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Paper 9
Entered: January 14, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN, INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2015-01514
Patent 8,916,157 B2

Before RAMA G. ELLURU, TINA E. HULSE, and ELIZABETH A. LAVIER, *Administrative Patent Judges.*

ELLURU, *Administrative Patent Judge.*

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

I. INTRODUCTION

Petitioner, Amgen, Inc. ("Amgen"), filed a Petition requesting an *inter partes* review of claims 1–8, 10–13, and 15–30 of U.S. Patent No. 8,916,157 B2 (Ex. 1001, "the '157 patent"). Paper 2 ("Pet."). Patent Owner, AbbVie Biotechnology Ltd. ("AbbVie"), filed a Preliminary Response. Paper 8 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

For the reasons set forth below, on this record, we find that Amgen has not established a reasonable likelihood of prevailing with respect to at least one challenged claim of the '157 patent. Accordingly, we deny the Petition and decline to institute an *inter partes* review of the '157 patent.

A. Related Matter

Amgen concurrently filed a petition for *inter partes* review of U.S. Patent No. 8,916,158 B2, which is in the same family as the '157 patent. Pet. 3; Paper 4, 1.

B. The '157 patent

The '157 patent is titled "FORMULATION OF HUMAN ANTIBODIES FOR TREATING TNF-α ASSOCIATED DISORDERS." Ex. 1001, at [54]. Tumor necrosis factor alpha ("TNF-α" or "TNFα") is a cytokine implicated in various diseases and disorders in humans, including sepsis, autoimmune diseases, and transplant rejection. *Id.* at 1:35–52. Thus, TNFα is a target for various therapeutic strategies, including antibodies that

bind to and neutralize TNFα, to counteract or inhibit its activity. *Id.* at 1:53–57. The '157 patent focuses especially on antibody formulations, including the anti-TNFα antibody D2E7. *See, e.g.*, *id.* at 17:19–20 ("In the most preferred embodiment, the antibody is D2E7."). AbbVie states that the '157 patent covers the commercial product HUMIRA®. Prelim. Resp. 16; *see also* Pet. 59 (stating the challenged claims "may encompass" HUMIRA®).

C. Illustrative Claim

Amgen challenges claims 1–8, 10–13, and 15–30 of the '157 patent. Of the challenged claims, claims 1 and 24 are independent. Claim 1 is illustrative of the claimed subject matter and recites the following:

> 1. A stable liquid aqueous pharmaceutical formulation comprising
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> (a) a human IgG1[1] anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof, at a concentration of 20 to 150 mg/ml,
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> (b) a tonicity agent,
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> (c) a surfactant, and
>
> (d) a buffer system having a pH of 4.0 to 8.0,
>
> wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7.

Ex. 1001, 39:1–10.

[1] Immunoglobulin G1 (IgG1) is a subclass of antibodies found in humans. *See* Ex. 2031, 5–7.

D. Asserted Grounds of Unpatentability

Amgen asserts the following grounds of unpatentability (Pet. 5):

Challenged Claims	Basis	References
1–8, 10–13, 15–30	§ 103(a)	Lam[2] and Barrera[3]
1–8, 10–13, 15–30	§ 103(a)	Salfeld[4] and Heavner[5]

II. ANALYSIS

A. 35 U.S.C. § 325(d)

As a preliminary matter, we briefly address AbbVie's request that we reject the Petition pursuant to 35 U.S.C. § 325(d) on the basis that the Petition presents "the same or substantially the same prior art or arguments" as were previously presented to USPTO. *See* Prelim. Resp. 55–58. Under § 325(d), the Director, and by extension the Board, has broad discretion to deny a petition that raises substantially the same prior art or arguments previously presented to the Office. *See Unilever, Inc. v. Procter & Gamble Co.*, Case IPR2014-00506, slip op. at 6 (Paper 17) (PTAB July 7, 2014) (informative). Specifically, AbbVie contends that the Examiner advanced substantially the same prior art combinations during the prosecution of the '157 patent and its parent patents, but nonetheless found the claims of the '157 patent patentable. Prelim. Resp. 55 (stating the four asserted references

