Trials@uspto.gov
571-272-7822

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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 IPR2017-00822
Patent 9,085,619 B2

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

MITCHELL, *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. 1001). Paper 10 ("Pet."). AbbVie Biotechnology Ltd. ("Patent Owner") filed a Preliminary Response. Paper 13 ("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. 3–5; Paper 7, 2. The parties identify additional petitions requesting an *inter partes* review of the '619 patent: IPR2017-00823, IPR2017-01008, and IPR2017-01009.[1] Pet. 4–5; *see* Paper 7, 1 (Patent Owner's listing of Office proceedings involving the '619 patent). Petitioner and Patent Owner

[1] Petitioner originally filed two petitions requesting an *inter partes* review of the '619 patent in IPR2017-00826 and IPR2017-00827. Paper 7, 2. The Board dismissed those petitions at Petitioner's request, so Petitioner could proceed with the petitions in IPR2017-01008 and IPR2017-01009, which Petitioner represents are "substantively the same as, and intended to replace," the petitions filed in IPR2017-00826 and IPR2017-00827. Paper 8, 1; *see* IPR2017-00826, Paper 11; IPR2017-00827, Paper 11.

also note that U.S. Patent No. 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. 5; Paper 7, 1. Patent Owner further identifies U.S. Patent Application No. 15/423,503, which claims priority to the application that matured into the '619 patent, and is pending. Paper 7, 2.

B. The '619 Patent

The '619 patent, titled "Anti-TNF Antibody Formulations," issued on July 21, 2015. Ex. 1001, [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 the "[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 uses a membrane to separate components of a solution based on molecular size (i.e., small molecules pass through, while macromolecules

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

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like proteins are retained), and also can be used to increase the concentration of the protein. Ex. 1001, 9:21–28, 22:44–47. DF utilizes a solvent to reduce the 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. 8–9, 33; Prelim. Resp. 10.

> SEQ ID NO: 6, and a CDRl domain comprising the amino acid 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. 1001, 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:

Reference(s)	Statutory Basis	Claims Challenged
Gokarn PCT[4]	§ 102	16–19, 24–30
Gokarn PCT and Humira Label[5]	§ 103	16–19, 24–30

Petitioner supports its assertions with the testimony of Klaus-Peter Radtke, Ph.D. (Ex. 1002).

[4] WO 2006/138181 A2, published December 28, 2006 (Ex. 1003, "Gokarn PCT").
[5] Physicians' Desk Reference, Humira entry 470–474 (58th ed. 2004) (Ex. 1005, "Humira Label").

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 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. 18–19 (citing Ex. 1002 ¶ 61–62).

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. 11 ("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," which appears in independent claim 16, to encompass formulations that have a *de minimis* amount of buffer components. Pet. 19–20. Although Patent Owner does not dispute Petitioner's proposed construction at this stage of the proceeding, it suggests that construction of this term is unnecessary at this stage. *See* Prelim. Resp. 11. Because Petitioner does not identify a dispute we need to resolve that turns on the meaning of the phrase "does not comprise a buffering system," *see generally* Pet., 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. Principles of Law

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). "A reference anticipates a claim if it discloses the claimed invention such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention." *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (internal citation and emphasis omitted). Moreover, "it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled

in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

A patent claim is unpatentable under 35 U.S.C. § 103(a) 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. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). 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 ordinary skill in the art; and, when presented, (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

D. Overview of Asserted References

Before turning to the instituted grounds, we begin with a brief summary of the asserted references.

1. Gokarn PCT

Gokarn PCT, titled "Self-Buffering Protein Formulations," describes methods for designing, making, and using self-buffering biopharmaceutical

protein compositions. Ex. 1003, 1:1–12.[6] Because of the problems associated with using buffers in pharmaceutical formulations, Gokarn PCT states that it is an object of its invention to provide:

> protein formulations comprising a protein, particularly pharmaceutically acceptable formulations comprising a pharmaceutical protein, that are buffered by the protein itself, that do not require additional buffering agents to maintain a desired pH, and in which the protein is substantially the only buffering agent (i.e., other ingredients, if any, do not act substantially as buffering agents in the formulation).

Id. at 3:15–21. Gokarn PCT does describe, however, formulations in which the protein does not provide all of the buffering capacity. *See id.* at 5:30–6:3 (describing a composition wherein the buffering capacity of the protein ranges from 55% to 99.5%).

