Trials@uspto.gov
571-272-7822

Paper No. 16
Entered: February 9, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2017-01823
Patent 8,802,100 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

Sandoz Inc. ("Petitioner") requests an *inter partes* review of claims 1–29 of U.S. Patent No. 8,802,100 B2 ("the '100 patent," Ex. 1001). Paper 1 ("Pet."). AbbVie Biotechnology Ltd. ("Patent Owner") filed a Preliminary Response. Paper 8 ("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.[1]

II. BACKGROUND

A. Related Matters

The parties do not identify any litigation or other Office proceedings involving the '100 patent. *See* Pet. 3–4; Paper 4, 1. Petitioner and Patent Owner collectively identify two litigations involving one or more patents that are related to the '100 patent, captioned *AbbVie Inc. v. Amgen Inc.*, No. 1:16-00666-MSG-SRF (D. Del. Aug. 4, 2016), and *AbbVie Inc. v. Boehringer Ingelheim International GMBH*, No. 1:17-cv-01065 (D. Del. Aug. 2, 2017). Pet. 4; Paper 5, 2.

[1] Because we deny the Petition, we dismiss as moot Petitioner's pending motions for Daniel L. Reisner and Abigail Langsam to appear *pro hac vice* in this proceeding (Papers 3 and 10, respectively). We also dismiss as moot Patent Owner's pending motion to withdraw J. Patrick Elsevier, Ph.D. as its backup counsel in this proceeding (Paper 12).

Petitioner and Patent Owner also identify three previous Petitions requesting an *inter partes* review of patents related to the '100 patent: (1) *Amgen Inc. v. AbbVie Biotechnology Ltd.*, Case IPR2015-01514 ("1514 IPR"), challenging U.S. Patent No. 8,916,157; (2) *Amgen Inc. v. AbbVie Biotechnology Ltd.*, Case IPR2015-01517 ("1517 IPR"), challenging U.S. Patent No. 8,916,158;[2] and (3) *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, Case IPR2016-01018 ("Coherus IPR"), challenging U.S. Patent No. 9,114,166.[3] Pet. 5. The Board issued decisions denying institution of all three petitions. 1514 IPR, slip op. at 24 (PTAB Jan. 14, 2016) (Paper 9) ("1514 Dec."); 1517 IPR, slip op. at 26 (PTAB Jan. 14, 2016) (Paper 9) ("1517 Dec."); Coherus IPR, slip op. at 14 (PTAB Nov. 7, 2016) (Paper 10) ("Coherus Dec.").

Petitioner and Patent Owner further identify a number of United States patent applications and patents that claim the benefit of priority to the '100 patent, or to which the '100 patent claims the benefit of priority. Pet. 6; Paper 5, 2.

B. The '100 Patent

The '100 patent, titled "Formulation of Human Antibodies for Treating TNF-Alpha Associated Disorders," issued on August 12, 2014. Ex. 1001, [45], [54]. According to the '100 patent, tumor necrosis factor alpha (TNFα) is a cytokine implicated in the pathophysiology of various

[2] We refer to the 1514 IPR and the 1517 IPR collectively as the "Amgen IPRs."
[3] The parties explain that the '100 patent and the patents challenged in the Amgen IPRs and the Coherus IPR all claim priority to the same initial application, U.S. Serial No. 10/222,140, filed August 16, 2002. Pet. 5; Paper 5, 2.

diseases and disorders in humans, including sepsis, autoimmune diseases, and transplant rejection. *Id.* at 1:30–48. 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 1:49–53. Accordingly, the '100 patent states that there is a need for a stable aqueous pharmaceutical formulation with an extended shelf-life, comprising an antibody that is suitable for therapeutic use to inhibit or counteract detrimental TNFα activity. *Id.* at 3:7–10. The '100 patent further states that there is a need for a stable, aqueous pharmaceutical formulation with an extended shelf-life comprising an antibody suitable for therapeutic use that is easily administered and contains a high protein concentration. *Id.* at 3:10–14, 3:52–54 ("the concentration of the antibody in the liquid aqueous pharmaceutical formulation is about 1-150 mg/ml"). The '100 patent focuses especially on antibody formulations including the anti-TNFα antibody D2E7. *See, e.g., id.* at 4:25–26 ("In still another embodiment, the claimed formulation includes the D2E7 antibody."), 17:19–20 ("In the most preferred embodiment, the antibody is D2E7.").

