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Filed on behalf of: AbbVie Biotechnology Ltd.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COHERUS BIOSCIENCES INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-00172
Patent No. 8,889,135

PATENT OWNER'S PRELIMINARY RESPONSE

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PATENT OWNER'S EXHIBIT LIST

EXHIBIT	DESCRIPTION
2001	Declaration of Janet Pope Under 37 C.F.R. § 1.132 dated January 31, 2014, submitted during prosecution of U.S. Application No. 10/163,657 (U.S. Patent No. 8,889,135) (corresponds to Ex. 1002 at 1141-1171)
2002	Declaration of Michael E. Weinblatt, MD Under 37 C.F.R. § 1.132 dated February 3, 2014, submitted during prosecution of U.S. Application No. 10/163,657 (U.S. Patent No. 8,889,135) (corresponds to Ex. 1002 at 1173-1199)
2003	Declaration of Diane R. Mould Under 37 C.F.R. § 1.132 dated January 29, 2014, submitted during prosecution of U.S. Application No. 10/163,657 (U.S. Patent No. 8,889,135) (corresponds to Ex. 1002 at 1201-1233)
2004	Declaration of Mr. Medgar Williams Under 37 C.F.R. § 1.132 dated February 7, 2014, submitted during prosecution of U.S. Application No. 10/163,657 (U.S. Patent No. 8,889,135) (corresponds to Ex. 1002 at 1240-1251)
2005	Declaration Under 37 C.F.R. § 1.132 of Harmut Kupper dated July 1, 2008, submitted during prosecution of U.S. Application No. 10/163,657 (U.S. Patent No. 8,889,135) ("Kupper I Decl.") (corresponds to Ex. 1002 at 600-604)
2006	Declaration Under 37 C.F.R. § 1.132 by Dr. Harmut Kupper dated June 4, 2010, submitted during prosecution of U.S. Application No. 10/163,657 (U.S. Patent No. 8,889,135) ("Kupper II Decl.") (corresponds to Ex. 1002 at 808-818)
2007	Rituximab/RITUXAN® label (Nov. 1997)
2008	Trastuzumab/HERCEPTIN® label (Sept. 1998)
2009	Abciximab/REOPRO® label (Nov. 4, 1997)
2010	Daclizumab/ZENAPAX® label (Dec. 1997)
2011	Basiliximab/SIMULECT® label (May 1998)
2012	Palivizumab/SYNAGIS® label (Mar. 2014)
2013	Gemtuzumab/MYLOTARG® label (Aug. 2005)
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2015	Adalimumab M10-261 Clinical Study Report R&D/09/173 (Apr. 9, 2010)

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2017	Malcom Rowland, Ph.D. & Thomas N. Tozer , Ph.D., *Chapter 3: Intravenous Dose*, and *Chapter 4: Extravascular Dose*, in CLINICAL PHARMACOKINETICS CONCEPTS AND APPLICATIONS (3d ed. 1995)
2018	Christopher J. H. Porter & Susan A. Charman, *Lymphatic Transport of Proteins After Subcutaneous Administration*, J. PHARM. SCI., 89(3):297-310 (2000)
2019	R. Rau, *Erfahrungen mit D2E7*, ZETTSCHRIFT FUR RHEUMATOLOGIE, 58(Supplement 1):Abstract S51 (1999) (original German)
2020	R. Rau, *Experiences with D2E7*, J. RHEUMATOL., 58(Supplement 1):Abstract S51 (1999) (certified English translation)
2021	L. B. A. van de Putte, et al., *Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed*, ANN. RHEUM. DIS., 63(5):508-516 (2004)
2022	Fabien B. Vincent, et al., *Antidrug antibodies (ADAb) to tumor necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective*, ANN. RHEUM. DIS., 72:165-178 (2013)
2023	Pauline A. van Schouwenburg, et al., *Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis*, NAT. REV. RHEUMATOL., 9:164-172 (2013)
2024	Ravinder N. Maini, et al., *Therapeutic Efficacy of Multiple Intravenous Infusions of Anti-Tumor Necrosis Factor α Monoclonal Antibody Combined with Low-Dose Weekly Methotrexate in Rheumatoid Arthritis*, ARTHRITIS & RHEUMATISM, 41(9):1552-1563 (1998)
2025	Frederick Wolfe, et al., *Consensus Recommendations for the Assessment and Treatment of Rheumatoid Arthritis*, J. RHEUMATOL., 28(6):1423-1430 (2001)

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2027	Zhiqiang An, *Monoclonal antibodies - a proven and rapidly expanding therapeutic modality for human diseases*, PROTEIN CELL, 1(4):319-330 (2010)
2028	Peter F. Bross, et al., *Approval Summary: Gemtuzumab Ozogamicin in Relapsed Acute Myeloid Leukemia*, CLINICAL CANCER RES., 7:1490-1496 (June 2001)
2029	U.S. Application No. 11/443,943, January 29, 2008 Amendment and Response to Office Action
2030	Direct Narrative Statement of Brian C. Reisetter, Ph.D., *Novo Nordisk A/S et al. v. Caraco Pharm. Labs., Ltd. et al.*, No. 2:05-cv-40188 (E.D. Mich. Aug. 11, 2010) (D.I. 488)
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I. INTRODUCTION

Coherus BioSciences Inc. ("Petitioner") seeks *inter partes* review of U.S. Patent No. 8,889,135 ("the '135 patent"), contending that claims 1-5 are rendered obvious by the combination of the van de Putte abstract and Kempeni. The claims of the '135 patent cover the FDA-approved method of using D2E7 (the active ingredient in HUMIRA®) to treat rheumatoid arthritis ("RA"). The Board should deny the Petition because it fails to demonstrate a reasonable likelihood that Petitioner will prevail on its single ground.

