACOL. 1012–1015 (1996) (Ex. 1304).
[6] Physicians' Desk Reference, Gamimune N, 5% entry 925–928 (56th ed. 2002) (Ex. 1307).

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. 22–23 (citing Ex. 1302 ¶¶ 62–63).

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. 13 ("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. 23–24. Although Patent Owner does not dispute

Petitioner's proposed construction at this stage of the proceeding (*see* Prelim. Resp. 13), 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 Gamimune Label

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 Gamimune Label. Pet. 24–49.

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. 1305, 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. 1304, 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. Gamimune Label

Gamimune Label provides a description of the Immune Globulin Intravenous, 5% product, marketed as Gamimune N, 5%. Ex. 1307, 925. Gamimune N, 5% "is a sterile 4.5%–5.5% solution of human protein in 9%–11% maltose." *Id.* Each milliliter of product contains "approximately 50 mg of protein, not less than 98% of which has the electrophoretic mobility of gamma globulin." *Id.* The product is administered intravenously. *Id.* Gamimune N, 5% "has a buffer capacity of 16.5 mEq/L of solution (~0.33 mEq/g of protein)." *Id.* Gamimune N, 5% "supplies a broad spectrum of opsonic and neutralizing IgG antibodies for the prevention or attenuation of a wide variety of infectious diseases." *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. 25–26 (citing Ex. 1302 ¶¶ 68, 85; Ex. 1305, 470 (setting forth the components of the 2003 HUMIRA formulation)). Petitioner asserts that Gamimune Label accounts for that difference because Gamimune Label teaches a "commercially available . . . aqueous, buffer-free formulation[] containing about 50 mg/mL IgG antibodies." *Id.* at 26–27 (citing Ex. 1302 ¶¶ 95–106, 116; Ex. 1307, 925; Ex. 1332, 6).

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 27–32. 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. 28–29; Ex. 1303 ¶¶ 22, 26–28), 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 (*id.* at 30–32). *See also id.* at 46–47 ("A [person of ordinary skill in the art] would have readily combined Fransson's strategies to reduce pain on subcutaneous injection to solve the problem of injection site pain identified in the 2003 Humira® Label."); Ex. 1302 ¶ 86 ("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 a skilled artisan would have eliminated the buffer system from the 2003 HUMIRA formulation. Pet. 30 (quoting Ex. 1304, 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 31–32 (citing Ex. 1302 ¶¶ 90–94). 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 32–34 (citing Ex. 1302 ¶¶ 49, 91–94; Ex. 1304, 1014; Ex. 1307, 925; Ex. 1316, 294–295, 297; Ex. 1337, 3; Ex. 1338, 3).

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 [disclosures of] the Gamimune® Label." Pet. 34 (citing Ex. 1302 ¶¶ 95–100, 116); *see id.* at 35–47. Specifically, Petitioner asserts that a person of skill in the art "would have recognized that a buffer-free formulation like Gamimune®'s would be suitable for a wide variety of high concentration IgG antibodies, including adalimumab," because Gamimune Label "describes an aqueous pharmaceutical formulation containing about 50 mg/mL of IgG antibodies and water which 'does not comprise a buffering system.'" *Id.* at 35 (citing Ex. 1301, claim 16; Ex. 1307, 925; Ex. 1302 ¶¶ 49, 77–79, 83, 95–97); *see also id.* at 39–40 (discussing two additional buffer-free immunoglobulin products). Petitioner also contends that a skilled artisan "would have understood that the protein [in the Gamimune formulation] imparted the buffer capacity to the formulation," based on Gamimune Label's description of the buffering capacity of the formulation as ~0.33 mEq/g of protein and knowledge that

proteins can act as buffers. *Id.* at 35–36, 46 (citing Ex. 1302 ¶¶ 95–103, 116). Thus, argues Petitioner, a person of ordinary skill in the art "would have expected that proteins with similar amino acid sequences and configurations [e.g., Gamimune and adalimumab] would have similar buffering capacity at a given concentration." *Id.* at 36.

"[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).

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. Specifically, 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. 1304, 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 prompted 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." *Id.* at 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. 1302 ¶ 86), that Fransson would have prompted 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 prompted 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 prompted 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. 1304, 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. 1303 ¶ 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. 1373, 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.

Petitioner also appears to argue that Gamimune Label itself would have prompted an ordinarily skilled artisan to remove or eliminate the buffer system from the 2003 HUMIRA formulation. *See* Pet. 47. Specifically,

Petitioner asserts that a person of ordinary skill in the art "also would have been motivated to combine the Humira® and Gamimune® formulations, because both products are liquid pharmaceutical formulations for IgG antibodies at a concentration of 50 mg/mL." *Id.* (citing Ex. 1302 ¶¶ 77–83, 94–95). According to Petitioner, an ordinarily skilled artisan "would have recognized that the buffer-free formulation of Gamimune® would elegantly conform with Fransson's guidance to avoid citrate and reduce the buffering capacity of a formulation to reduce injection site pain." *Id.* (citing Ex. 1302 ¶¶ 87–89, 93–96; Ex. 1304, 1012).