C. Illustrative Claim

Of the challenged claims, claims 1 and 19 are independent. Claim 1 is illustrative of the claimed subject matter and recites:

> 1. A stable liquid aqueous pharmaceutical formulation comprising
>
> (a) a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof, at a concentration of 45 to 150 mg/ml,
>
> (b) a polyol,
>
> (c) a polysorbate at a concentration of 0.1 to 10 mg/ml, and
>
> (d) a buffer system having a pH of 4.5 to 7.0,
>
> wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7.

Ex. 1001, 39:2–11.

D. The Asserted Ground of Unpatentability

Petitioner asserts claims 1–29 of the '100 patent are unpatentable under 35 U.S.C. § 103(a) over the combination of Salfeld,[4] van de Putte,[5] Barrera,[6] Remington,[7] and Lam.[8] Petitioner supports the Petition with the testimony of Richard L. Remmele, Jr., Ph.D. (Ex. 1002).

---

[4] U.S. Patent No. 6,090,382, issued July 18, 2000 (Ex. 1003).
[5] L.B.A. van de Putte et al., *Efficacy of the Fully Human Antibody D2E7 in Rheumatoid Arthritis*, 42 ARTHRITIS & RHEUMATISM S400 (1999) (Ex. 1004).
[6] Barrera et al, *Effects of Treatment with a Fully Human Anti-Tumor Necrosis Factor α Monoclonal Antibody on the Local & Systemic Homeostasis of Interleukin 1 and TNFα in Patients with Rheumatoid Arthritis*, 60 ANN. RHEUM. DIS. 660–69 (2001) (Ex. 1011).
[7] REMINGTON: THE SCIENCE & PRACTICE OF PHARMACY (Alfonso R. Gennaro et al. eds., 20th ed. 2000) (Ex. 1008).
[8] U.S. Patent No. 6,171,586 B1, issued January 9, 2001 (Ex. 1005).

III. ANALYSIS

We organize our analysis into four sections. First, we address Patent Owner's argument that we should use our discretion under 35 U.S.C. §§ 314(a) and 325(d) to deny institution. Second, we discuss the level of ordinary skill in the art. Third, we turn to claim construction. Fourth, taking account of the information presented, we consider whether the Petition meets the threshold showing for instituting an *inter partes* review based on obviousness.

A. Discretionary Denial of Institution Under 35 U.S.C. § 314(a) and/or 35 U.S.C. § 325(d)

As a preliminary matter, we briefly address Patent Owner's request that we reject the Petition pursuant to 35 U.S.C. §§ 314(a) and 325(d). Patent Owner argues that we should deny institution under § 314(a) because the non-exhaustive factors set forth in the Board's *General Plastic*[9] decision "collectively support denying institution." Prelim. Resp. 26–31 (addressing the non-exhaustive list of seven factors the Board considers as a framework for determining whether to exercise discretion to deny institution of an *inter partes* review under § 314(a)). Patent Owner also argues that we should deny institution under § 325(d) because the Petition presents substantially the same prior art and arguments previously presented to the Office in the Amgen IPRs and the Coherus IPR. *Id.* at 23–25.

As we explain below, we deny the Petition on its merits. Accordingly, we decline to reach Patent Owner's additional arguments that

[9] *General Plastic Industrial Co., Ltd. v. Canon Kabushiki Kaisha*, Case IPR2016-01357 (PTAB Sept. 6, 2017) (Paper 19) (§ II.B.4.i. precedential).

we should exercise discretion to deny the Petition under §§ 314(a) and/or 325(d).