At the outset, the Board should deny this Petition pursuant to 35 U.S.C. § 325(d) because Petitioner merely rehashes the same arguments thoroughly considered by the Examiner during prosecution. The exact same combination of references that forms the basis for Petitioner's sole obviousness ground was considered by the Examiner. The issues raised by Petitioner and its declarants correspond directly to the issues that were raised during prosecution by the Examiner and overcome by Patent Owner. Because Petitioner has failed to present any persuasive new evidence that was not before the Examiner, the Petition is cumulative, and the Board should decline to institute trial.

As summarized here and discussed in more detail in sections that follow, Petitioner fails to meet its burden for several reasons.

First, Petitioner's arguments are based on a hindsight evaluation of the art that picks and chooses portions of references while ignoring the art as a whole. The van de Putte and Kempeni references taken together describe early clinical studies involving D2E7 having different routes of administration, dosing schedules, and dosing amounts. Most of those studies utilized body-weight dosing, consistent with recognized concerns that a fixed-dose regimen would not safely and effectively treat patients of different weights. Petitioner's selection of the fixed-dose regimens described in van de Putte as the basis of its obviousness attack is pure hindsight. And even as to van de Putte, Petitioner's focus on the 20 mg dose is driven by hindsight given that the 20 mg dose was inferior to the other doses disclosed by van de Putte.

Second, Petitioner's argument that a POSA would have been motivated to "stretch" a weekly dose based on patient convenience ignores critical efficacy and safety issues. Under-dosing a monoclonal antibody such as D2E7 presented serious concerns due to the increased risk of forming anti-drug antibodies, which significantly decrease efficacy and increase side effects. The prior art, including Kempeni, showed that patients receiving a weight-based dose supposedly equivalent to the claimed 40 mg dose had to be "up-dosed" to higher doses due to inadequate clinical response. A POSA would have been concerned about under-

dosing and would have considered a 20 mg weekly dose too low to serve as the starting point for stretching the dose to an every-other-week interval.

Third, Petitioner's conclusory assertions about half-life, which serve as the touchstone for its arguments regarding motivation and reasonable expectation of success, lack scientific merit. The crux of Petitioner's theory is the assumption that serum half-life alone can meaningfully inform the choice of a dosing interval. But the evidence shows that for therapeutic monoclonal antibodies, half-life is ***not*** a reliable predictor of dosing interval. Determining an appropriate dosing interval requires patient-specific data on therapeutic response and drug serum concentrations. Dr. Baughman, Petitioner's pharmacokineticist, admits that this information was important and also acknowledges it was unknown for D2E7 as of the effective filing date of the '135 patent. Moreover, Petitioner's half-life argument is premised on the scientifically incorrect assumption that the full dose of a subcutaneously administered antibody would reach the patient's blood stream.

Fourth, objective evidence supports the patentability of the claims. During prosecution, Patent Owner demonstrated the commercial success of HUMIRA® and its nexus to the challenged claims. The Examiner agreed. *See* Ex. 1002, 1586 (Notice of Allowance). Petitioner's attempt to attribute HUMIRA®'s commercial success to other factors is insufficient to overcome the Examiner's conclusion that

the Patent Owner's showing was "convincing and considered to be commensurate in scope with the breadth of the now claimed invention." *Id.*

Fifth, the expert declarations submitted by Petitioner do not address or dispute the scientific facts relevant to obviousness but rely instead on conclusory opinions and irrelevant contentions. Moreover, outside of the context of this proceeding, each of Petitioner's declarants has made statements consistent with Patent Owner's position. For example, while Dr. Baughman argues in this proceeding that it would have been routine to develop the claimed dosing regimen, a document submitted in support of one of her own patent applications takes the exact opposite position: "The determination of the ***dosing schedule of a drug, such as a therapeutic antibody, . . . is very complex going far beyond routine optimization***." Ex. 2029 (Jan. 29, 2008 Response in U.S. Application No. 11/443,943), 7 (emphasis added).

In short, Petitioner's arguments are duplicative of issues considered thoroughly by the Examiner during prosecution and are wholly without merit. The Board should therefore refuse to institute trial because the Petition is cumulative or deny the Petition on its merits.

II. FACTUAL STATEMENT

A. State of the Art

Therapeutic Monoclonal Antibodies. In June 2001 when the priority application for the '135 patent was filed, there was limited experience with the use of antibodies as therapeutic agents. Only ten antibodies were approved for clinical use in the United States. Ex. 2027 (An), Table 1 (reporting monoclonal antibodies approved for clinical use); *see also* labeling information for those antibodies, including Ex. 2014, 13; Ex. 2008, 2; Ex. 1012, 1; Ex. 2009, 17; Ex. 2007, 2; Ex. 2011, 7; Ex. 2012, 1; Ex. 2010, 2; and Ex. 2028 (Bross), 2. None was approved for subcutaneous administration as recited in the '135 patent. *Id.* Indeed, HUMIRA® was the first FDA-approved antibody labeled for subcutaneous administration. *Id*.; *see also* Ex. 1034, 1.

Rheumatoid Arthritis. RA is a life-long, progressive inflammatory disease of the joints and surrounding tissue. Left untreated, the persistent inflammation causes joint pain, bone destruction, deformity, and potentially life-threatening

complications. *See* Ex. 2001 (Pope Decl.) ¶ 49.[1] There is no cure; patients require long-term, usually life-long, treatment.

In the 1990s, RA was treated with an assortment of non-steroidal anti-inflammatory drugs, corticosteroids, and so-called disease modifying anti-rheumatic drugs ("DMARDs"). Ex. 1003 (Kempeni), 1. These therapies were only "moderately successful" in alleviating the discomforts of swollen, painful joints and typically failed to halt the aggressive course of the disease long-term. *Id.*

Anti-TNFα Biologics. In a 1999 "Guidance for Industry," the FDA reviewed the state of existing RA therapies and remarked that there was an "ongoing search for more effective therapeutics that have a positive impact on the natural history of the disease . . . ." Ex. 1016, 4. The search for new treatments focused on inhibiting tumor necrosis factor alpha ("TNFα"). Ex. 1015 (Updated Consensus Statement), 1-2.