After describing myriad proteins that allegedly may be formulated as self-buffering, *see id.* at 7:21–10:18, including "HUMIRA (Adalimumab)," *id.* at 9:25, 51:24, Gokarn PCT states that "it has not heretofore been recognized that proteins, particularly biopharmaceutical proteins, can have enough buffer capacity to maintain a formulation within a desired pH range, without additional buffering agents," *id.* at 27:14–16.

Gokarn PCT states that determining protein buffer capacity is important to developing self-buffering protein formulations and describes methods for doing so. *Id.* at 28:12–13, 28:20–34:5. In describing these methods for determining a protein's buffering capacity, Gokarn PCT concludes:

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[6] When citing Gokarn PCT, we refer to the original page numbers at the bottom of each page in Exhibit 1003, not the page numbers added by Petitioner on the bottom right side of each page.

> It is to be further appreciated that the pH of self-buffering protein compositions in accordance with the invention generally will not be at the pK_a of the self-buffering protein, or any acid-base substituent therein. Indeed proteins are polyprotic and, as discussed herein, often will have several substituents, each with a somewhat different pK_a that contribute to its buffer capacity in a given pH range. Accordingly, the buffer capacity of self-buffering protein formulations in accordance with the invention preferably is determined empirically by both acid titration and base titration over a given range of pH change from the desired pH of the composition.

Id. at 31:14–21.

Gokarn PCT also states the following concerning determining protein hydrogen equilibria and buffer capacity:

> Proteins invariably contain many acidic and basic constituents. As a result hydrogen ion equilibrium of proteins is highly complex. In fact, a complete description of the hydrogen ion equilibria of a protein in a given environment is beyond the reach of current theoretical and computational methods. Empirical measurements of protein buffer capacities, thus are preferred.

Id. at 36:10–14. Gokarn PCT further describes using both base and acid titrations to determine the pH titration curve for a protein for a graded series of concentrations over the pH range of interest. *Id.* at 37:21–26.

Gokarn PCT does offer ways to predict a protein's hydrogen ion equilibria and buffer capacity, namely, by taking into account the ionizable hydrogens of amino acid side chains, and the terminal amino and carboxyl groups. *Id.* at 38:17–25. Gokarn PCT describes how the micro environment around an amino acid side chain in a protein influences the pK_a of a given amino acid ionization in a protein. *Id.* at 38:29–34. Therefore, Gokarn PCT concludes, "[t]he pK_as for specific residues in a given protein, thus, can vary dramatically from that of a free amino acid." *Id*. at 38:34–39:2. Gokarn

PCT concludes that such estimated buffer capacity calculations "generally will be of less utility and less accurate than empirical determinations of protein buffer capacity, in accordance with the methods described elsewhere herein. But they can be useful to provide rough maximum estimates of the buffer capacity of proteins in solution." *Id.* at 40:15–18.

Gokarn PCT states that a self-buffering protein formulation preferably includes a protein and a carrier that is preferably a liquid in which the self-buffering protein is highly soluble. *Id.* at 55:32–56:7. Most preferably, the liquid carrier is aqueous and "largely or entirely comprised of pure water." *Id.* at 56:8. Gokarn PCT further describes that in making the self-buffering protein formulation, "[r]esidual buffering agents can be removed using the counter ions [i.e., any polar or charged constituent that acts to displace buffer from the composition during its preparation,] in this regard, using a variety of well-known methods, including but not limited to, standard methods of dialysis and high performance membrane diffusion-based methods such as tangential flow diafiltration." *Id.* at 69:31–70:1.

2. Humira Label

Humira Label provides a description of HUMIRA and the commercially available HUMIRA formulation. Specifically, 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. 1005, 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.*

E. Asserted Anticipation by Gokarn PCT

Petitioner asserts that claims 16–19 and 24–30 of the '619 patent are unpatentable under 35 U.S.C. § 102 as anticipated by Gokarn PCT.[7] Pet. 23–36. Patent Owner disputes Petitioner's assertion. Prelim. Resp. 11–25. On this record, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the challenged claims are anticipated by Gokarn PCT.