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[2] Lam et al., US 6,171,586 B1, issued January 9, 2001 (Ex. 1003).
[3] Barrera et al., *Effects of Treatment with a Fully Human Anti-Tumour Necrosis Factor α Monoclonal Antibody on the Local and Systemic Homeostasis of Interleukin 1 and TNFα in Patients with Rheumatoid Arthritis*, 60 ANN. RHEUM. DIS. 660–69 (2001) (Ex. 1004).
[4] Salfeld et al., US 6,090,382, issued July 18, 2000 (Ex. 1005).
[5] Heavner et al., US 7,250,165 B2, issued July 31, 2007 (Ex. 1006).

were "cited and considered" in an Information Disclosure Statement submitted during prosecution of the '157 patent). AbbVie further asserts that "during prosecution of claims in parent patents, the PTO expressly raised the *same arguments* Petitioner now advances." *Id.* at 55–56. Because AbbVie alleges that the "same arguments" advanced by Amgen in its Petition were advanced against claims in related patent applications, not the challenged claims of the '157 patent, we decline to exercise our discretion to apply § 325(d) to deny the Petition.

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *See In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015); 37 C.F.R. § 42.100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See 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. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). "Absent some clear intent to the contrary," examples from a patent's specification are not to be imported into the claims. *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1372 (Fed. Cir. 2007).

Whether a term appearing in the claim's preamble is limiting "is a determination 'resolved only on review of the entire[ ] . . . patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim.'" *Catalina Mktg. Int'l, Inc. v. Coolsavings.com,*

Inc., 289 F.3d 801, 808 (Fed. Cir. 2002) (quoting *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989)). Generally, however, "a preamble limits the invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim," *id.* (quoting *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999)), but not "'where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention,'" *id.* (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)).

1. "stable"

"[S]table" appears in the preamble of claims 1 and 24, and modifies "liquid aqueous pharmaceutical formulation." The Specification expressly states that "[a] 'stable' formulation is one in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage." Ex. 1001, 7:20–22.

Amgen argues that "stable" bears no patentable weight, solely on the basis that "stable" appears only in preamble language. Pet. 10–11. But this factor is not dispositive. *See Catalina*, 289 F.3d at 808 (designating "guideposts," not a "litmus test," in preamble analysis). We are not persuaded that this factor alone outweighs the consistent focus in the Specification on stability, including the express definition of "stable," Ex. 1001, 7:20–22. Likewise, we do not consider "stable" as stating merely an intended use or purpose of the claimed invention; rather, it describes a mandatory characteristic thereof. Accordingly, based on our review of the '157 patent as a whole and on this record, we conclude that "stable," as used in the preambles of claims 1 and 24, breathes life and meaning into claims 1

and 24 and, therefore, limits its scope.

Having determined "stable" is limiting, we turn to its broadest reasonable construction. Amgen argues that if "stable" is limiting, then a formulation is "stable" under the definition given in the Specification. According to Amgen, a formulation is "stable" if it retains its physical, chemical, and/or biological stability upon storage "for any period of time, no matter how short," but does not *require* storage at a specific temperature or for a specific time. Pet. 11. In support, Amgen argues the Specification only expresses preferences (not requirements) for certain time and temperature conditions, and that there is "no evidence that the broadly disclosed and claimed formulations . . . are stable for any particular time under any particular conditions." *Id.*