[1] The Pope (Ex. 2001), Weinblatt (Ex. 2002), Mould (Ex. 2003), Williams (Ex. 2004), and Kupper (Exs. 2005, 2006) Declarations were submitted during prosecution of the '135 patent and can be found in Petitioner's Ex. 1002. For ease of reference they have been separated out as discrete exhibits.

TNFα is an important protein in the immune system. However, as of June 2001, it was known to be implicated in different autoimmune diseases, including RA. Ex. 1001 ('135 patent), 25:35-37. Biologic agents designed to block TNFα activity, including antibodies and TNFα receptor fusion proteins, were a new class of drugs with promise for treating RA. Ex. 1003 (Kempeni), 1; Ex. 2003 (Mould Decl.) ¶ 17.

These drugs presented unique safety and efficacy issues. Ex. 1003 (Kempeni), 1; *see also* Ex. 1016 (FDA Guidance), 17. By targeting TNFα, anti-TNFα biologics suppress the patient's immune system, creating an associated risk of infection. Ex. 2001 (Pope Decl.) ¶¶ 55-56; Ex. 2003 (Mould Decl.) ¶¶ 52-53. Further, because they are foreign proteins, biologics stimulate the patient's immune system to generate antibodies against the drugs themselves (anti-drug antibodies). Ex. 2001 (Pope Decl.) ¶ 46; Ex. 2002 (Weinblatt Decl.) ¶¶ 36-37; Ex. 2003 (Mould Decl.) ¶ 57. Anti-drug antibodies were known to cause infusion- or injection-site reactions as well as more serious effects such as anaphylaxis. Ex. 2001 (Pope Decl.) ¶ 46; Ex. 2002 (Weinblatt Decl.) ¶ 36. The FDA characterized the formation of anti-drug antibodies as a "particular concern with biological agents . . . ." Ex. 1016, 14.

Anti-drug antibodies can also lessen efficacy. Once a patient has generated anti-drug antibodies, a drug that once alleviated symptoms may no longer be

suitable for future use. Ex. 2003 (Mould Decl.) ¶ 55. This concern was expressly recognized by the FDA in its 1999 Guidance on developing biologics for the treatment of RA. Ex. 1016, 14 (noting that anti-drug antibodies may "result[] in changes in therapeutic benefit over time"). There, the FDA advised that RA clinical trials should be "of at least six months' duration," in part because "products with the potential to elicit antibody formation should be assessed for durability, since antibodies may block effectiveness." *Id.* at 5.

These safety and efficacy concerns were explicitly recognized for the only two TNFα inhibitors approved by the FDA as of 2001, REMICADE® and ENBREL®. REMICADE® is a chimeric monoclonal antibody (containing both murine and human amino acid sequences) administered as a series of intravenous infusions at a dose based on a patient's body weight. Ex. 1012 (REMICADE® label), 1, 12. Despite the ability of health-care providers to tailor the dose administered, the REMICADE® label contained a black-box warning disclosing the risk of serious infection, "including sepsis and fatal infections," that could result from blocking TNFα. *Id.* at 6; *see also* Ex. 2001 (Pope Decl.) ¶ 55; Ex. 2003 (Mould Decl.) ¶ 52. And it also warned of the formation of anti-drug antibodies, explaining that "[p]atients who were antibody-positive were more likely to experience an infusion reaction" and "development of a lupus-like syndrome." Ex. 1012, 7; *see also* Ex. 2001 (Pope Decl.) ¶ 55; Ex. 2002 (Weinblatt Decl.) ¶ 37;

Ex. 2003 (Mould Decl.) ¶ 57. ENBREL®, a TNFα receptor fusion protein, was administered at a dose of 25 mg given twice weekly via subcutaneous injection. Ex. 1011 (ENBREL® label), 1, 5. Anti-drug antibodies were detected in 16% of RA patients receiving ENBREL®, and its label warned that "long-term immunogenicity of ENBREL is unknown." *Id.* at 3.

Importantly, the risk of developing anti-drug antibodies was known to correlate with ***lower*** concentrations of drug in the blood. Ex. 2003 (Mould Decl.) ¶ 55. For example, clinical data with REMICADE® showed that "the rate of [anti-drug antibody] responses was ***inversely proportional*** to the dosage; thus, [anti-drug antibody] formation occurred in 53%, 21%, and 7% of the patients who were receiving repeated treatment with [REMICADE®] at 1, 3, and 10 mg/kg, respectively." Ex. 2024 (Maini), 12 (emphasis added); *see also* Ex. 1012 (REMICADE® label), 7; Ex. 2001 (Pope Decl.) ¶ 46; Ex. 2002 (Weinblatt Decl.) ¶ 37; Ex. 2003 (Mould Decl.) ¶ 57. This inverse relationship occurs because lower doses of monoclonal antibodies have lower minimum serum levels (trough levels or concentrations) between doses. Ex. 2003 (Mould Decl.) ¶ 73. This mimics the natural intermittent exposure of the immune system to foreign antigens, contributing to the production of antibodies against the antigens. *Id.* at ¶ 55. Lengthening the dosing interval of a drug was known to cause lower trough

concentrations and an increased risk of developing anti-drug antibodies. *Id.* at ¶ 60.

In short, treatment with anti-TNFα antibodies raised safety and efficacy concerns related to both over-dosing ***and*** under-dosing. Over-dosing exposed patients to the risk of serious infections as reflected in REMICADE®'s black-box label warning. Under-dosing carried the risk of developing anti-drug antibodies, causing the drug to become less effective or even unsuitable for further use, as well as raising the possibility of causing anaphylaxis, a serious, life-threatening allergic reaction. It was against this backdrop that the clinical trials for D2E7 began.