B. Level of Ordinary Skill in the Art

We consider the asserted ground of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends that, as of August 16, 2002, a person of ordinary skill in the art "would have had a Pharm. D. or Ph.D. in biology, biochemistry, or chemistry" and "at least two years of experience preparing stable formulations of therapeutic protein drugs." Pet. 11 (citing Ex. 1002 ¶ 33).

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. 5 ("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) (explaining that the prior art, itself, can reflect the appropriate level of ordinary skill in art). Further, based on Dr. Remmele's statement of qualifications and curriculum vitae, for the purposes of this decision, we find that he is qualified to opine from the perspective of a person of ordinary skill in the art at the time of the invention. Ex. 1002 ¶¶ 3–10 (statement of qualifications), App'x A (curriculum vitae).

C. 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 and Patent Owner propose one claim term for construction—the term "stable." Petitioner and Patent Owner point out that we previously construed the term "stable" in the Amgen IPRs and the Coherus IPR, and that the patents challenged in those proceedings have the same specification as the '100 patent. Pet. 11; Prelim. Resp. 1, 5. Both parties contend we should adopt here our prior construction of the term. Pet. 11–12; Prelim. Resp. 5.

Patent Owner further asserts, however, that Petitioner seeks to redefine our prior construction of the term "stable" to require "only 'some degree of stability,' a 'minimal level of stability,' or a 'minimal degree of stability.'" Prelim. Resp. 5 (citing Pet. 9, 33, 39, 40). Patent Owner contends that we previously rejected such an interpretation in the Amgen IPRs. *Id.* at 5–6. Patent Owner also avers that, in the Coherus IPR, we "further found that the claim term 'stable' required that 'the formulation must be sufficiently stable for use when administered subcutaneously to a human.'" *Id.* at 6. Thus, argues Patent Owner, a person of ordinary skill "would recognize that formulations that retain stability only for very short periods of time are not 'stable' and would not satisfy the Board's prior claim construction." *Id.*

We agree with Patent Owner. Here, Petitioner asserts that the '100 patent "does not provide any limitation on the time a formulation must retain stability to qualify as 'stable.'" Pet. 9. Similarly, Petitioner asserts that the '100 patent requires the formulation to have a "minimal level of stability." *Id.* at 39. Such arguments essentially are the same as those the petitioner made in the Amgen IPRs, which we rejected. *See* 1514 Dec. 7 (setting forth Petitioner's argument that "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 . . . for a specific time"); 1517 Dec. 7–8 (same). In the Amgen IPRs, we agreed with Patent Owner that the ordinarily skilled artisan "would have understood that a formulation would need to be stable for storage and use." 1514 Dec. 7 (quoting preliminary response); 1517 Dec. 8 (same). We clarified in the Coherus IPR that "the formulation must be sufficiently stable for use when administered subcutaneously to a human." Coherus Dec. 6. Petitioner's arguments to the contrary, which we previously considered, do not persuade us that we should deviate from our prior constructions of the term "stable" in the related patents. Thus, we construe "stable" to mean "a formulation in which the antibody therein essentially retains its physical stability, and/or chemical stability, and/or biological stability upon storage and use as a pharmaceutical formulation."

D. Asserted Obviousness over the Combination of Salfeld, van de Putte, Barrera, Remington, and Lam

Petitioner asserts that claims 1–29 of the '100 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 Salfeld, van de Putte, Barrera, Remington, and Lam. Pet. 24–38. Patent Owner opposes. Prelim. Resp.

31–57. Having considered the arguments and evidence before us, for the reasons set forth below, we find that Petitioner does not establish a reasonable likelihood of prevailing on its asserted ground.

1. Salfeld

Salfeld discloses the D2E7 antibody. *See* Ex. 1003, 2:59–67. Salfeld generally describes incorporating the antibody or antibody-portions into pharmaceutical compositions, including, *inter alia*, liquid dosage forms that may comprise polyalcohols, 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.