AbbVie counters that such an interpretation would "define 'stable' to encompass formulations stable . . . only for a fraction of a second—which is to say, not stable at all." Prelim. Resp. 8. Although AbbVie does not attempt to define "stable" quantitatively, AbbVie points to the Summary of the Invention of the '157 patent, which focuses on the need for a formulation "'with an extended shelf life.'" Prelim. Resp. 7 (quoting Ex. 1001, 3:9–10). AbbVie further asserts that "stable" should be read in context of the phrase it modifies, i.e., "pharmaceutical formulation," and, thus, necessitates a preparation that is biologically effective and not significantly toxic. *Id.* at 7–8 (citing Ex. 1001, 7:10–15 (defining "pharmaceutical formulation")). Thus, AbbVie contends, and we agree, that one of skill in the art "would have understood that a formulation would need to be stable for storage and use." *Id.* at 7. A more specific threshold is unnecessary to understand the broadest reasonable interpretation of "stable" with sufficient clarity to further analyze

the claims in light of the cited prior art. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting claim terms require construction "only to the extent necessary to resolve the controversy").

2. "a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof, . . . wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7"

This language is recited in claim 1. Amgen breaks this phrase into several separate terms in need of construction, *see* Pet. 12–13, whereas AbbVie considers it as a whole, *see* Prelim. Resp. 9–11. We begin with the component parts, as necessary, building to an understanding of the entire phrase.

The first portion, "a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody," is further defined at the end of the claim, by the language "wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7." As both parties recognize, (*see* Pet. 13; Prelim. Resp. 10–11), "D2E7" refers to an antibody disclosed in Salfeld,[6] incorporated by reference in the '157 patent. *See* Ex. 1001, 9:54–55. Salfeld provides amino acid sequences for the light chain variable region (SEQ ID NO: 1), light chain CDR3[7] domain (SEQ ID NO: 3), heavy chain variable region (SEQ ID NO: 2), and heavy chain CDR3 domain (SEQ ID NO: 4) for the D2E7 antibody. *See* Ex. 1005, 2:59–67.

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[6] In addition to the Salfeld patent relied on as prior art by Amgen in this *inter partes* review, the '157 patent also identifies a second patent to Salfeld, US 6,258,562 B1. Ex. 1001 9:54–55.

[7] "CDR" stands for "complementarity determining regions." CDRs are hypervariable sub-regions of the variable regions of the heavy and light chains of an antibody. Ex. 1001, 9:45–49.

The parties dispute, however, how the phrase "or an antigen-binding portion thereof" affects the scope of the claim. As Amgen notes (Pet. 12), the Specification defines "antigen-binding portion" as "one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hTNFα)." Ex. 1001, 9:56–59. Amgen argues that the phrase "antigen-binding portion" thus "encompasses an antibody fragment that can be as small as one CDR (5 to 17 amino acids)." Pet. 12.

In contrast, AbbVie argues that claim 1 is limited to an antibody, or antibody fragment, that "includes the complete light chain variable (V_L) region and the heavy chain variable (V_H) region of the antibody D2E7." Prelim. Resp. 9. Thus AbbVie contends that the clamed "antigen-binding portion" includes the complete light chain variable region and the heavy chain variable region of the antibody D2E7. AbbVie presumably relies on the language of the "wherein" clause as support for further limiting the term "an antigen-binding portion." As explained above, however, the "wherein" clause is modifying the "antibody" term, and not the term "an antigen-binding portion thereof." Thus, although we agree that the claimed "antibody" must include the light chain variable region and the heavy chain variable region of D2E7, we do not agree that the claimed "an antigen-binding portion" must include the complete light chain and heavy chain variable regions of D2E7, as AbbVie asserts. This is particularly true given the claim's use of a "(TNFα) antibody, *or* an antigen-binding portion thereof" (emphasis added), which is disjunctive.

Accordingly, on the present record, we find that the broadest reasonable interpretation of the entire phrase allows for *either* an antibody comprising the light chain variable region and the heavy chain variable

region D2E7, *or* one or more fragments of D2E7 that retain the ability to specifically bind TNFα.

C. Obviousness

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (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 (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The level of ordinary skill in the art may be reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

If all the claimed elements are taught or suggested by the prior art references, the obviousness inquiry turns to the combination of those references:

> [P]roper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

Par Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1196 (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006)).