B. Preliminary D2E7 Clinical Trial Data

Prior to June 2001, the art contained preliminary data from five D2E7 clinical trials designed and conducted by Patent Owner. Limited information about these trials was published in abbreviated form in review articles and conference abstracts, including the van de Putte (Ex. 1004) and Kempeni (Ex. 1003) references. *See also* Exs. 1005 (Rau #907); 1009 (Rau #1978); 1017 (van de Putte 1998); 1018 (Rau 1998); 1019 (Schattenkirchner); 1023 (Weisman 2000); 1024 (van de Putte 2000). Taken as a whole, the prior art showed a variety of possible dosing strategies for D2E7 involving different routes of administration, different dosing schedules, different dosing amounts, and different response rates. Moreover, as explained below, these prior art studies consistently report "up-

dosing" from weight-based doses Petitioner alleges are equivalent to the claimed 40 mg fixed dose due to inadequate clinical responses.

Kempeni discusses several early D2E7 trials, including the DE001/DE003, DE004, and DE010 studies. Ex. 1003. In the DE001 study, patients received a single intravenous dose of D2E7 in an amount based on body weight, with doses ranging from 0.5 mg/kg (0.5 mg of drug per 1 kg of body weight) up to 10 mg/kg. *Id.* at 2; *see also* Ex. 1017 (van de Putte 1998); Ex. 1018 (Rau 1998); Ex. 2006 (Kupper II Decl.) ¶ 12. The estimated terminal half-life of D2E7 in serum following intravenous administration of a single dose was reported as ranging from 11.6 to 13.7 days. Ex. 1003 (Kempeni), 2.

The DE003 study was an open-label continuation of the DE001 study. *Id.* at 2; Ex. 2006 (Kupper II Decl.) ¶ 13. D2E7 was administered intravenously based on body weight, with some patients dosed once every other week. Ex. 1003 (Kempeni), 2. No efficacy data were reported, but Kempeni explains that "patients [in DE003] who did not respond well after 0.5 or 1 mg/kg ***received higher doses*** . . . ." *Id.* (emphasis added); Ex. 2006 (Kupper II Decl.) ¶ 13.

Petitioner equates the 0.5 mg/kg intravenous dose disclosed in Kempeni with the claimed subcutaneous 40 mg dose (Petitioner multiplies the 0.5 mg/kg dose by an assumed 80 kg patient). Pet. 27 (Table). As explained during prosecution and as addressed in § IV.C.1 below, it is improper to (1) transform a weight-based dose

into a fixed dose without knowledge of the actual distribution of patient weights and (2) convert an intravenous dose to a subcutaneous dose. *See* Ex. 2003 (Mould Decl.) ¶¶ 34, 40; Ex. 2002 (Weinblatt Decl.) ¶ 31. But even accepting Petitioner's faulty assumption that weight-based dosing could be equated to fixed dosing in this manner, the only logical conclusion a POSA would have drawn from Kempeni with respect to an every-other-week 40 mg fixed dose is that this dose provided ***insufficient efficacy*** across the patient population.

The DE004 and DE010 trials reported in Kempeni evaluated subcutaneous administration. The DE004 trial included weekly, subcutaneous administration of a weight-based dose of 0.5 mg/kg. Ex. 1003 (Kempeni), 2-3; *see also* Ex. 1019 (Schattenkirchner), 2; Ex. 2006 (Kupper II Decl.) ¶ 17. Again, "non-responders or those losing their responder status" were up-dosed to 1 mg/kg weekly. Ex. 1003 (Kempeni), 3; Ex. 2006 (Kupper II Decl.) ¶ 17.

The DE010 trial compared head-to-head a 1 mg/kg dose administered subcutaneously to a 1 mg/kg dose administered intravenously. Ex. 1003 (Kempeni), 3; Ex. 2006 (Kupper II Decl.) ¶ 20. Although "preliminary data" had suggested that multiple subcutaneous doses produced D2E7 concentrations in plasma comparable to intravenous administration, intravenously administered D2E7 showed better efficacy than subcutaneously administered D2E7 for every

reported metric. Ex. 1003 (Kempeni), 3; Ex. 2006 (Kupper II Decl.) ¶ 20; Ex. 1005 (Rau #907), 3; Ex. 2003 (Mould Decl.) ¶ 32.

Preliminary data from the first phase II trial of D2E7 were reported in van de Putte in the form of a conference abstract. Ex. 1004. This trial, called DE007, featured a three-month placebo-controlled study in which patients received a fixed dose of 20, 40, or 80 mg of D2E7 administered subcutaneously on a weekly schedule. *Id.* The data reported for the 40 and 80 mg doses are on their face superior to the 20 mg dose, but van de Putte reported that all doses "were statistically significantly superior to placebo ($p<0.001$)." Ex. 1004. Another prior art report of the DE007 trial reported results exclusively for the 40 mg and 80 mg doses. Ex. 2019 ("Rau S51" original German), 3; Ex. 2020 ("Rau S51" English translation), 4; Ex. 2003 (Mould Decl.) ¶ 26. This is contemporaneous evidence suggesting that a POSA would have recognized the superiority of the available data for the 40 mg and 80 mg weekly doses. Ex. 2001 (Pope Decl.) ¶¶ 24-25.

Finally, the Weisman 2000 reference (Ex. 1023) reports on the DE005 trial. In that study, patients received weight-based intravenous injections at doses ranging from 0.25 mg/kg to 5 mg/kg every-other-week. Ex. 1023, 4. Yet again, patients initially receiving the lower doses (0.25 mg/kg and 0.5 mg/kg) were up-dosed to 1 mg/kg, again indicating that the lower doses were insufficient. *Id.*; Ex. 2002 (Weinblatt Decl.) ¶¶ 66-70; Ex. 2003 (Mould Decl.) ¶ 81.

None of the D2E7 prior art reports disclosed any meaningful pharmacokinetic data following subcutaneous dosing or patient-specific pharmacokinetic information of any kind.

C. The ’135 Patent

The ’135 patent claims priority to an application filed June 8, 2001. Ex. 1001 (’135 patent), (60). It contains five claims directed to methods of treating RA in a human involving administering an anti-TNFα antibody having the six CDRs and heavy chain constant region of D2E7. *Id.* at 45:11-25. Each of the claims requires administering a total body dose of 40 mg subcutaneously once every 13-15 days for a period of time sufficient to treat RA. *Id.*

D. Prosecution of the ’135 Patent

During prosecution of the ’135 patent, the Examiner considered each of the references relied on by Petitioner and made the same arguments Petitioner now advances.