Petitioner asserts that Gokarn PCT teaches each limitation of claims 16–19 and 24–30 of the '619 patent arranged as in the claims. Pet. 23–36. Specifically, Petitioner asserts that

> The Gokarn PCT teaches that "[a]ny protein that provides sufficient buffer capacity within the required pH range at a concentration suitable for its intended use can be prepared as a self-buffering protein formulation." Ex. 1003, 27:4–7; *see also* Ex. 1003, 40:21–28. "HUMIRA (Adalimumab)" is specifically identified as a suitable protein for use in the self-buffering formulation. *Id.* at 9:25 and 51:24. Therefore, "a person of skill in the art, reading the [Gokarn PCT], would 'at once envisage' the claimed arrangement or combination" of adalimumab in an aqueous, buffer-free formulation. *Kennametal*, [*Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376,

[7] Petitioner asserts that Gokarn PCT is prior art under 35 U.S.C. § 102(e) as well as 35 U.S.C. § 102(a). Pet. 20–21. We need not determine whether one or both sections apply to Gokarn PCT, as we determine that Petitioner is not reasonably likely to succeed on its anticipation challenge. *See also* Prelim. Resp. 3, n.1 (Patent Owner stating it will assume Gokarn PCT is prior art for purposes of the decision on institution only).

> 1381 (Fed. Cir. 2015)] (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)); Ex. 1002 ¶ 79.

Pet. 25.

Because commercially available "HUMIRA" was formulated at a concentration of 50 mg/mL and a pH of 5.2, Petitioner contends that one of skill in the art reading Gokarn PCT's reference to "HUMIRA (Adalimumab)" would have understood the disclosure of "HUMIRA" to teach specifically adalimumab at a concentration of 50 mg/mL, which is in the claimed range. *Id*. 26–27. Petitioner also points to claim 23 of Gokarn PCT that claims a composition comprising adalimumab where the "concentration of the protein is between approximately 20 and 400 mg/ml." Pet. 28 (citing Ex. 1001, 84:18).

Patent Owner asserts that Petitioner's anticipation challenge based on Gokarn PCT is fatally flawed. Prelim. Resp. 1. Patent Owner asserts that "Petitioner's anticipation argument requires one to (i) choose HUMIRA (adalimumab) from a virtually limitless list of proteins and categories of proteins in Gokarn PCT, (ii) then choose, without guidance, at which concentration to formulate adalimumab, and (iii) also choose whether to use a buffering system." *Id*.; *see id*. at 11. Such picking and choosing with no guidance in the prior art as to which choices to make is not anticipation, Patent Owner asserts. *Id*. at 11–12. Patent Owner concludes that this anticipation challenge fails because Gokarn PCT does not disclose each element arranged as in the claims. *Id*.

We agree with Patent Owner that Petitioner is not reasonably likely to prevail on its anticipation challenge based on Gokarn PCT, because we agree with Patent Owner that Gokarn PCT does not teach each of the limitations of the challenged claims arranged as in the claims.

First, as Patent Owner points out, Gokarn PCT provides innumerable possibilities for proteins that may provide sufficient buffering capacity. *See* Prelim. Resp. 13–14. As Patent Owner notes, "Gokarn PCT does not identify adalimumab in any example or as a preferred antibody." *Id*. at 14. In fact, Gokarn PCT provides examples of only four self-buffering protein formulations, none of which are adalimumab. *See* Ex. 1003, 75–80. Petitioner's assertion that "[i]t is of no moment that the Gokarn PCT also teaches that other proteins could be formulated without a buffering system, because it clearly contemplates the use of adalimumab in an aqueous formulation that does not comprise a buffering system" is not persuasive. Pet. 25–26 (citing Ex. 1002 ¶¶ 79, 84).

Petitioner and its declarant, Dr. Radtke, draw this conclusion from three references to "HUMIRA (Adalimumab)" in two listings of proteins in Gokarn PCT and claim 23 of Gokarn PCT. *See* Ex. 1003, 9:25, 51:24, 84:18; Pet. 25; Ex. 1002 ¶ 79. Dr. Radtke states:

> The Gokarn PCT discloses adalimumab formulations that do not comprise a buffering system. The Gokarn PCT describes its invention as formulations "that are buffered by the protein itself, that do not require additional buffering agents to maintain a desired pH, and in which the protein is substantially the only buffering agent (i.e., other ingredients, if any, do not act substantially as buffering agents in the formulation)." *Id*. at 3:18–21. The Gokarn PCT's entire disclosure is directed to formulations that are "a self-buffering protein formulation." *Id*. at Abstract, 25:24–26. Thus, a person of ordinary skill in the art would have understood that the Gokarn PCT's entire disclosure was directed to formulations that do not comprise a buffer system. In fact, the Gokarn PCT discloses that approximately at least 99.5% of the buffer capacity of the formulation can be attributable to the protein. *Id*. at 57:28–33. Thus, a person of ordinary skill in the art would have

> understood that the formulations of the Gokarn PCT do not comprise a buffering system.