Although obviousness does not require absolute predictability, *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986), there must be "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness," *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). An explicit teaching of a motivation to combine is not required, however, as a tribunal "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* Nonetheless, "[t]o the extent an art is unpredictable . . . *KSR's* focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

1. General State of the Art

Before considering the specific grounds of unpatentability asserted by Amgen, we begin with a discussion of the state of the art, both for background purposes and because Amgen relies in part on the general state of the art to support its rationale for combining the proffered references. *See* Pet. 14–17; *cf. Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015) ("Art can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." (citation omitted.)). For example, the parties refer to commercialized prior art antibody formulations that were available at the time of the invention, and on what we refer to as "the Wang

article," a journal article from 1999 (Ex. 1017).[8] *See, e.g.*, Pet. 15–16, 29; Prelim. Resp. 24–26, 56.

a. Commercially Available Antibody Formulations

By 2002,[9] various parenteral antibody formulations had been approved by the United States Food and Drug Administration (USFDA), including REMICADE™ (infliximab), a prior art IgG1 anti-TNFα antibody product, "formulated at pH 7.2 with sucrose (a tonicity agent) and polysorbate 80 (a surfactant)." Pet. 16.

Amgen maintains that the formulation of antibodies was generally known at that time, Pet. 14 (citing Ex. 1002 ¶¶ 45, 72–73), and that the ordinarily skilled artisan would have been motivated to optimize different parameters such as pH, and components such as surfactants and polyols, *see id.* at 14–16. Because D2E7 was of the same antibody class (IgG) as other known antibody formulations, Amgen concludes that the skilled artisan "would have understood that the formulation components of an antibody formulation could be applied to a new formulation of a structurally similar antibody." Pet. 16–17 (citing Ex. 1002 ¶¶ 74–77).

AbbVie counters that "development of stable liquid antibody formulations, especially those at a concentration high enough to be suitable for [subcutaneous] administration, was far from routine." Prelim. Resp. 20 (citing Ex. 2005 at 1906). AbbVie maintains that the commercial antibody

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[8] Wang, *Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals*, 185 INT'L J. PHARMACEUTICS 129–188 (1999) (Ex. 1017). For consistency, we refer to pages in Wang by their exhibit page numbers, not their publication page numbers.

[9] The '157 patent claims priority to an application filed on August 16, 2002. Ex. 1001, at [63].

formulations on which Amgen relies, *see* Pet. 14–17 (citing Ex. 1002 ¶ 74, Table 2), were either: (1) low-concentration (10 mg/ml or less) liquid formulations, or (2) lyophilized (i.e., freeze-dried) formulations. *See* Prelim. Resp. 16–19. As AbbVie notes, REMICADE™ was lyophilized, and included instructions to use within three hours after liquid reconstitution. Prelim. Resp. 35–36 (citing Ex. 1002 ¶74; Ex. 1035 at 10). In its reconstituted liquid form, REMICADE™'s concentration was 10 mg/ml. *Id.* at 17 (citing Ex. 1035).

b. The Wang Article

Both parties cite the Wang article as evidence of the state of the art at the time of the invention. *See* Pet. 15–16, 29; Prelim. Resp. 24–26, 56. The Wang article begins: "One of the most challenging tasks in the development of protein pharmaceuticals is to deal with physical and chemical instabilities of proteins." Ex. 1017, 1.

Amgen asserts that the Wang article acknowledges the challenges, but then "teaches *all* of the excipient components recited in the challenged claims of the '157 patent, and *how* to optimize those features to develop a stable formulation." Pet. 29 (citing Ex. 1002 ¶ 74). Amgen does not quote or cite specific portions of the Wang article for this proposition, but instead relies on further discussion in the Randolph Declaration. *See id.* at 29.[10]

[10] AbbVie asserts that Amgen's "extensive reliance" on the Randolph Declaration throughout the Petition constitutes improper incorporation by reference and amounts to a page limit violation. Prelim. Resp. 6 (citing, *inter alia*, 37 C.F.R. §§ 42.24(a)(1)(i), 42.6(a)(3)). Instead of denying the Petition on this basis, as AbbVie urges, we consider only those arguments Amgen presents squarely in its Petition. For example, as is relevant to our analysis regarding the general state of the art, Amgen cites to the Randolph

