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Paper 8
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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 IPR2016-00188
Patent 9,017,680 B2

Before TONI R. SCHEINER, JAMES T. MOORE, and ERICA A. FRANKLIN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

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

I. INTRODUCTION

Coherus BioSciences Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") on December 7, 2015, requesting an *inter partes* review of claims 1–4 of U.S. Patent No. 9,017,680 B2 (Ex. 1001, "the '680 patent"). AbbVie Biotechnology Ltd. ("Patent Owner") filed a Preliminary Response (Paper 7, "Prelim. Resp.") on March 15, 2016. We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the information presented in the Petition and the Preliminary Response, we are persuaded that Petitioner has established a reasonable likelihood that it would prevail in its challenges to claims 1–4 of the '680 patent. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

The '680 patent is a continuation of U.S. Patent Application No. 10/163,657, which issued as U.S. Patent 8,889,135 ("the '135 patent"). U.S. Patent 9,073,987 ("the '987 patent") is also a continuation of Application No. 10/163,657. In addition to the present Petition, Petitioner filed petitions seeking *inter partes* review of the '135 and '987 patents: IPR2016-00172 and IPR2016-00189, respectively. Pet. 3, Paper 6, 1. Patent Owner further identifies two additional petitions—filed by a different petitioner—seeking *inter partes* review of the '135 patent: IPR2016-00408 and IPR2016-00409. Paper 6, 1.

B. The '680 Patent (Ex. 1001)

Tumor necrosis factor α ("TNFα"), a cytokine produced by numerous cell types, has been implicated in activating tissue inflammation and causing joint destruction in the auto immune disease, rheumatoid arthritis ("RA"). Ex. 1001, 1:15–16, 25:36–40. The '680 patent, titled "Methods of Administering Anti-TNFα Antibodies," discloses administering a total body dose of 20, 40, or 80 mg of an anti-TNFα antibody having the six complementarity determining regions ("CDRs") and heavy chain regions of D2E7—a known recombinant human anti-TNFα antibody— together with the anti-rheumatic drug methotrexate ("MTX"), to rheumatoid arthritis patients according to a "biweekly dosing regimen[] . . . preferably via a subcutaneous route . . . [p]referably . . . every 9–19 days, more preferably, every 11–17 days, even more preferably, every 13–15 days, and most preferably, every 14 days." *Id.* at 3:7–42, 6:26–39, 9:53–67, 29:15–30:29.

C. Illustrative Claim

Petitioner challenges claims 1–4 of the '680 patent. Claim 1, the only independent claim, is illustrative.

> A method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis, comprising:
>
> administering to said patient, in combination with methotrexate, a human anti-TNFα antibody,
>
> wherein the human anti-TNFα antibody is administered subcutaneously in a total body dose of 40 mg once every 13–15 days, and
>
> wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising

> a CDR1 having the amino acid sequence of SEQ ID NO:7, a CDR2 having the amino acid sequence of SEQ ID NO:5, and a CDR3 having the amino acid sequence of SEQ ID NO:3; and a variable heavy ("V_H") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:8, a CDR2 having the amino acid sequence of SEQ ID NO:6 and a CDR3 having the amino acid sequence of SEQ ID NO:4.

Ex. 1001, 51:23–52:25.

D. The Asserted Ground of Unpatentability

Petitioner asserts that claims 1–4 are unpatentable under 35 U.S.C. § 103(a) as obvious over van de Putte[1] (Ex. 1004) and Kempeni[2] (Ex. 1003). Petitioner also relies on the Declarations of Sharon Baughman, Ph.D. (Ex. 1006), James O'Dell, M.D. (Ex. 1007), and Brian Reisetter, RPh, MBA, Ph.D. (Ex. 1025).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); Office Patent Trial

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[1] L.B.A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42(S9) ARTHRITIS & RHEUM. S400, Abstract 1977 (1999) ("van de Putte") (Ex. 1004).

[2] Joachim Kempeni, *Preliminary results of early clinical trials with the fully human anti-TNFα monoclonal antibody D2E7*, 58(Suppl. I) ANN. RHEUM. DIS. 170–72 (1999) (Ex. 1003).

Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Under that standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999).

For purposes of this decision, we determine that the following claim terms require discussion.

1. "method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis"

This claim term appears only in the preamble of claim 1. Petitioner argues that "the broadest reasonable interpretation of the phrase 'method of reducing signs and symptoms' does not require a particular level of efficacy . . . [but] merely require[s] that the 'signs and symptoms' the patient exhibits are reduced relative to their level prior to administration of the antibody plus methotrexate.'" Pet. 16.

Patent Owner argues, on one hand, that "[t]he plain and ordinary meaning of a 'method of reducing signs and symptoms' is clear . . . [and] no construction is needed." Prelim. Resp. 19. On the other hand, however, Patent Owner argues that we "should reject Petitioner's proposed interpretation of the preamble because it is inconsistent with the specification, which discloses that administration of [anti-TNFα antibody] and [methotrexate] produces a meaningful improvement in a

variety of clinical outcome measures such as ACR20, ACR50, and SWJ (swollen joint count)." *Id.* (citing Ex. 1001, Figs. 1b, 2, 3, 30:23-26).

Generally speaking, "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." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (quoting *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999)). On the other hand, "a preamble is not limiting '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)).

We determine that the preamble of claim 1 gives life, meaning, and vitality to the claims only to the extent that it specifies the patient to whom the anti-TNFα antibody is administered. The steps of the method, dosage amount, timing, route of administration, and active component, however, are all specified in the body of the claim. The phrase "reducing the signs and symptoms of rheumatoid arthritis," therefore, merely recites an intended use. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003) (statements of intended use typically do not limit the scope of a claim because they "usually do no more than define a context in which the invention operates"). Accordingly, for purposes of this Decision, and based on the current record, we determine that the preamble is not limiting beyond specifying the patient to whom the anti-TNFα antibody is administered.

2. "40 mg dosage unit form"

According to the '680 patent, "dosage unit form" "refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound[.]" Ex. 1001, 23:9–12. Petitioner contends, "[b]ased upon this definition, a '40 mg dosage unit' form would encompass a syringe filled with 40 mg of D2E7." Pet. 17.

"For the limited purpose of [its] preliminary response, Patent Owner does not contest this." Prelim. Resp. 20.

For purposes of this decision, we agree that the broadest reasonable interpretation of "40 mg dosage unit form" encompasses a syringe filled with 40 mg of D2E7.

B. 35 U.S.C. 325(d)

Patent Owner urges us to deny the Petition pursuant to 35 U.S.C. § 325(d) because substantially the same prior art and arguments were advanced by the Examiner during prosecution of the '135 and '680 patents. Prelim. Resp. 49–50. Specifically, Patent Owner contends that "Petitioner relies on the exact same references that were presented and thoroughly considered by the Examiner during prosecution" without presenting "any persuasive new evidence to supplement the record considered during examination." *Id.* at 49.

Section 325(d) provides: "[i]n determining whether to institute or order a proceeding . . . , the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments

previously were presented to the Office." In other words, the decision whether to deny a petition under § 325(d) is discretionary, not mandatory.

Having considered the record before the Office during examination, as well as the parties' arguments and the present record, we decline to exercise our discretion to deny the Petition. Rather, we are persuaded that sufficient reason exists, based on the record presently before us, to address the arguments and information presented in the Petition, as discussed below.

C. Obviousness over van de Putte and Kempeni

Petitioner asserts that the subject matter of claims 1–4 would have been obvious over the combination of van de Putte and Kempeni. Pet. 32–44. For the reasons set forth below, we are persuaded that there is a reasonable likelihood that Petitioner would prevail on its asserted ground.

1. Overview of Kempeni (Ex. 1003)

Kempeni teaches that D2E7 is a fully human anti-TNFα monoclonal antibody that "may have advantages in minimising antigenicity in humans" compared to biologic TNF antagonists, e.g., chimeric monoclonal antibodies, which are not fully human. Ex. 1003, 1. Kempeni further describes the results of several clinical studies investigating the use of D2E7 to treat RA patients. *Id.* at 1–3.