Ex. 1002 ¶ 84.

Petitioner and Dr. Radtke overstate what Gokarn PCT teaches about self-buffering proteins, especially in regard to adalimumab. Although Gokarn PCT describes self-buffering protein formulations, it repeatedly emphasizes that empirical data is needed to determine the buffering capacity of any particular protein. *See* Ex. 1003, 31:14–28 (stating "the buffer capacity of self-buffering protein formulations in accordance with the invention preferably is determined empirically by both acid titration and base titration over a given range of pH change from the desired pH of the composition"); *id*. at 36:10–14 (stating empirical measurements of protein buffer capacities are preferred); *see also id*. at 36:29–38:9 (describing determining protein buffer capacity from pH titration curves).

Gokarn PCT does describe methods of predicting protein buffer capacity, but cautions that "[s]uch calculations generally will be of less utility and less accurate than empirical determinations of protein buffer capacity, in accordance with the methods described elsewhere herein. But they can be useful to provide rough maximum estimates of the buffer capacity of proteins in solution." *Id*. at 40:15–18; *see also id*. at 38:10–14 (stating while "empirical determinations as described herein are generally a crucial aspect of formulating self-buffering compositions in accordance with various aspects and preferred embodiments of the invention, theoretical and computations methods also can be productively employed to guide the design, manufacture, and use of such compositions (in conjunction with empirical determinations)").

Gokarn PCT explains why empirical data is so crucial in determining protein buffer capacity:

> Conformational folding typically partitions large polypeptides and proteins in polar solvents into exposed solvent-accessible regions and more or less non-polar core regions that have little or no contact with the ambient environment. Folding produces many environments between these two extremes. Furthermore, the micro environment around a given amino acid side chain in a protein typically is affected by one or more of: solvent effects; binding of ions, chelation; complexation; association with co-factors; and post-translational modifications; to name just a few possibilities. Each of these 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.

Id. at 38:26–39:2. No such empirical data is provided for adalimumab. *See generally* Ex. 1003; Prelim. Resp. 16. Rather, Gokarn PCT only provides examples of four different self-buffering proteins: Ab-hOPGL, Ab-hB7RP1, Ab-hCD22, and Ab-hIL4R. Prelim. Resp. 5 (citing Ex. 1003, 74:19–80:24).

As Patent Owner points out, "Gokarn PCT refers to 'HUMIRA (Adalimumab)' in a voluminous list of *potentially* 'self-buffering' proteins (proteins that may provide sufficient buffering capacity at high enough concentrations). The list is *silent* as to any threshold adalimumab concentration needed in a formulation lacking a buffering system." *Id.* at 2, 11 (citing Ex. 1003, 9:25, 51:24).

The reference to "HUMIRA (Adalimumab)" in claim 23 also is not helpful in showing anticipation of the challenged claims. We agree with Patent Owner that claim 23 recites the same extensive list of commercial proteins that appears in the specification of the '619 patent, adding no additional specificity to its disclosure. *See* Prelim. Resp. 14–15. Also,

claim 1, the only independent claim from which claim 23 depends, encompasses other components that can provide buffering capacity in addition to the protein. *See* Ex. 1003, 81:2–11; Prelim. Resp. 15. Therefore, claim 23 does not set forth a formulation in which adalimumab is self-buffering.