2. van de Putte

Van de Putte is an abstract describing a dose-finding phase II study comparing three dose levels of D2E7 administered to patients with long-standing active rheumatoid arthritis. Ex. 1004, 3.[10] The patients received weekly doses of either D2E7 at 20, 40, or 80 mg, or placebo by subcutaneous injection for three months. *Id.* Van de Putte concludes that all three doses were superior to placebo, and were nearly equally efficacious. *Id.*

3. 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. 1011, 660–661.

[10] We refer to the page numbers Petitioner has added to the reference.

4. Remington

Remington is a treatise on the theory and practice of pharmaceutical sciences. Ex. 1008, v. Remington explains that non-isotonic solutions "generally cause tissue irritation, pain on injection, and electrolyte shifts." *Id.* at 250. Remington teaches that tonicity agents can be used in injectable formulations to achieve isotonic solutions. *Id.* Remington also describes non-ionic surfactants as a "major class of compounds used in pharmaceutical systems" due to the advantages they provide with respect to compatibility, stability, and potential toxicity. *Id.* at 286–87. Remington discloses polysorbate 20 and polysorbate 80 as types of non-ionic surfactants. *Id.* at 1037.

5. 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. 1005, 2:25–29. Lam discloses polysorbate 20 and polysorbate 80 as exemplary non-ionic surfactants and states that surfactant "may be present in the formulation in an amount from about 0.001% to about 0.5%," with "0.01% to about 0.1%" most preferred. *Id.* at 22:49–59. Lam's examples involve formulations comprising anti-CD18 with the surfactant Tween 20 and anti-CD20 antibodies with the surfactant polysorbate 20. *Id.* at 24:28–40:26 (anti-CD18), 40:29–46:32 (anti-CD20).

6. Analysis

With the disclosures of the asserted references in mind, we turn to Petitioner's asserted ground, focusing on independent claims 1 and 19.

Petitioner argues that Salfeld was a roadmap to the challenged claims, because Salfeld discloses "stable, buffered, subcutaneously-injectable aqueous D2E7 formulations containing a polyol, and a surfactant." Pet. 15 (citing Ex. 1003 21:4–11, 21:21–23, claim 29). With respect to claims 1 and 19, Petitioner asserts that Salfeld discloses "every element [of those claims] except the D2E7 concentration and the surfactant type and concentration." *Id.* at 20 (citing 1517 IPR Dec. 21). Petitioner relies on the teachings of van de Putte, Remington, and Lam to provide the limitations missing from Salfeld. *See, e.g.*, *id.* at 16 ("Any details missing from Salfeld are provided by van de Putte (the concentration of D2E7) . . . Remington (polysorbate 80 as a surfactant), and Lam (the concentration of polysorbate 80).").

Petitioner asserts that van de Putte teaches a D2E7 concentration within the claimed concentration ranges.[11] Pet. 29–33. In particular, Petitioner asserts that van de Putte's 20, 40, and 80 mg doses of D2E7 "correspond to a concentration of 6 to 160 mg/ml based on reasonable assumptions of injection volume and number of injections" or, "at most correspond to a range of 2.5 to 400 mg/ml making less reasonable assumptions." *Id.* at 24–25, 31. Petitioner relies on Dr. Remmele's

[11] Petitioner acknowledges our finding in the 1517 IPR that the calculations the petitioner provided were insufficient to show that Salfeld's dose information (i.e., the 0.1–20 mg/kg broader range, or the 1–10 mg/kg preferred range) teaches a high-concentration antibody. Pet. 31; *see* 1517 IPR Dec. 23. Petitioner does not rely on Salfeld's dose information as disclosing D2E7 concentrations within the claimed ranges. Pet. 16 (noting that van de Putte provides the D2E7 concentration that is missing from Salfeld's disclosure), 20 (Salfeld discloses "every element [of claims 1 and 19] except the D2E7 concentration and the surfactant type and concentration").

testimony and calculations converting van de Putte's disclosed doses to the above-noted concentration ranges. *Id.* at 31–33 (citing Ex. 1002 ¶¶ 67–87).