First, the Examiner cited the van de Putte abstract as teaching that “each of the antibody doses, i.e., 20, 40, or 80 mg of the anti-TNFα antibody D2E7 were of nearly equal efficacy.” Ex. 1002, 1094 (emphasis omitted). Kempeni was cited as teaching that “[t]he D2E7 antibody has a half-life of about 12 days” and “[t]he plasma levels of the D2E7 antibody after multiple subcutaneous or intravenous injections are equivalent.” *Id.* at 1099 (internal citations omitted). Petitioner

focuses on the very same references and excerpts. Pet. 25-26. The Examiner also argued that a POSA would have been motivated to modify the dosing regimen of van de Putte from weekly to every-other-week "because patient apprehended pain and real pain associated with injection can be diminished by decreasing the number of injections required for the patient to receive therapeutic benefit, thereby increasing patient compliance." Ex. 1002, 1095. The identical argument is made by Petitioner. Pet. 35.

The Examiner also argued that a POSA would have had a reasonable expectation of success in achieving a therapeutic benefit from every-other-week dosing based on Kempeni's disclosure of the intravenous half-life of D2E7, articulating the same rationale as Petitioner: "it would have been routine to use the principals [*sic*] of pharmacokinetics to approximate how decreasing the frequency of subcutaneous D2E7 administration from weekly to biweekly would affect the levels of D2E7 in the serum . . . ." Ex. 1002, 1099; *compare* Ex. 1006 (Baughman Decl.) ¶¶ 66-68. Thus, the Examiner contended that "given the desirability of decreasing the frequency and/or dosage of D2E7 administration one of ordinary skill in the art would have arrived at the claimed invention merely as a matter of routine dose optimization." Ex. 1002, 1095; *compare* Ex. 1006 (Baughman Decl.) ¶ 49.

Patent Owner rebutted these arguments by presenting evidence demonstrating the errors in the Examiner's reasoning and the inherent unpredictability in developing dosing regimens for antibody therapies as of June 2001. Ex. 1002, 1269-1330. Patent Owner also rebutted the obviousness rejection with evidence demonstrating HUMIRA®'s commercial success. *Id.* at 1282-1290; Ex. 2004 (Williams Decl.). The evidence relied on by Patent Owner included declarations from Drs. Weinblatt and Pope, preeminent rheumatologists, as well as a declaration from Dr. Mould, a pharmacokineticist with significant expertise in therapeutic monoclonal antibodies. Ex. 2001 (Pope Decl.) ¶¶ 1-8; Ex. 2002 (Weinblatt Decl.) ¶¶ 1-8; Ex. 2003 (Mould Decl.) ¶¶ 1-10.

The Examiner found Patent Owner's arguments persuasive. He concluded that "one of ordinary skill in the art would *not* have understood that 20, 40 and 80 mg D2E7 administered subcutaneously weekly are equally effective . . . ." Ex. 1002, 1584-85 (Notice of Allowance; emphasis in original). Instead, a POSA would "interpret the data of Van de Putte to demonstrate that 20 mg D2E7 administered subcutaneously weekly is clearly inferior to the 40 or 80 mg D2E7 dose . . . ." *Id.* at 1585. The Examiner further found that "applicant's showing of commercial success is convincing and considered to be commensurate in scope with the breadth of the now claimed invention." *Id.* at 1586.

III. LEVEL OF ORDINARY SKILL IN THE ART AND CLAIM CONSTRUCTION

Because the Petition is deficient for the reasons discussed in detail below, it should be denied regardless of the definition of a person of ordinary skill in the art or whether the proposed claim constructions offered by Petitioner are accepted. For the sake of completeness, however, Patent Owner responds below to Petitioner's proposed interpretations.

A. Level of Ordinary Skill in the Art

Petitioner defines the POSA as having the skill sets of both a physician treating RA patients and a pharmacokineticist with experience related to monoclonal antibodies. Pet. 27. For the limited purpose of this response, Patent Owner does not contest Petitioner's definition.

B. Claim Construction

Petitioner's proposed claim constructions are unnecessary and inconsistent with the specification.

1. Treatment terms

Patent Owner	Petitioner
"A method for treating rheumatoid arthritis"	
No construction required (preamble)	A method for reducing the signs, symptoms, and/or progression of rheumatoid arthritis, to some extent

Patent Owner	Petitioner
"for a time period sufficient to treat the rheumatoid arthritis"	
for a time period sufficient to reduce significantly the signs and symptoms of rheumatoid arthritis	No construction provided

Rather than offering a construction of the phrase "for a time period sufficient to treat the rheumatoid arthritis," which appears in the body of the claim, Petitioner seeks to construe language in the preamble. A preamble is not limiting and requires no construction "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***." *Symantec Corp. v. Computer Assoc. Int'l, Inc.*, 522 F.3d 1279, 1288-89 (Fed. Cir. 2008) (emphasis added). Moreover, a preamble should not be construed "if it is reasonably susceptible to being construed to be merely duplicative of the limitations in the body of the claim." *Id*. at 1288-89. Here, the preamble provides the intended use of treating RA in a human subject, and the claim thereafter requires that the drug must be administered "for a time period sufficient to treat the rheumatoid arthritis." Ex. 1001 ('135 patent), 45:12-17.

Even if one were to construe the preamble, Petitioner's proposed interpretation is incorrect because it minimizes the degree of efficacy required by

the claims. Petitioner contends that the claims "do not require a particular level of efficacy" but should instead be interpreted as reducing the signs, symptoms, and/or progression of rheumatoid arthritis "***to some extent***." Pet. 14-15 (emphasis added). Petitioner relies on the following sentence from the '135 patent describing Example 3:

> Figs. 1B and 2-4 indicate that subcutaneous, biweekly D2E7 treatment combined with methotrexate was significantly better than placebo in reducing the signs and symptoms of RA at twenty-four weeks.