Additionally, Gokarn PCT provides many options for the percentage of a formulation's buffering capacity that may be attributable to self-buffering that may be provided by a particular protein, and does not link adalimumab to any specific percentage. *See* Ex. 1003, 5:30–6:3 (providing percentages ranging from 55% to 99.5% for the buffering capacity a protein contributes to the composition); Prelim. Resp. 15 (stating Gokarn PCT "fails to say which of the countless proteins could provide which listed percentage of total buffer capacity"). As such, we do not agree with Petitioner that "Gokarn PCT's *entire* disclosure is therefore directed to formulations that 'do not comprise a buffering system.'" Pet. 24–25 (emphasis added). Although Gokarn PCT discusses self-buffering proteins, it provides no specific teaching concerning adalimumab for use as a self-buffering protein "wherein the formulation does not comprise a buffering system" as required by the challenged claims. *See* Ex. 1001, 152:31–32; *In re Arkley*, 455 F.2d 586, 587–88 (CCPA 1972) (stating a reference must clearly and unequivocally disclose the invention or direct those skilled in the art to the invention without any need for picking and choosing among the various disclosures of a reference).

Also, as Patent Owner points out, there is "nothing that would have directed a skilled artisan to the claimed antibody concentration of 50-200 mg/ml, particularly because this range is not explicitly disclosed in Gokarn

PCT." Prelim. Resp. 16. Gokarn PCT provides several possible concentration ranges for a self-buffering protein, including a range as broad as 20–400 mg/ml, which is linked to adalimumab in claim 23. Ex. 1003, 6:4–8, 81:19–24, 84:8–18). We find this disclosure of the broader 20–400 mg/ml for adalimumab insufficient to teach one of skill in the art that adalimumab may self-buffer at a concentration range from 50–200 mg/ml. *See Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) (stating that given the considerable difference between disclosed temperature range of 100 to 500°C and the claimed range of 330 to 450°C, "no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this limitation of the claim").

We also agree with Patent Owner that Petitioner cannot rely on knowledge of Humira's commercial formulation as disclosed in Humira Label to fill in the antibody concentration range that is not disclosed in Gokarn PCT. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274–75 (Fed. Cir. 2017) (stating that a reference missing a limitation cannot anticipate a claim even if a skilled artisan viewing the reference would "at once envisage" the missing limitation); *see In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997) (a single prior art reference must disclose every limitation of the claimed invention to anticipate).

Accordingly, we are not persuaded the record before us establishes a reasonable likelihood that Petitioner will prevail in showing that claims 16–19 and 24–30 are anticipated by Gokarn PCT.

F. Asserted Obviousness over Gokarn PCT and Humira Label

Petitioner asserts that claims 16–19 and 24–30 of the '619 patent are unpatentable under 35 U.S.C. § 103 because the subject matter of those claims would have been obvious over the combination of Gokarn PCT and Humira Label. Pet. 36–41. Patent Owner disputes Petitioner's assertion. Prelim. Resp. 26–46. On this record, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the challenged claims are obvious over the combination of Gokarn PCT and Humira Label.

Petitioner asserts that "even if any of the challenged claims are not anticipated by the Gokarn PCT, they would have been obvious to a POSA" because

> Humira® was known in the prior art as an FDA-approved therapeutic IgG1 antibody (adalimumab) in a liquid formulation at a concentration of 50 mg/mL and pH of 5.2. It would have been obvious to a POSA to select the specific adalimumab concentration and pH known in the prior art, with an expectation of success in preparing a buffer-free formulation of adalimumab as taught by the Gokarn PCT.

Pet. 37–38 (citing Ex. 1002 ¶¶ 97–105).

Patent Owner asserts that the mere fact that Gokarn PCT lists "HUMIRA (Adalimumab)" is insufficient to have prompted a person of skill in the art to modify HUMIRA to achieve the claimed buffer-free formulation. Prelim. Resp. 26–34. Patent Owner also asserts that one of skill in the art would have had no reasonable expectation of success in arriving at the claimed buffer-free formulation for adalimumab. *Id*. at 34–45.

As we found in our analysis of Petitioner's anticipation challenge based on Gokarn PCT, Gokarn PCT does not teach a buffer-free adalimumab formulation. *See supra* Section III.E. Both Petitioner and Dr. Radtke admit that Humira Label teaches a formulation with a phosphate/citrate buffering system. Pet. 27, n.3; Ex. 1002 ¶ 81, n.1. Therefore, neither asserted reference in Petitioner's obviousness challenge teaches a buffer-free formulation of adalimumab. Accordingly, we find that the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would not have been obvious at the time the invention was made to a person having ordinary skill in the art. *See KSR*, 550 U.S. at 406.