During the clinical trials, D2E7's efficacy was assessed using, *inter alia*, the American College of Rheumatology improvement criteria (ACR 20 criteria). *Id.* at 1–2. To be classified as a responder according to ACR 20 criteria, a patient must

demonstrate: (1) greater than or equal to 20% improvement in swollen joint count ("SWJC"), (2) greater than or equal to 20% improvement in tender joint count ("TJC"), and (3) at least 20% improvement in three of five other measures, including patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain, an acute phase reactant (e.g., C reactive protein ("CRP")), and a measure of disability. *Id.* at 2.

In the first study, each patient received a single dose of D2E7 (from 0.5 to 10 mg/kg) or placebo by intravenous injection. *Id.* Patients were evaluated for four weeks to determine the pharmacokinetics of D2E7 and to evaluate the safety and efficacy of the compound in terms of onset, duration, and magnitude of response. *Id.*

Kempeni describes the results of the study as "encouraging," noting that the "therapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1–2 weeks, with dose response reaching a plateau at 1 mg/kg D2E7." *Id.* Pharmacokinetic parameters were calculated for patients from all dose groups and the estimated mean terminal half-life of D2E7 was determined to be 11.6 to 13.7 days. *Id.*

Patients who continued in the study were given a second blinded dose that was identical to the first and, subsequently, given active drug every two weeks until a "good" response was achieved. *Id.* Patients who did not respond well after 0.5 or 1 mg/kg dosing, however, received higher doses of up to 3 mg/kg. *Id.* Kempeni discloses that 86% of patients continued to receive treatment with D2E7

after six months, "indicating that long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." *Id.*

In a second study that evaluated the safety and efficacy of weekly subcutaneous 0.5 mg/kg weight-based administration of D2E7, patients were given either D2E7 or placebo weekly for a period of three months. *Id.* at 2–3. The dose was increased to 1 mg/kg subcutaneously weekly for nonresponders or patients losing responder status. *Id.* at 3.

According to the preliminary data, "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration." *Id.* Further, up to 78% of patients achieved an ACR 20 response after three months of treatment, leading to the conclusion that "D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery." *Id.*

In a third clinical study that evaluated the safety of 1 mg/kg single subcutaneous or intravenous injections of D2E7—in some cases in combination with the anti-rheumatic drug methotrexate—it was determined that the safety profile of single dose D2E7 administration was "comparable to that of placebo." *Id.*

According to Kempeni, the data from these studies collectively suggest D2E7 "is safe and effective as monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous

injections." *Id.* Kempeni indicates that "[a]dditional studies are underway to further define optimal use of this novel treatment." *Id.*

2. Overview of van de Putte (Ex. 1004)

van de Putte describes the results of a dose-finding phase II study that compared three dose levels of D2E7 and placebo over three months in patients with long-standing active RA. Ex. 1004, 1. In the study, patients received "weekly [fixed] doses of either D2E7 at 20, 40, [or] 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months." *Id.* van de Putte reports the percentage of patients receiving an ACR 20 response, as well as the median percent improvement in TJC, SWJC, and CRP for each of the dosing regimens and placebo.

The results of the study described in van de Putte are reproduced below.

	Placebo	D2E7	D2E7	D2E7
	(n=70)	20 mg (n=71)	40 mg (n=70)	80 mg (n=72)
% of pts achieving ACR 20 response	10	49	57	56
Median % improvement in TJC	5	57	61	55
Median % improvement in SWJC	16	42	59	61
Median % improvement in CRP	1	55	67	65

Ex. 1004, 1. The table shows the results of the clinical study described in van de Putte. Based on the results, van de Putte concludes that "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$)" and that "20, 40, and 80 mg/week were nearly equally efficacious when given s.c. in patients with active RA." *Id.*