Petitioner further asserts that the person of ordinary skill in the art would have had a reason to combine van de Putte's concentration ranges with Salfeld's disclosure of stable liquid D2E7 formulations; namely, that van de Putte was "the definitive source for determining an efficacious amount of D2E7" because it reported Patent Owner's "own D2E7 clinical data." *Id.* at 24 (citing Ex. 1002 ¶¶ 153–154).

Regarding surfactant type and concentration, Petitioner asserts that Salfeld teaches using surfactants in formulating D2E7. Pet. 27. According to Petitioner, Salfeld's teaching would have prompted the person of ordinary skill in the art to look to Remington, "an undisputed leading formulation reference" in choosing a particular surfactant to use in a D2E7 formulation, such as polysorbate 80. *Id.*; *see id.* at 19. Similarly, Petitioner argues that a skilled artisan would have been prompted to look to "similar antibody formulations," such as the formulations Lam discloses, "to identify typical amounts of polysorbate that have been used," for example, 0.001% –0.5%, or 0.01–5 mg/ml. *Id.* at 27; *see id.* at 18; Ex. 1002 ¶ 101.

Petitioner contends that the combined teachings of Salfeld, van de Putte, Remington, and Lam would have provided the skilled artisan with a reasonable expectation of success in preparing a stable, liquid formulation of D2E7 having a protein concentration and polysorbate concentration within the recited ranges, based on Salfeld's disclosure of the formulation components, Salfeld's statement that "[t]herapeutic compositions typically must be sterile and stable," and "numerous prior art examples of stable, injectable, high concentration antibody and other protein formulations." *Id.*

at 33–36 (citing Ex. 1002 ¶¶ 37–44; Ex. 1003 21:28–36; Ex. 1012, 31:18–19, 44:42–51, 42:59–64; Ex. 1014, 5:23, 107:9–10, 107:18–20, 108:13–15, 108:18–21; Ex. 1020, 25:15–17, table 4; Ex. 1017, 40:13, 40:17–22, 56:30–35; Ex. 1018, 5:17–19, 35:17–19).

Having considered the arguments and evidence, we are not persuaded that Petitioner shows a reasonable likelihood of prevailing in its assertion that the subject matter of the '100 patent would have been obvious over the cited prior art. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each element 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 art to combine the elements as the 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).

Initially, we note that although Salfeld generally describes formulation components, dosage forms, and methods of administration, Salfeld does not provide a "roadmap" to the claims as Petitioner suggests, because it does not include any working examples or other guidance regarding how one of ordinary skill in the art would have prepared a stable, liquid, high-concentration D2E7 formulation. We also find the evidence of record indicates that the art of antibody formulation was unpredictable in August 2002, further evidencing that Salfeld's disclosure would not have been viewed by one of skill in the art as such a "roadmap." *See infra* Section III.D.6.a.

In addition, Petitioner does not show sufficiently on this record that a skilled artisan would have had a reason to combine the concentration ranges van de Putte allegedly discloses and Salfeld's teachings with a reasonable expectation of success in preparing a stable, liquid formulation of 45–150 mg/ml D2E7 (claim 1) or 45–105 mg/ml D2E7 (claim 19). Nor does Petitioner show sufficiently that an ordinarily skilled artisan would have had a reason to combine the teachings of Lam with the teachings of Salfeld to prepare a stable liquid D2E7 formulation comprising 0.1–10 mg/ml of a polysorbate (claim 1) or 0.1–10 mg/ml of polysorbate 80 (claim 19).

a. D2E7 concentration

Regarding D2E7 concentration, we found in the Coherus IPR that van de Putte "does not disclose whether the administered D2E7 formulation was in liquid form or lyophilized form" and "offers no guidance" as to how an ordinarily skilled artisan would have prepared a stable, liquid high-concentration (i.e., 50 mg/ml) D2E7 formulation.[12] Coherus Dec. 10. Although Petitioner relies on Dr. Remmele's calculations of the ranges of concentrations van de Putte allegedly discloses, neither Petitioner nor Dr. Remmele adequately addresses our findings in the Coherus IPR. Instead, Petitioner's arguments in this proceeding appear to be based, in part, on the assumption that the '100 patent "covers reconstituted formulations," i.e., lyophilized formulations. Pet. 35, n.32. Implicit in Petitioner's assumption is that one of skill in the art would have used teachings related to