Id. at 15 (citing Ex. 1001, 30:25-28). However, this sentence does not indicate that the claimed methods should be understood to reduce the signs, symptoms, or progression of RA "to some extent." It specifies that, ***at twenty-four weeks***, the disclosed treatment regimen "***significantly***" reduced ***both*** the signs and the symptoms of RA. Ex. 1001, 30:25-28 (emphasis added). The only other intrinsic evidence cited by Petitioner is irrelevant because it merely identifies the types of disorders that could potentially be treated by the disclosed therapies. *See* Pet. 15 (citing Ex. 1001 at 24:25-28 and 58-60). It does not discuss treatment regimens for rheumatoid arthritis.

The Patent Owner's proposed construction of "for a time period sufficient to treat the rheumatoid arthritis" is consistent with the specification, which states that biweekly dosing "refer[s] to ***the time course of administering a substance (e.g., an anti-TNFα antibody) to a subject to achieve a therapeutic objective*** (e.g., the

treatment of a TNFα-associated disorder)." Ex. 1001, 6:23-27 (emphasis added). The inclusion of a temporal limitation in the claim ("for a time period sufficient to treat") shows that the claimed method requires meaningful therapeutic efficacy. If any effect whatsoever satisfied the claims, as Petitioner contends, the temporal limitation would be rendered meaningless.

2. "Once every 13-15 days"

Patent Owner	Petitioner
No construction required (plain and ordinary meaning)	a dosage regimen of every 13-15 days that would encompass a dosing regimen of every 14 days, i.e., a biweekly dosing regimen

Claims 1-5 require administering the recited human anti-TNFα antibody "once every 13-15 days." The plain and ordinary meaning of "once every 13-15 days" is clear. Consequently, no construction is needed.

3. "Pharmaceutically acceptable composition"

Patent Owner	Petitioner
No construction required (plain and ordinary meaning)	a composition containing an anti-TNFα antibody suitable for administration to a patient via biweekly subcutaneous dosing

Claim 5 recites the phrase "in the form of a pharmaceutically acceptable composition." The limitation is unambiguous and does not require construction.

Petitioner proposes that the limitation means "a composition containing an anti-TNFα antibody suitable for administration to a patient via biweekly subcutaneous dosing." Pet. 17. The Board should reject this construction because it creates confusion where none exists by merging into an unambiguous term portions of other claim limitations concerning the antibody, the patient, the dosing regimen, and the method of administration. These specific limitations are provided elsewhere in the body of the claim.

IV. THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER VAN DE PUTTE AND KEMPENI

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. Petitioner's argument instead uses the claims as a road map to arrive at the claimed dosing regimen. The result is a textbook example of hindsight that fails to carry Petitioner's burden of demonstrating that the claims are obvious. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070-73 (Fed. Cir. 2012) (finding argument that extended release formulation would have been obvious to try was based on impermissible hindsight where PK/PD relationship of drug was unknown);

Orthopedic Equip. Co., Inc. v. United States, 702 F.2d 1005, 1012 (Fed. Cir. 1983) ("It is wrong to use 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.").

A. A POSA Would Not Have Been Drawn Toward a Subcutaneously-Administered Fixed Dose

Petitioner's argument fails at the threshold. Central to its analysis is the proposition that a POSA would have been drawn to the subcutaneous, fixed-dose regimens described in van de Putte rather than the intravenous, weight-based dosing that predominated in the art. But a preference for subcutaneous fixed dosing can only be derived through hindsight.

As of June 2001, there was a clear preference in the antibody therapeutics art generally, and in the early D2E7 clinical trial reviews and conference abstracts specifically, for weight-based dosing administered intravenously.

- With respect to D2E7, other than the three-month trial described in the van de Putte abstract, ***all*** of the other D2E7 clinical trials reported in the prior art utilized body-weight-based dosing. Ex. 1003 (Kempeni); Ex. 1023 (Weisman 2000).
- REMICADE®, the only anti-TNFα antibody approved for treating RA as of 2001, was approved only for intravenous, weight-based dosing. Ex. 2003 (Mould Decl.) ¶¶ 41, 46.

- The FDA had yet to approve ***any*** therapeutic antibody for subcutaneous administration; indeed, HUMIRA® was the ***first*** such antibody.[2]
- It was recognized that the effects of subcutaneous dosing were complex and unpredictable compared to intravenous dosing. Ex. 2017 (Rowland), 13, 29, 31; Ex. 2003 (Mould Decl.) ¶¶ 40, 82-83; Ex. 2018 (Porter), 9-11.
- Publications reporting on the early D2E7 trials, including Kempeni, indicated that body-weight-based doses administered intravenously provided ***better*** efficacy than body-weight-based doses administered subcutaneously. Ex. 1003 (Kempeni), 3; Ex. 1005 (Rau #907), 3; Ex. 2001 (Pope Decl.) ¶ 34.

Petitioner's argument ignores these aspects of the art, and fails to provide a credible explanation for why a POSA would have acted in a contrary manner. Petitioner contends that a POSA would have been motivated to pursue van de Putte's fixed-dose, subcutaneous approach due to purported "well known

[2] Although ENBREL® was administered subcutaneously twice a week, contrary to Petitioner's representation (Pet. 31-32), ENBREL® was not and is not an antibody—it is a fusion protein containing a portion of the human TNFα receptor that is structurally and functionally different from an anti-TNFα antibody. Ex. 1011 (ENBREL® label).

advantages," including patient convenience, improved patient compliance, and cost savings. Pet. 31-33; Ex. 1006 (Baughman Decl.) ¶¶ 51-52, 55. But, prior to first approval, such considerations would have been much less significant to a POSA than developing a dosing regimen that was effective and safe. Ex. 2001 (Pope Decl.) ¶ 44; Ex. 2003 (Mould Decl.) ¶ 44-45. A POSA would have considered intravenous, weight-based dosing a better alternative for addressing those concerns. Indeed, Petitioner's expert, Dr. Baughman, used intravenous, weight-based dosing for the antibody HERCEPTIN®, in part due to "concerns" about "monitoring the rate of delivery of large amounts of the novel biologic." Ex. 1006 (Baughman Decl.) ¶ 7; Ex. 2008, 2.