AbbVie responds that the Wang article demonstrates unpredictability, not predictability, in the art of formulating proteins: "'[v]ery often, proteins have to be evaluated individually and stabilized on a trial-and-error basis.'" Prelim. Resp. 24 (quoting Ex. 1017, 2). AbbVie further points to Amgen's prior reliance on Wang as evidence of unpredictability in the art during prosecution of Amgen's own protein formulation patent applications, as well as to Dr. Randolph's prior published statements regarding the complexities of protein folding and instability. *See id.* at 24–28.

c. Analysis

Upon consideration of the parties' arguments regarding commercially available antibody formulations including REMICADE™, the Wang article, and other evidence presented regarding the general state of the art at the time of the invention, we are not persuaded by Amgen's evidence and argument. Specifically, on this record, we are not persuaded that the prior art provided sufficient guidance such that a skilled artisan would have had a reasonable expectation of success in arriving at the formulation of stable, liquid pharmaceutical compositions comprising antibodies at a concentration of 20 to 150 mg/ml.

For example, Amgen fails to direct us to a commercially available antibody product that was available in liquid form, within the claimed antibody concentration range. As noted above, REMICADE™ was sold in lyophilized form, and its product information indicated it should be used

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Declaration's discussion of various other background references (in addition to the Wang article), without any additional argumentation or explanation in the Petition. *See* Pet. 15. We decline to consider further these other background references.

within three hours of liquid reconstitution. Prelim. Resp. 35–36 (citing Ex. 1002 ¶ 74; Ex. 1035, 10). In other words, REMICADE™ was not a stable liquid antibody formulation.

Further, Amgen does not persuade us that the Wang article "provide[d] guidance on how to formulate such compositions," Pet. 29, to a sufficient degree to have provided a skilled artisan at the time with a reasonable expectation of success to arrive at the claimed composition. Although the Wang article indeed provides general guidance, the Wang article also underscores the unpredictability of the undertaking. *See* Ex. 1017, 2 (noting that "the structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful"). Amgen asserts that "[j]ust because each new formulation must be optimized on a case-by-case basis does not mean that the formulation development is complex or not routine." Pet. 29. Although this is true to an extent, Amgen's statement flips the burden on its head. Amgen, as the Petitioner in these proceedings, bears the burden of proving (at this stage) a reasonable likelihood of prevailing in its assertion that one or more of the claims is unpatentable. Thus, as is relevant here, Amgen also bears the burden of persuasion as to the teachings of the prior art as used to bolster the rationale for combining the cited references. As far as the Wang article is concerned, Amgen has not persuaded us that Wang provides a reasonable expectation of success in making stable liquid antibody formulations as a general matter. In contrast, we agree with AbbVie that, on the whole, Wang suggests a high degree of *un*predictability in the antibody formulation art.

d. Conclusion

On this record, Amgen has not persuaded us that "[t]he skilled person would have had a reasonable expectation of success in applying the formulations commercially available and taught in the literature to D2E7." Pet. 17.

2. Obviousness over Lam and Barrera

Amgen asserts that claims 1–8, 10–13, and 15–30 are unpatentable under 35 U.S.C. § 103(a) as having been obvious over Lam and Barrera. Pet. 17–32. In support, Amgen relies on a Declaration of Theodore W. Randolph, Ph.D. Ex. 1002. AbbVie counters that one of ordinary skill in the art would not have combined the references as arranged in the challenged claims, nor would have had a reasonable expectation of success in doing so. Prelim. Resp. 31–40. AbbVie makes additional arguments with respect to the dependent claims. *See id.* at 40–45.