Petitioner also fails to show any reason that would have prompted a skilled artisan to combine Gokarn PCT and Humira Label to arrive at the claimed buffer-free formulation, and fails to show that a skilled artisan would have had a reasonable expectation of success in doing so. "[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." *KSR*, 550 U.S. at 418 (2007). 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).

We agree with Patent Owner that Petitioner has failed to identify any problem with Humira (or any problem known in the art generally) that would have prompted one of skill in the art to remove the buffer system from the Humira formulation. *See* Prelim. Resp. 26–30. Petitioner states that

> A POSA would have been motivated to use a concentration and pH that were already used in an FDA-approved adalimumab commercial product. Ex. 1002 ¶¶ 100–103. A POSA would have understood from the 2003 Humira® Label that the optimal pH range for adalimumab had already been determined to be around 5.2. Ex. 1002 ¶ 103; Ex. 1012, 297 ("The stability of a protein drug is usually observed to be maximal in a narrow pH range."). The POSA also would have found it obvious to use the same FDA-approved concentration of 50 mg/mL that already was known to be suitable for treatment of rheumatoid arthritis. Ex. 1002 ¶ 101; Ex. 1005, 470–71.

Pet. 39–40. As Patent Owner notes, Humira "was successfully formulated with a multi-component citrate-phosphate buffering system," Prelim. Resp. 27 (citing Ex. 2047, 2; Ex. 1005, 470), and we agree that Petitioner identifies no reason why, in the absence of hindsight, one of skill in the art would have changed such a formulation, *id*. at 28. *See also id.* at 29–30 ("The history of commercial antibody formulations subsequent to the disclosure of Gokarn PCT confirms that those of ordinary skill in the art were not, in fact, motivated to exclude buffers. Even as late as 2015, *all* commercially available aqueous monoclonal antibody formulations were provided with a buffering system. (Ex. 2051, 94–101 (Table 4.1); Ex. 2055, 852.)"), 30–33 (explaining no impetus to select adalimumab from "Gokarn PCT's immense number of *potentially* suitable proteins and protein categories spanning *more than a dozen pages*").

Also, as we state above, Gokarn PCT emphasizes the need to use empirical data to determine the buffering capacity of any protein, and no reference cited by Petitioner provides any such data for adalimumab, much less such data for a buffer-free formulation of adalimumab. *See supra* Section III.E. Moreover, we find misplaced Petitioner's reliance upon

Gokarn PCT's teachings regarding specific antibodies to establish that "[g]iven the substantial identity of amino acid sequences and tertiary structures across all IgG antibodies, a POSA would have expected that different antibodies within the IgG class would have similar buffering capacity." Pet. 40 (citing Ex. 1002 ¶ 104). To the contrary, we agree with Patent Owner that, at the critical time, "there was a general consensus in the art that a formulation that worked for one antibody (such as Ab-hOPGL, Ab-hB7RP1, Ab-hCD22, or Ab-hIL4R of Gokarn PCT) would *not* be predicted to work for a different antibody (such as adalimumab)." Prelim. Resp. 36; *see id.* at 35–36 (quoting a 2007 Wang[8] article that states that "[d]evelopment of commercially viable antibody pharmaceuticals has, however, not been straightforward. This is because the behavior of antibodies seems to vary, even though they have similar structures." Ex. 2047, 5). Therefore, Petitioner has not shown a reasonable expectation of success in arriving at a buffer-free formulation of adalimumab.

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 Gokarn PCT and Humira 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

[8] Wei Wang et al., *Antibody Structure, Instability, & Formulation*, 96 J. PHARM. SCI. 1–26 (2007) (Ex. 2047).

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.

For PETITIONER:

E. Anthony Figg
Joseph A. Hynds
ROTHWELL FIGG, ERNST & MANBECK, P.C.
efigg@rfem.com
jhynds@rfem.com
CoherusIPR619@rothwellfigg.com

For PATENT OWNER:

Anthony M. Insogna
Tamera M. Weisser
S. Christian Platt
David M. Maiorana
JONES DAY
aminsogna@jonesday.com
tmweisser@jonesday.com
cplatt@jonesday.com
dmaiorana@jonesday.com

William B. Raich
Michael J. Flibbert
Maureen D. Queler
Pier D. DeRoo
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
william.raich@finnegan.com
michael.flibbert@finnegan.com
maureen.queler@finnegan.com
pier.deroo@finnegan.com