B. A POSA Would Not Have Been Drawn Toward the 20 mg Weekly Dose in van de Putte

Even assuming a POSA would have been motivated to develop a subcutaneous, fixed-dose regimen for D2E7, there is no basis for the Petitioner's argument that a POSA would have pursued the 20 mg weekly dose disclosed in the van de Putte abstract. Petitioner's premise would require a POSA to ignore data in van de Putte showing that 40 and 80 mg weekly doses were clinically superior to the 20 mg dose.

As explained at length during prosecution and as supported by expert testimony submitted to the Office, the 20 mg dose was inferior to the 40 mg dose in all outcome measures and the 80 mg dose in 3 out of 4 outcome measures.

Ex. 1004 (van de Putte; data reproduced below); Ex. 2001 (Pope Decl.) ¶ 20; Ex. 2002 (Weinblatt Decl.) ¶ 20; Ex. 2003 (Mould Decl.) ¶ 22.

	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

This was expressly acknowledged by the Examiner in the Notice of Allowability:

> It is quite clear that the 20 mg weekly s.c. dose is not as good as the 40 mg or 80 mg doses. Look, for example, at the swollen joint count (SWJC): the 20 mg dose provides a 42% improvement, whereas the 40 mg and 80 mg doses provide improvements of 59% and 61%. . . . Looking at these data, the person of ordinary skill in the art would have concluded that the 20 mg weekly s.c. dose is simply not as effective as either the 40 mg or 80 mg weekly s.c. doses.

Ex. 1002, 1585-86 (quoting Ex. 2002 (Weinblatt Decl.) ¶ 20).

Despite this demonstrated inferiority, Petitioner argues that a POSA would have focused on the 20 mg dose because the study was not powered to permit a statistical comparison among the three doses. Pet. 41-43. But even without the benefit of statistical certainty, a POSA would have taken into account the numerical differences in the four clinical outcome measures reported and the consistency of these differences across multiple outcome measures. Ex. 2001 (Pope Decl.) ¶¶ 18-22; Ex. 2002 (Weinblatt Decl.) ¶¶ 18-22; Ex. 2003 (Mould

Decl.) ¶¶ 21-25. From these data, a POSA would have concluded that 20 mg administered subcutaneously weekly was too low a dose to pursue, particularly in light of risks arising from under-dosing. Ex. 2001 (Pope Decl.) ¶ 22; *see also* Ex. 2002 (Weinblatt Decl.) ¶ 20.

Petitioner contends that the Examiner's reliance on the numerical superiority of the 40 mg and 80 mg results versus the 20 mg dose "is inherently contradictory" because van de Putte was not designed to make statistical comparisons between these doses. *See* Pet. 12. But there is nothing contradictory about it, as rheumatologists routinely rely on numerical trends as demonstrated by the practices of Petitioner's own declarant. Specifically, Dr. O'Dell, in his own publications, has relied on numerical differences in data, even if not statistically validated. Ex. 2026, 18 ("It is also important to note that secondary endpoints in this [combination] trial, including ACR 20 and 50 responses, ***were numerically better, but not statistically different*** from those patients who received mono-therapy with sulfasalazine. With the data provided from the COBRA and Fin-RA [combination] trial, ***a convincing case can be made to treat most patients initially with combination therapy***.") (emphases added).

Petitioner's reliance on the superiority of the 20 mg dose to placebo as evidence of efficacy is also misplaced. Pet. 12-13. The extent to which a POSA would have viewed the 20 mg dose as efficacious is not the point. Assuming a

POSA would have been motivated to pursue a subcutaneous treatment regimen in the first place, the issue is which dosing regimen in van de Putte the POSA would have been motivated to pursue.[3]

Petitioner's experts do not and cannot dispute that the motivation of a POSA engaged in the design of a D2E7 dosing regimen was to provide the highest level of efficacy possible while maintaining patient safety. Ex. 2001 (Pope Decl.) ¶ 44; Ex. 2003 (Mould Decl.) ¶¶ 44-45. Dr. O'Dell wrote in a 2001 article that "the fundamental goal" of treating RA was to treat "disease activity to ***the fullest extent possible***." Ex. 2025, 3 (emphasis added). The goal was not to obtain mere superiority over placebo, to achieve marginal efficacy, or to reduce a sign or symptom of RA "to some extent." A POSA would not have been motivated to modify a dosing regimen on the basis of it being merely adequate; especially when more promising data are reported in the very same reference. *See Yamanouchi*

[3] Petitioner also argues that a POSA would have considered the 20 mg dose of van de Putte as efficacious by comparing it to data from the trial resulting in FDA approval of REMICADE®. Pet. 42-43. This cross-drug, cross-study comparison is invalid and wholly inconsistent with Petitioner's argument that, absent statistics, one cannot even compare results among different dosing groups in the same clinical trial.

Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1345 (Fed. Cir. 2000) (demonstrating a motivation to modify the prior art requires more than a showing that the ordinarily skilled artisan would have expected "baseline level" of functionality).

Petitioner also improperly asserts that Example 2 of the '135 patent, which discloses the same study initially reported in the van de Putte abstract, bolsters its argument that a POSA would have selected the 20 mg dose. Pet. 33-34; *see also id*. at 9-11, 36. Example 2 is not prior art and therefore cannot be relied upon by Petitioner as part of its obviousness challenge. Moreover, contrary to Petitioner's allegation (Pet. 10), Example 2 is entirely consistent with Patent Owner's position during prosecution, as it concludes that "[t]hese data illustrate that subcutaneous D2E7, ***particularly at a dose of 40 mg/week***, generates a good response." Ex. 1001, 29:8-10 (emphasis added).