a. Lam

Lam describes "a stable aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody not subjected to prior lyophilization, a buffer maintaining the pH in the range from about 4.5 to about 6.0, a surfactant and a polyol." Ex. 1003, 2:25–29. Lam's examples involve formulations comprising anti-CD18 and anti-CD20 antibodies. *Id.* at 24:28–40:26 (anti-CD18), 40:29–46:32 (anti-CD20). Lam lists TNFα among various exemplary target antigens. *See id.* at 10:5–52 (specifically at 10:19).

b. Barrera

Barrera describes administering a single dose of D2E7 to study short-

term effects in rheumatoid arthritis patients, using a preparation of "25 mg/ml D2E7 mAb in 1.2% mannitol, 0.12% citric acid, 0.02% sodium citrate" in an intravenous infusion. Ex. 1004, 1, 3. Amgen characterizes Barrera's formulation as "short-term . . . appropriate for phase I clinical trials." Pet. 20. Barrera, however, does not expressly discuss the stability of its formulation. Barrera also is silent as to pH and whether it includes a surfactant. *Id.* at 21.

c. Analysis

Amgen argues that the combination of Lam and Barrera teaches each of the limitations of the challenged claims, and that a skilled artisan would have had reason to combine them in either of two ways. Both of these combinations rely on the references themselves as well as on Amgen's characterization of the state of the art at the time of the invention.

Amgen's first proposed rationale for combining Lam and Barrera is that because "the Lam patent discloses every feature recited in the '157 patent claims except the particular anti-TNFα antibody, D2E7," Pet. 19, the successful trial with "a short-term formulation" of D2E7 reported in Barrera would have provided the skilled artisan a reason to "select D2E7 as the anti-TNFα antibody included in the Lam formulation, resulting in the same formulation recited in the challenged claims." *Id.* at 20. Amgen maintains that there would have been a reasonable expectation of success "because the Lam patent taught formulations for anti-TNFα antibodies and D2E7 was an anti-TNFα antibody, and because the art provided guidance on formulating antibodies." *Id.* at 20–21. In support of these statements, Amgen offers no additional explanation in its brief, but rather relies on the Randolph Declaration (Ex. 1002). *See*, *e.g.*, *id*.

Second, because Barrera "discloses everything recited in claim 1 of the '157 patent except the pH range and surfactant," Amgen maintains that the skilled artisan "would have been motivated to build off [Barrera's] success by designing a stable formulation for long-term storage" as shown in Lam, including a pH between about 4.5 and 6.0 and a surfactant such as polysorbate 80. Pet. 21–22. Amgen further maintains, and refers to the Randolph Declaration in support, that "nearly all commercially available protein formulations, including antibody formulations, had a pH within that range," and that "surfactants were known to prevent antibodies from aggregating," thus increasing formulation stability, and were included in "many" commercial formulations. *Id.* at 21–22 (citing Ex. 1002).

Both of these arguments, as presented in the Petition, are too general to be persuasive. As AbbVie points out, Lam primarily relates to anti-CD18 and anti-CD20 antibodies; TNFα is but one of many other antigens listed in Lam, for which there is no additional disclosure regarding sequence or formulation. Prelim. Resp. 31 (discussing Ex. 1003, 10:5–63, 24:29–46:20). We are unpersuaded that the inclusion of TNFα in a laundry-list of untested potential targets in Lam would have provided sufficient direction to one of ordinary skill in the art to select TNFα, much less combine Lam's formulation with the teachings regarding D2E7 in Barrera, to achieve the claimed formulation (whether starting with Lam, or starting with Barrera). This is not a situation in which "there are a finite number of identified, predictable solutions," *KSR*, 550 U.S. at 421, such as might render combining the references "obvious to try." Instead, the proffered combinations seem to be exercises in impermissible hindsight reconstruction. *See Grain Processing Corp. v. Am.-Maize Prods. Co.*, 840

F.2d 902, 907 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" (quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983))).