3. Analysis

Petitioner, with supporting testimony from Drs. Baughman and O'Dell, contends that the disclosures of van de Putte and Kempeni would have motivated a person of ordinary skill in the art to administer 40 mg of D2E7 biweekly, i.e., "once every 13–15 days," as recited in claims 1–4 of the '680 patent, and that person would have expected such a dose to be safe and effective in treating RA. Pet. 2, 32–39 (citing Ex. 1006 ¶¶ 48, 51–53, 56–58, 60–61, 63–68, and 73; Ex. 1007 ¶¶ 25–33, 43). Moreover, Petitioner contends that that person would have known, "based upon the clinical studies described in Kempeni, that D2E7 could be co-administered with methotrexate." *Id.* at 32 (citing Ex. 1003, 2–3; Ex. 1007 ¶¶ 24, 33). Petitioner asserts, when viewed in the context of the advanced state of the art at the time of filing, the subject matter of the challenged claims would have represented no more than "'a routine optimization of the therapy outlined in [the prior art], which would have been achievable through the use of standard clinical trial procedures.'" *Id.* at 2, 37 (quoting *Biomarin Pharms. Inc. v. Genzyme Therapeutic Prods. Ltd. P'ship*, Case IPR2013-00534, slip op. at 12–14 (PTAB Feb. 23, 2015) (Paper 81)).

Patent Owner takes issue with Petitioner's contention that selecting (1) subcutaneous fixed dosing, (2) a 40 mg dose strength, and (3) biweekly administration from the cited clinical data is nothing more than routine optimization. Prelim. Resp. 21–35. Patent Owner argues that "Petitioner's obviousness analysis gives insufficient weight to the uncertainty in the art, the significant safety and efficacy concerns associated with dosing anti-TNFα

biologics, and the lack of critical pharmacokinetic information regarding D2E7 in the art," and "[t]he result is a textbook example of hindsight that fails to carry Petitioner's burden of demonstrating that the claims are obvious." *Id.* at 20–21.

With respect to subcutaneous fixed dosing, Patent Owner contends that there was a clear preference in the antibody therapeutics art and early D2E7 clinical trials for weight-based dosing administered intravenously. *Id.* at 21–22 (citing Ex. 1003, 3; Ex. 1005,[3] 3; Ex. 1012,[4] 1, 12; Ex. 1023;[5] Ex. 2001[6] ¶ 34; Ex. 2003[7] ¶¶ 40, 41, 46, 82, 83; Ex. 2017,[8] 13, 29, 31; Ex. 2018,[9] 9–11). Patent Owner further contends that a skilled artisan would have considered intravenous, weight-based dosing "a better alternative" for addressing safety and efficacy concerns,

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[3] R. Rau et al., *Effective Combination of Fully Human Anti-TNF Antibody D2E7 Methotrexate in Active Rheumatoid Arthritis*, ANN. RHEUM. DIS. 217, Abstract 907 (1999) (Ex. 1005).

[4] Infliximab/REMICADE® label (Nov. 1999) (Ex. 1012).

[5] Weisman et al., *A dose escalation study designed to demonstrate the safety, tolerability and efficacy of the fully human anti-TNF antibody, D2E7, given in combination with methotrexate (MTX) in patients with active RA*, 43 ARTHRITIS & RHEUM. S391, abstract 1948 (2000) (Ex. 1023).

[6] Declaration of Janet Pope, MD, MPH, FRCPC, dated Jan. 31, 2014 (Ex. 2001).

[7] Declaration of Diane R. Mould, Ph.D., dated Jan. 29, 2014 (Ex. 2003).

[8] MALCOLM ROWLAND & THOMAS N. TOZER, *Chapter 3: Intravenous Dose*, and *Chapter 4: Extravascular Dose*, *in* CLINICAL PHARMACOKINETICS CONCEPTS AND APPLICATIONS (3d ed. 1995) (Ex. 2017).

[9] Christopher J.H. Porter & Susan A. Charman, *Lymphatic Transport of Proteins After Subcutaneous Administration*, 89 J. PHARM. SCI. 297–310 (2000) (Ex. 2018).

"particularly for patients ***also*** receiving MTX, itself a chemotherapy agent known to be capable of suppressing the immune system." *Id.* at 24 (citing Ex. 2033,[10] 3).