Petitioner's arguments are not clear. Nevertheless, as to the latter argument, we remain unpersuaded for the same reasons provided above. Namely, Petitioner does not explain sufficiently how Fransson's teaching of using a *low* buffer concentration to reduce pain would have prompted 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. We note further that Petitioner's assertion that an ordinary artisan would have been prompted "to combine the Humira® and Gamimune® formulations, because both products are liquid pharmaceutical formulations for IgG antibodies at a concentration of 50 mg/mL" establishes, at best, that the references are analogous art. Such an assertion, however, falls short of an articulated reasoning with a rational underpinning to support the conclusion of obvious. *KSR*, 550 U.S. at 418.

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 Gamimune Label's disclosure that Gamimune N, 5%, a polyclonal antibody, "supplies a broad spectrum of . . . IgG antibodies" and is formulated at a concentration of about 50 mg/mL without a buffer. Pet. 35–37; *see id.* at 39–40 (discussing two additional human plasma-derived immunoglobulin products that were formulated without a buffer system). Petitioner also points to Gamimune Label's reported buffering capacity of the Gamimune N, 5% formulation, ~0.33 mEq/g of protein. *Id.* at 35–36. Petitioner contends that an ordinary artisan would have understood such teachings to apply to "a wide variety of high concentration IgG antibodies, including adalimumab," which Petitioner asserts has a similar amino acid sequence and configuration to the prevalent protein (IgG) in the Gamimune formulation. Pet. 35–37 (citing Ex. 1302 ¶¶ 36, 49, 78–79, 96–100, 116). In other words, Petitioner contends that a skilled artisan "would have appreciated" from the teachings of Gamimune Label and the state of the art that adalimumab (and other IgG antibodies), like Gamimune, could be formulated at 50 mg/mL without an extraneous buffering system. *Id.* at 37. Dr. Radtke's testimony mirrors Petitioner's arguments. *See, e.g.*, Ex. 1303 ¶¶ 95–98.

Petitioner's arguments and Dr. Radtke's testimony attempt to apply what was known about the polyclonal antibody formulation described in

Gamimune Label to the entire class of IgG antibodies. We find that such an attempt disregards the known challenges and unpredictability in the field of antibody formulation. Specifically, it was known in the 2006–2007 timeframe, 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. 1378, 5; Ex. 2021, 690. For example, a 2007 review article by Wang[7] 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. 1378, 5. Wang 2007 concludes that a formulation "should be evaluated individually for each antibody drug candidate" because "antibodies are structurally different." *Id.* at 21; *see* Ex. 2028,[8] 271 (A 2014 article explaining that "[d]espite recent advances, the identification of suitable formulation conditions for a specific monoclonal antibody remains challenging and cannot be determined from its amino acid sequence"); *see also 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.").

Petitioner contends that the challenges Wang 2007 and other references describe 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

[7] Wei Wang et al., *Antibody Structure, Instability, & Formulation*, 96 J. PHARM. SCI. 1–26 (2007) (Ex. 1378).
[8] Romain Rouet et al., *Stability engineering of the human antibody repertoire*, 588 FEBS LETTERS 269–277 (2014) (Ex. 2028).

composition" and "the [person of ordinary skill in the art] knew that 50 mg/ml of IgG antibodies did not require an extraneous buffer" (based on Gamimune Label and similar IgG products). Pet. 45–46; Ex. 1302 ¶¶ 112–115 (Dr. Radtke's testimony that Wang 2007's teachings are "largely irrelevant" for adalimumab). The commercial formulation of adalimumab, 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 either the same antibody (i.e., one lacking a buffer system) or a different antibody. 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. 42; *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).

Further, we note that 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

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

> 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 the proteins comprising the Gamimune formulation (a polyclonal antibody) and adalimumab (a monoclonal antibody). And, although Dr. Radtke testifies that "the amino acid residues His, Glu, and Asp are responsible for an antibody's ability to provide pH control in the 4-6 pH range," *id.* ¶ 99, and acknowledges that such groups "must be exposed to the solvent . . . to contribute significantly to buffer capacity," *id.* ¶ 98, Petitioner and Dr. Radtke do not direct us to any teaching of the total number of Asp, Glu, and His residues in the proteins comprising the Gamimune formulation or adalimumab, or to the number of those residues that are solvent exposed in the proteins comprising the Gamimune formulation or adalimumab. *See generally* Pet.; Ex. 1302. Rather, both Petitioner and Dr. Radtke point to the similarity of the constant regions and tertiary structure in IgG antibodies. Pet. 36–37; Ex. 1302 ¶¶ 98–100. In other words, contrary to Daugherty's teachings, Petitioner and Dr. Radtke advocate a one-size-fits-all approach to IgG antibody formulation.

Given the foregoing, we are not persuaded by Petitioner's argument that Gamimune Label's disclosure of a buffer-free polyclonal antibody

formulation (i.e., Gamimune N, 5%) translates 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 Gamimune Label.

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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