Nor is Amgen's reliance on the general state of the art persuasive to shore up either rationale for combining the references. As discussed *supra* in § II.C.1, Amgen has not persuaded us that either the commercially available antibody formulations (e.g., REMICADE™) or the contemporaneous literature (e.g., the Wang article) would have provided the skilled artisan with a reasonable expectation of success in formulating the claimed invention. To the contrary, the difficulty of formulating liquid antibodies as described in the Wang article and the dearth of high-concentration, stable liquid antibody formulations available at the time of the invention together appear to paint a prior art landscape of unpredictability.

d. Conclusion

Amgen has not persuaded us, on this record, that it is reasonably likely to prevail in establishing that one of ordinary skill in the art would have had a reasonable likelihood of success in combining Lam and Barrera.[11] Accordingly, on this record, we conclude that Amgen has not established a reasonable likelihood of prevailing with respect to its challenge of claims 1 and 24 based on Lam and Barrera.

[11] Accordingly, we need not address the parties' arguments with respect to secondary considerations of non-obviousness. *See* Pet. 45–58; Prelim. Resp. 54–55.

As the other challenged claims depend on claims 1 and 24, respectively, and Amgen has not established a reasonable likelihood of prevailing with respect to claims 1 and 24, it follows that Amgen likewise has not established a reasonable likelihood of prevailing with respect to the remaining challenged claims.

3. Obviousness over Salfeld and Heavner

Amgen also asserts that claims 1–8, 10–13, and 15–30 are unpatentable under 35 U.S.C. § 103(a) as having been obvious over Salfeld and Heavner, again relying on Dr. Randolph's Declaration for support. Pet. 32–45. AbbVie disagrees. Prelim. Resp. 45–54.

a. Salfeld

As noted *supra* in § II.B.2, Salfeld discloses the D2E7 antibody. *See* Ex. 1005, 2:59–67. Salfeld further teaches incorporating the antibody or antibody-portions into pharmaceutical compositions, including, *inter alia*, liquid dosage forms that may comprise buffers and/or surfactants. *See id.* at 20:59–21:49. Salfeld identifies a preferred antibody dosage range of 1–10 mg/kg. *Id.* at 23:13–15. Salfeld does not expressly disclose a pH range, but includes "phosphate buffered saline" among other pharmaceutically-acceptable carriers. *Id.* at 21:2.

b. Heavner

Heavner teaches anti-TNF antibodies and therapeutic formulations thereof. Ex. 1006, at [57]. The "TNV" antibodies and fragments thereof specifically disclosed in Heavner differ in sequence from D2E7. *See* Pet. 42; Prelim. Resp. 46; *see also* Ex. 1006 (sequence listing). Heavner's sprayer-suitable aqueous formulations include antibody concentrations in the

range of about 0.1 mg/mL to about 100 mg/mL, and can include a surfactant, a buffer, and a polyol. Ex. 1006, 44:43–61. Heavner discloses a "wide range of pHs," from about 4 to about 10, and preferably between about 6.8 and about 7.8. *Id.* at 32:28–33.

c. Analysis

Amgen argues that Salfeld alone expressly or implicitly (as to concentration and pH) discloses all the limitations of the challenged claims, and that even if Salfeld does not teach the claimed antibody concentration and pH ranges, Heavner does. Pet. 33–35. AbbVie disputes the alleged implicit teachings of Salfeld, Prelim. Resp. 48–49, and argues more generally that "Heavner or Salfeld, alone or in combination, do not disclose any specific antibody formulation at all, but only broad sweeping lists of possible components leading to an endless number of possible combinations," *id.* at 47.

i. Salfeld: Antibody Concentration

In arguing that the asserted combination teaches the claimed concentration, Amgen refers to a 1 mg/kg "effective dose" (instead of the disclosed 1–10 mg/kg preferred range), presumes an average patient size of 70 kg and a "practical injection volume for a subcutaneous administration" of about 0.3–1.5 ml, to arrive at an antibody concentration of about 50–90 mg/ml. Pet. 34 (citing Ex. 1002 ¶¶ 52, 119; Ex. 1005, 23:12–15).