At this stage of the proceeding, we are not persuaded by Patent Owner's arguments with respect to subcutaneous fixed dosing, because they disregard the collective teachings of van de Putte and Kempeni upon which Petitioner relies. Specifically, van de Putte discloses that administering fixed doses of D2E7 to RA patients by subcutaneous injection is effective (Ex. 1004, 3), while Kempeni concludes that D2E7 given subcutaneously is "safe and as effective as when administered intravenously," and moreover, that "D2E7 is safe and effective . . . in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections." Ex. 1003, 3. Further, on the record before us, Petitioner shows sufficiently that ordinarily skilled artisans would have recognized subcutaneous injection as preferable to intravenous infusion, because patients can self-administer the treatment. *Id.* at 33 (citing Ex. 1022,[11] 9; Ex. 1006 ¶ 51); *see* Ex. 1008,[12] 21:25–27. Likewise, Petitioner identifies known advantages of fixed dosing over weight-based dosing, including that fixed dosing requires no patient action beyond injection. *Id.* 33–34 (citing 1006 ¶ 52; Ex. 1008, 22:65–23:1).

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[10] Peter A. Anderson et al., *Weekly Pulse Methotrexate in Rheumatoid Arthritis: Clinical and Immunologic Effects in a Randomized, Double-Blind Study*, 103 ANN. INTERN. MED. 489-96 (1985) (Ex. 2033).

[11] WO 98/04281, International Application of Davis et al., published Feb. 5, 1998.

[12] U.S. Patent No. 6,090,382, issued July 18, 2000 to Salfeld et al.

Regarding dose strength, Patent Owner argues that pursuing the 20 mg weekly dose disclosed in van de Putte would have required a skilled artisan to "ignore data . . . showing that 40 and 80 mg weekly doses were clinically superior to the 20 mg dose." Prelim. Resp. 24–25 (citing Ex. 2001 ¶ 20; Ex. 2002[13] ¶ 20; Ex. 2003 ¶ 22). Thus, argues Patent Owner, a skilled artisan would have concluded from the van de Putte data that a 20 mg dose administered subcutaneously weekly "was too low a dose to pursue." *Id.* at 26 (citing Ex. 2001 ¶ 22; Ex. 2002 ¶ 20). Similarly, Patent Owner argues that the goal of a skilled artisan engaged in the design of a D2E7 dosing regimen was not to obtain mere superiority over placebo, to achieve marginal efficacy, or to reduce a sign or symptom of RA "to some extent"—rather, the goal "was to provide the highest level of efficacy possible while maintaining patient safety." *Id.* at 27 (citing Ex. 2001 ¶ 44; Ex. 2003 ¶¶ 44–45).

We are not persuaded by Patent Owner's arguments regarding superiority of the 40 and 80 mg doses to the 20 mg dose disclosed in van de Putte. van de Putte discloses that 20, 40, and 80 mg D2E7 administered weekly were "nearly equally efficacious" and "statistically significantly superior to placebo" for all efficacy parameters studied. Ex. 1004, 1. Further, van de Putte's tabulated clinical responses show similar percentages of patients achieving ACR 20 response and median percent improvement in TJC, SWJC, and CRP for each of the 20, 40, and 80 mg doses. Ex. 1004, 1. van de Putte's clinical data for the 20, 40, and 80 mg

[13] Declaration of Michael E. Weinblatt, MD, dated Feb. 3, 2014 (Ex. 2002).

doses also are all higher than the 20 percent improvement thresholds for SWJC, TJC, and CRP that Kempeni discloses as demonstrating efficacy pursuant to the ACR 20 criteria. Ex. 1003, 2. Moreover, we are not persuaded, based on the current record, that the broadest reasonable interpretation of the claims requires any particular level of efficacy (*see* Section II.A.1).

Patent Owner contends that Petitioner gives insufficient weight to the uncertainty in the art, the significant safety and efficacy concerns associated with dosing anti-TNFα biologics, and the lack of critical pharmacokinetic information regarding D2E7. Prelim. Resp. 20. In particular, Patent Owner argues that transforming weight-based doses into fixed doses simply by multiplying by an average patient weight (as Petitioner does when multiplying the 0.5 mg/kg intravenous biweekly dose into a 40 mg fixed dose based on an 80 kg patient) is a "well-known pharmacokinetic fallacy." *Id.* at 30 (citing Ex. 2003 ¶ 34). Patent Owner further asserts that the art as a whole at the relevant time taught away from using 0.5 mg/kg as a fixed dose across all patients, instead favoring higher doses, and that Petitioner fails to explain sufficiently why dose-stretching would have focused on a 40 mg dose every other week. *Id.* at 32. According to Patent Owner, if a clinician were to experiment with different doses, routes of administration, and dosing frequencies, as Petitioner contends, there would be innumerable possible combinations. *Id.* at 32–33.