[12] As Patent Owner points out, van de Putte is nearly identical to the van de Putte reference that the petitioner in the Coherus IPR asserted, except that Petitioner's van de Putte reference reports efficacy data over a period of three months, whereas the van de Putte reference in the Coherus IPR reported efficacy data over a period of six months. *See* Prelim. Resp. 20.

lyophilized formulations to prepare liquid formulations. Petitioner, however, does not direct us to evidence supporting its assumption. Thus, Petitioner's unsupported argument carries no weight. *See Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017) ("Attorney argument is not evidence."); *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997).

Moreover, in calculating the concentration ranges that van de Putte allegedly discloses, Dr. Remmele describes the van de Putte formulations as "liquid formulations." Ex. 1002 ¶ 68. Although not clear from his testimony, it appears that Dr. Remmele either assumes that van de Putte teaches stable liquid formulations, or that even if van de Putte's formulations were lyophilized, a skilled artisan would have utilized the concentration ranges from a lyophilized formulation in preparing a stable, liquid formulation. As to the former, Dr. Remmele does not direct us to evidence supporting a finding that van de Putte's 20, 40, and 80 mg doses refer to stable, liquid formulations. As to the latter, evidence in the record suggests that a skilled artisan would not have utilized teachings regarding lyophilized formulations when preparing stable, liquid formulations. For example, as Patent Owner points out all commercially available high-concentration antibody formulations as of August 2002 were lyophilized, whereas liquid formulations contained low antibody concentrations. Prelim. Resp. 7–9 (citing Exs. 2016–2020 (high-concentration lyophilized formulations); Exs. 1029; 1031; 2009–2012; 2014 (low-concentration liquid formulations)). Patent Owner also directs us to evidence that ordinarily skilled artisans would not have utilized teachings regarding lyophilized formulations to prepare stable, liquid formulations. *See* Ex. 2038, 9–10 (explaining that

liquid formulations are "an extremely important distinction from lyophilized formulations, which do not suffer the same stability issues as high-concentration liquid antibody formulations").

In other words, neither Petitioner's argument nor Dr. Remmele's testimony provides us with a persuasive reason to reconsider or deviate from our determination in the Coherus IPR that van de Putte "does not disclose whether the administered D2E7 formulation was in liquid form or lyophilized form" and "offers no guidance" as to how an ordinarily skilled artisan would have prepared a stable, liquid, high-concentration D2E7 formulation. Coherus Dec. 10. Petitioner, therefore, does not establish sufficiently that one of ordinary skill in the art would have had a reason to combine the teachings of Salfeld and van de Putte with an expectation of success in achieving a stable, liquid, high-concentration D2E7 formulation based on Salfeld's general statement that "[t]herapeutic compositions typically must be sterile and stable" and the concentration ranges van de Putte allegedly discloses.

Nor does Petitioner establish that a skilled artisan would have had a reasonable expectation of success in preparing a stable, liquid high-concentration D2E7 formulation based on the state of the art in 2002. In that regard, Petitioner asserts that "numerous prior art examples of stable, injectable, high concentration antibody and other protein formulations" would have "bolstered" a skilled artisan's reasonable expectation of success. Pet. 35. Petitioner points to six prior art patents as supporting that assertion. *Id.* (citing Ex. 1005; Ex. 1012; Ex. 1014; Ex. 1017; Ex. 1018; Ex. 1020). We disagree for several reasons.

First, at least two of the patents Petitioner cites (the '463 publication[13] and Andya[14]) disclose lyophilized formulations. *Id.* at 35–36 (citing Ex. 1018, 5:17–17, 35:17–19 (disclosing high-protein concentration formulations that are "lyophilized and then reconstituted"); Ex. 1020, 25:15–17 (disclosing a reconstituted high-concentration rhuMAB formulation)). For the same reasons discussed above, we find Petitioner fails to establish sufficiently that a skilled artisan would have had a reasonable expectation of success in preparing a stable, liquid high-concentration D2E7 formulation based on references disclosing high-concentration lyophilized formulations.