We are not persuaded, on this record, that Salfeld's dose information teaches an antibody concentration range within the scope of claims 1 and 24. At the very least, Amgen's calculations make too many assumptions and are not explained in sufficient detail for us to rely on them. As AbbVie notes,

one factor that could skew Amgen's concentration calculations is whether a single-dose or a multi-dose therapy is assumed. *See* Prelim. Resp. 48. Because Heavner expressly teaches the claimed antibody concentration range, however, this deficiency in Salfeld is not dispositive of this asserted ground of unpatentability.

ii. Salfeld: pH Range

In arguing that the asserted combination teaches the claimed pH range, Amgen asserts that Salfeld teaches phosphate buffered saline, which "buffers at a pH that falls within the claimed range," and that Salfeld's "physiologically compatible" carrier likewise would have indicated a pH between 4 and 8 to one of ordinary skill in the art. Pet. 34–35 (citing Ex. 1002 ¶ 118). AbbVie responds that this analysis amounts to "making conclusory statements" (Prelim. Resp. 48–49), but we find Amgen's position to be sufficiently persuasive, on this record, regarding an implicit teaching of pH within the claimed range.

iii. Combination of Salfeld and Heavner

According to Amgen, a skilled artisan would have had reason to combine Salfeld and Heavner "because both focus on anti-TNFα antibodies, both focus on IgG antibodies, and both teach how to formulate these antibodies." Pet. 35 (citing Ex. 1002). Amgen notes that the parameters taught in Heavner are "consistent" with the state of the antibody formulation art. *Id.* Again, in support of its rationale to combine, Amgen offers little additional explanation in its brief, but rather relies on the Randolph Declaration (Ex. 1002).

AbbVie responds that Salfeld provides wide-ranging formulation information "merely as a general approach" and offers no stability data.

Prelim. Resp. 46–47. Further, AbbVie contends that Heavner provides only "bulk recitations of potential formulation ingredients" covering "virtually every imaginable route of administration," and "offers no guidance at all on how to actually select from this massive number of possible combinations to prepare *any* antibody—much less a D2E7 antibody—as a stable liquid antibody formulation." *Id.* at 46 (discussing Ex. 1006, 42:59–48:4).

Although Heavner's antibody concentration range overlaps with that of claims 1 and 24, we agree with AbbVie that the lack of teachings regarding specific pharmaceutical formulations in Heavner would have left one of ordinary skill in the art "with an utter lack of guidance as to which of the many combinations would work." Prelim. Resp. 46; *see generally* Ex. 1006, 28:30–39:28 (compositions, formulations, and therapeutic applications); 71:5–74:17 (in vivo murine studies). And, as with the other asserted ground, *see supra* § II.C.2.c, Amgen's proffered rationale for combining Salfeld and Heavner finds no additional support in the general state of the art at the time of the invention, as we are unconvinced that the art was sufficiently predictable to offer the ordinarily skilled artisan a reasonable chance of success in combining the references as claimed.

d. Conclusion

Amgen has not persuaded us, on this record, that it is reasonably likely to prevail in establishing that a skilled artisan would have had a reasonable likelihood of success in combining Salfeld and Heavner to arrive at the claimed antibody formulation.[12] Accordingly, on this record, we

[12] As with the challenge based on Lam and Barrera, *see supra* § II.C.2.d, our conclusion here obviates the need to analyze secondary considerations of

conclude that Amgen has not established a reasonable likelihood of prevailing with respect to its challenge of claims 1 and 24 on this basis. We are likewise unpersuaded of Amgen's likelihood of prevailing with respect to the other challenged claims, which depend on claims 1 and 24.

III. CONCLUSION

For the foregoing reasons, we determine, based on the Petition and the accompanying evidence, that Amgen has not shown a reasonable likelihood of prevailing on any of its challenges to claims 1–8, 10–13, and 15–30 of the '157 patent.

IV. ORDER

For the foregoing reasons, it is

ORDERED that the Petition is *denied*, and no trial is instituted.

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nonobviousness.

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