Petitioner's analysis, however, is not based primarily on transforming a 0.5 mg/kg intravenous biweekly dose into a 40 mg subcutaneous biweekly dose. Rather, Petitioner asserts, with supporting testimony from Dr. Baughman, that a

skilled artisan would have been led to biweekly dosing based on the known 11.6 to 13.7 day half-life of D2E7. Pet. 32, 35–36; Ex. 1006 ¶¶ 66, 67, 72, 73. Pointing to the clinical results reported in van de Putte, Petitioner explains that a skilled artisan would have recognized that at least 30 mg of D2E7 would have remained circulating in a patient's blood one week after administration of a 40 mg dose, and that this amount is greater than the 20 mg dose van de Putte disclosed as efficacious when administered weekly. *Id.* at 37; Ex. 1006 ¶¶ 67–68, 71. Petitioner further points to Kempeni's teaching that D2E7 could be administered safely over a broad range of doses to show that a skilled artisan would have reasonably expected biweekly dosing of 40 mg to be safe. *Id.* at 38 (citing Ex. 1003, 2; Ex. 1006 ¶ 57).

Patent Owner disputes Petitioner's assertions regarding what knowledge of D2E7's half-life would have conveyed to the skilled artisan about a dosing regimen. Citing the expert declarations submitted during prosecution of the '135 patent and dosing regimens for other FDA-approved antibodies, Patent Owner contends that half-life alone would not have been a predictor for establishing a D2E7 dosing regimen, because there was no known correlation between the two for therapeutic antibodies and half-life was one of many factors that contributed to the ability to predict dosing frequency. Prelim. Resp. 36–39 (citing Ex. 2003 ¶¶ 76–78; Ex. 2002 ¶ 57; Ex. 2006[14] ¶ 5). Patent Owner also contends that Petitioner's calculations regarding the amount of D2E7 that would have been

[14] Declaration of Dr. Hartmut Kupper, dated June 4, 2010 (Ex. 2006).

circulating in the blood one and two weeks after injection are "indisputably incorrect," because they disregard the fact that delivery of a drug subcutaneously was known to cause a variable, and often significant, reduction in the amount of drug absorbed into the bloodstream. *Id.* at 41 (citing Ex. 2003 ¶ 40; Ex. 2006 ¶ 18; Ex. 2018, 8). Thus, argues Patent Owner, even assuming a 14-day half-life for each D2E7 dose was administered, the amount of D2E7 circulating in the blood one and two weeks after injection would have been "substantially lower" than the amounts Petitioner identifies in its analysis. *Id.* at 41–42.

Patent Owner further asserts that Petitioner's arguments ignore significant risks that a skilled artisan would have understood to be associated with dose-stretching. Prelim. Resp. 34. According to Patent Owner, among those known risks were the potential adverse consequences of under-dosing, including the formation of anti-drug antibodies that could compromise safety and efficacy. *Id.* at 34–35 (citing Ex. 2001 ¶¶ 46–48; Ex. 2002 ¶¶ 37–40; Ex. 2003 ¶¶ 57–60).

Patent Owner's arguments in this regard, at best, create genuine issues of material fact as to whether a skilled artisan would have relied upon half-life or dose-stretching based on known half-life to establish a dosing regimen for D2E7. We find these factual disputes best resolved during trial when we are able to assess Petitioner's and Patent Owner's evidence and arguments upon review of the entire record.

Patent Owner further contends that the Petition is deficient with respect to dependent claims 3 and 4, which recite that the dosage is administered "from a 40 mg unit dosage form," but "[n]one of Petitioner's experts address this limitation,

and the Petition itself addresses it only in a claim chart stating without explanation that van de Putte discloses 'self injection.'" Prelim. Resp. 47–48.