Second, Petitioner cites Heavner[15]—a reference we considered in the 1517 IPR. There, we determined that Heavner's "lack of teachings regarding specific pharmaceutical formulations" "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.'" 1517 Dec. 24. Petitioner does not address that finding, or otherwise persuade us that Heavner would have provided the ordinary artisan with a reasonable expectation of success in preparing any antibody as a stable liquid formulation.[16]

---

[13] International Publication No. WO 02/30463 A2, published April 18, 2002 (Ex. 1018).
[14] U.S. Patent No. 6,267,958 B1, issued July 31, 2001 (Ex. 1020).
[15] U.S. Patent No. 7,250,165 B2, issued July 31, 2007 (Ex. 1012).
[16] Petitioner also cites International Publication No. WO 02/12502 A2, published February 14, 2002 ("the '502 publication," Ex. 1017) to support its argument. Pet. 35–36. The disclosure of the '502 publication—a PCT application that lists the same inventors as Heavner and claims priority to Heavner (Ex. 1017 (30), (72))—is substantively similar to Heavner's disclosure. C*ompare generally id.*, *with* Ex. 1012. As with Heavner, Petitioner does not direct us to any teaching in the '502 publication of a

Third, the remaining patents on which Petitioner relies (Lam and the '772 publication[17]) describe different antibodies—not D2E7. Lam primarily relates to formulations comprising anti-CD18 and anti-CD20 antibodies, and the '772 publication is directed to formulations containing the IL-12 antibody. Ex. 1005, 24:28–40:26 (anti-CD18), 40:29–46:32 (anti-CD20)[18]; *e.g.*, Ex. 1014, Abstract, 3:23–26 (summary of invention), 15:8–10). We agree with Patent Owner that such references would not have provided a reasonable expectation of success in preparing a D2E7 formulation "because it was well known that a formulation developed for one antibody could not reasonably be expected to result in a stable, high-concentration, liquid formulation when transferred to another antibody." Prelim. Resp. 11–19, 54 (and evidence cited therein); *see also* 1514 Dec. 12–16 (finding that commercial antibody formulations and available literature "suggest[] a high degree of *un*predictability in the antibody formulation art"); Ex. 2025, 16 ("We further stress that the teaching[s] relating to one protein cannot simply be transferred to other proteins."), 17 ("Consequently, the skilled person would not simply apply the teaching[s] relating to one protein to a different

---

specific pharmaceutical formulation. *See* Pet. 35–36. As with Heavner, we find that the general disclosure of the '502 publication would not have provided one of ordinary skill in the art with a reasonable expectation of success in achieving any high-concentration protein formulation, much less a stable, liquid, high-concentration formulation comprising D2E7.

[17] International Publication No. WO 00/56772, published September 28, 2000 (Ex. 1014). Our citations are to the original page numbers of the reference.

[18] As we explained in the 1517 IPR, Lam's "inclusion of TNFα in a laundry-list of untested potential targets" would not have provided a skilled artisan "with sufficient direction" to select TNFα. 1517 Dec. 19.

protein."). For example, Wang[19] explains that, although certain factors have been identified that contribute to the stabilization of proteins, "the structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful." Ex. 1021, 130. Accordingly, Wang concludes that "the most formidable challenge in formulating a liquid protein pharmaceutical is to preserve the biological activity of the protein for an acceptable shelf life. Unfortunately, there is no single pathway to follow in formulating such a product. Usually, proteins have to be evaluated on a case-by-case basis." *Id.* at 178.

Dr. Remmele agrees with Wang's statements and has cited Wang "for the proposition that '[a]lthough antibodies share certain structural similarities, development of commercially viable antibody pharmaceuticals has not been straightforward because of their unique and somewhat unpredictable solution behavior.'" Ex. 1002 ¶ 182 (citing Ex. 1044, 2). Similarly, Dr. Remmele has stated that "[s]olution conditions producing adequate stability for protein pharmaceuticals are often empirically determined, which is essentially a 'hit' or 'miss' method for developing stable formulations." Ex. 2029, 2.[20] Thus, Petitioner does not persuade us that applying references disclosing formulations comprising other antibodies or proteins translates to a reasonable expectation of success in formulating a stable, liquid, high-concentration D2E7 formulation.