We are not persuaded. As discussed above in Section II.A.2, for purposes of this decision, the broadest reasonable interpretation of a "40 mg dosage unit form" encompasses a syringe filled with 40 mg of D2E7. As Petitioner points out, van de Putte describes subcutaneous "self injection" of 20, 40, and 80 mg doses of D2E7. Pet. 40–41. We are persuaded that Petitioner has shown sufficiently that van de Putte teaches or suggests syringes pre-filled with doses of 20, 40, and 80 mg of D2E7.

Finally, Patent Owner asserts that objective evidence of nonobviousness ("secondary considerations") supports the patentability of claims 1–4. Prelim. Resp. 43–47. Secondary considerations, when present, must "be considered en route to a determination of obviousness." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citation omitted). Secondary considerations may include any or all of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). To be relevant, evidence of nonobviousness must be commensurate in scope with the claimed invention. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Patent Owner argues that HUMIRA® is a commercial formulation of D2E7, that it "indisputably is a commercial success," and has achieved that commercial

success despite being the third anti-TNFα antibody product introduced to the market. Prelim. Resp. 44. Patent Owner further argues that the nexus between HUMIRA®'s commercial success and dosing regimen has been "widely recognized, with the dosing regimen identified as a 'key design feature'." *Id.* at 45 (citing Ex. 2004[15] ¶¶ 28–31; Ex. 2031,[16] 3).

We acknowledge that the Federal Circuit has indicated that if evidence shows that a referenced commercial embodiment is "the invention disclosed and claimed in the patent" (a fact not disputed in relation to HUMIRA® here), we are to presume that any commercial success of that product is due to the patented invention. *PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 734, 747 (Fed. Cir. 2016) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)). The record before us at this time, however, does not establish that the commercial success of HUMIRA® is commensurate in scope with the claimed invention—40 mg subcutaneous, every-other week administration to treat RA. For example, although the evidence Patent Owner presents attributes the overall sales of HUMIRA® in part to subcutaneous, biweekly flat dosing, there appears to be little indication that sales are due to the 40 mg dose amount recited in the claims. *See, e.g.*, Ex. 2004 ¶¶ 28–30; Ex. 2031, 3.

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[15] Declaration of Mr. Medgar Williams, dated Feb. 7, 2014 (Ex. 2004).

[16] Luke Timmerman, *Abbott's Humira, the 3rd-in-Class Drug that Toppled Lipitor as No. 1*, BIOBEAT (Apr. 16, 2012) (Ex. 2031).

Moreover, evidence cited by Patent Owner also attributes overall sales of HUMIRA® to the fully human D2E7 anti-TNFα antibody, which was known in the prior art. *See* Ex. 2031, 3. Patent Owner's evidence further indicates that HUMIRA® has been FDA-approved and "has enjoyed success" in treating autoimmune diseases other than the recited RA, such as psoriatic arthritis, and intestinal disorders, such as Crohn's disease, since October 2005 and February 2007, respectively. Ex. 2004 ¶¶ 5, 38. Accordingly, at this stage of the proceeding, the arguments and information of record do not persuade us to decline to go forward with a trial.

D. Summary

Based on the information and evidence presented in the Petition and Patent Owner's Preliminary Response, we are persuaded that Petitioner has shown a reasonable likelihood of prevailing in its assertion that the selection of a 40 mg total body dose administered subcutaneously biweekly would have been obvious and no more than a routine optimization of the dosing regimens disclosed and suggested by the combination of van de Putte and Kempeni, in view of the state of the art. Thus, we are persuaded that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing challenged claims 1–4 are unpatentable over van de Putte and Kempeni.

III. CONCLUSION

For the foregoing reasons, we are persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–4 of the '680 patent are unpatentable under 35 U.S.C. § 103(a).

The Board has not made a final determination on the patentability of any challenged claim or the construction of any claim term.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review of the '680 patent is hereby instituted as to the following claims and ground:

Claims 1–4 under 35 U.S.C. § 103(a) as unpatentable over van de Putte and Kempeni; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(d) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial commences on the entry date of this decision.

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