[19] Wei Wang, *Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals*, 185 INT'L J. PHARM. 129–188 (1999) (Ex. 1021).
[20] Exhibit 2029 is not paginated. Thus, we refer to the page numbers that Patent Owner has added to the exhibit.

b. Surfactant concentration

Turning next to surfactant concentration, Petitioner admits that Salfeld does not disclose the surfactant type or concentration that the claims recite. Pet. 16, 20. Petitioner asserts Remington teaches surfactants as common pharmaceutical excipients and identifies polysorbate 20 and polysorbate 80 as two common surfactants. *Id.* at 19. Petitioner further asserts that Lam teaches liquid protein formulations comprising 0.001–0.5%, or 0.01–5 mg/ml, polysorbate 80. *Id.* at 18. According to Petitioner, a skilled artisan would have looked to Lam's formulations and the surfactant amounts Lam discloses because Lam discloses "similar antibody formulations" that "identify typical amounts of polysorbate" used in such formulations. *Id.* at 27. As we explain above, however, Petitioner does not show sufficiently on this record that a teaching regarding one antibody formulation translates to a reasonable expectation of success in formulating a different antibody. Accordingly, we are not convinced that a person of ordinary skill in the art would have had a reason to apply Lam's teachings, which primarily relate to formulations comprising anti-CD18 and anti-CD20 antibodies, as well as the concentrations of components that may be used in such formulations, to a D2E7 formulation. Nor are we convinced that a skilled artisan would have had a reasonable expectation of success in preparing a stable, liquid D2E7 formulation comprising 0.1–10 mg/ml polysorbate (or polysorbate 80) based on the combined teachings of Salfeld, Remington, and Lam.

Given the foregoing, Petitioner does not establish a reasonable likelihood of prevailing in its assertion that the subject matter of independent claims 1 and 19 would have been obvious over the combination of Salfeld,

van de Putte, Barrera, Remington, and Lam. Because dependent claims 2–18 and 20–29 also require a stable, liquid, high-concentration D2E7 formulation (i.e., at least 45 mg/ml of D2E7) comprising at least 0.1 mg/ml of polysorbate, Petitioner likewise does not establish a reasonable likelihood of prevailing on its asserted ground as to those claims.

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 establish a reasonable likelihood of prevailing at trial as to any challenged claim. Accordingly, the Petition is *denied*, and we do not institute trial.

V. ORDER

It is hereby

ORDERED that the Petition is *denied* as to all challenged claims of the '100 patent, and no trial is instituted;

FURTHER ORDERED that Petitioner's *Pro Hac Vice* Motion to Admit Daniel L. Reisner Pursuant to 37 C.F.R. § 42.10(c) (Paper 3) is *dismissed as moot*;

FURTHER ORDERED that Petitioner's *Pro Hac Vice* Motion to Admit Abigail Langsam Pursuant to 37 C.F.R. § 42.10(c) (Paper 10) is *dismissed as moot*; and

FURTHER ORDERED that Patent Owner's Motion to Withdraw Backup Counsel (Paper 11) is *dismissed as moot*.

PETITIONER:

Deborah E. Fishman
David R. Marsh
David K. Barr
ARNOLD & PORTER KAYE SCHOLER LLP
deborah.fishman@apks.com
david.marsh@apks.com
David.Barr@apks.com

PATENT OWNER:

Tamera M. Weisser
Anthony M. Insogna
David M. Maiorana
JONES DAY
tweisser@jonesday.com
aminsogna@jonesday.com
dmaiorana@jonesday.com

David P. Frazier
Robert Steinberg
LATHAM & WATKINS LLP
david.frazier@lw.com
bob.steinberg@lw.com