Although ignored by Petitioner, another prior art report of the DE007 trial did not even disclose results for the 20 mg dose. Ex. 2019 ("Rau S51" original German), 3; Ex. 2020 ("Rau S51" English translation), 4; Ex. 2003 (Mould Decl.) ¶ 26. The contemporaneous evidence shows that a POSA would have recognized the superiority of the available data for the 40 mg and 80 mg weekly doses and would have dismissed the 20 mg dose as too low. Ex. 2001 (Pope Decl.) ¶¶ 24-25.

C. A POSA Would Not Have Been Motivated to Stretch the 20 mg Weekly van de Putte Dose into a 40 mg Every-Other-Week Dose

Petitioner's burden is not only to show that a POSA would have been motivated to select the 20 mg dose of van de Putte as a starting point, which as shown above it has not done. Petitioner's theory also requires it to prove that a POSA would have been motivated to convert the 20 mg weekly dose into a 40 mg every-other-week dose as recited in the claims. Petitioner fails to discharge this burden.

1. Petitioner ignores the prior art reports of up-dosing

According to Petitioner, the motivation to convert van de Putte's weekly dosing regimen into an every-other-week regimen comes from Kempeni, which "described studies investigating biweekly dosing of D2E7 . . . and demonstrated that it was a viable treatment protocol." Pet. 35. This argument is based on a misreading of Kempeni and the DE001/DE003 study it describes.

As an initial matter, a POSA would not have considered the dosing schedules discussed in Kempeni to be equivalent to a subcutaneous, fixed, every-other-week dosing regimen. Ex. 2005 (Kupper I Decl.) ¶ 4. Instead, patients in the DE001/DE003 studies received intravenous, weight-based doses according to a variety of different dosing schedules, including weekly, every-other-week, and every four weeks, depending on their responses. *Id.* Any conclusion drawn from

Kempeni therefore could not logically have been extended to any specific schedule of subcutaneous administration, as Petitioner argues.

Petitioner compounds this error by alleging that the 0.5 mg/kg weight-based ***intravenous*** dose disclosed in Kempeni can be equated to a 40 mg ***subcutaneous*** dose (Petitioner multiplies the 0.5 mg/kg dose by an assumed 80 kg patient). Pet. 27 (Table). But a POSA would have understood that an intravenous dose does not equate to a subcutaneous dose, because (1) only a fraction of the amount of drug administered following a subcutaneous dose is absorbed into the blood stream and (2) the rate of absorption is prolonged versus intravenous administration. Ex. 2003 (Mould Decl.) ¶ 40; Ex. 2006 (Kupper II Decl.) ¶ 18; Ex. 2018 (Porter), 300-01.

Moreover, a POSA would have understood that the weight-based studies reported in Kempeni are of limited relevance because weight-based doses cannot be transformed into fixed-doses by multiplying by average patient weight—this is a "well-known pharmacokinetic fallacy." Ex. 2003 (Mould Decl.) ¶ 34. Even assuming that one knew the average patient weight (which is not reported), the POSA would not know the distribution of patient weights, nor which specific patients at which specific weights contributed to the reported benefit. *Id.* at ¶ 36. Without knowing whether, and to what degree, patient weight affects antibody absorption and clearance, it is impossible to know how to transform a weight-based

dose into a fixed dose to achieve the same exposure. *Id.* at ¶ 39. This issue was discussed at length during prosecution (Ex. 1002, 1299-1304; Ex. 1003 (Mould Decl.) ¶¶ 33-41), yet Petitioner and its declarants apply the same flawed reasoning. Pet. 27 (Table); Ex. 1006 (Baughman Decl.) ¶ 70.

But even assuming for the sake of argument that Petitioner is correct, Petitioner ignores the fact that patients failing to respond to the 0.5 mg/kg dose in the DE001 phase were up-dosed to as high as 3 mg/kg during the DE003 phase (which, according to Petitioner's calculations, would correspond to a fixed dose of ***240 mg*** for an average 80 kg patient). Ex. 1003 (Kempeni), 2; *see also* Ex. 2006 (Kupper II Decl.) ¶ 13. If a 0.5 mg/kg dose was the equivalent of a 40 mg fixed dose (as Petitioner argues), then Kempeni teaches that a 40 mg every-other-week dose was too low to serve as a "one-size-fits all" fixed dose.

D2E7 up-dosing was consistently reported in the prior art. Indeed, ***all trials that evaluated the 0.5 mg/kg dose*** (DE001/DE003, DE004, and DE005), which Petitioner equates to a 40 mg fixed dose (Pet. 27), ***had to increase to greater doses due to inadequate clinical response***. *See* § II.B, *above*; Ex. 1003 (Kempeni), 2-3; Ex. 2002 (Weinblatt Decl.) ¶¶ 68-70; Ex. 2001 (Pope Decl.) ¶ 68; Ex. 2003 (Mould Decl.) ¶¶ 35, 81; Ex. 1023 (Weisman 2000), 4. The art as a whole at the relevant time therefore taught away from using a 0.5 mg/kg dose as a fixed dose across all patients and instead favored higher doses.

2. Petitioner's "dose-stretching" arguments are flawed

Petitioner's second theory in support of every-other-week fixed dosing is based on the premise of "dose-stretching" set forth by its expert, Dr. O'Dell. According to Dr. O'Dell, clinicians would have been motivated to "stretch out" the recommended dose for a drug to provide an optimal treatment regimen for an individual RA patient. Ex. 1007 ¶¶ 20-21. Petitioner's arguments and Dr. O'Dell's reasoning are flawed on multiple grounds.

First, while dose-stretching of an FDA-approved pharmaceutical may be a valid clinical practice to benefit individual patients, there was no approved or recommended dose of D2E7 available for Dr. O'Dell or his colleagues to stretch, because HUMIRA® had yet to be approved. Ex. 2002 (Weinblatt Decl.) ¶ 48; *see also* Ex. 2001 (Pope Decl.) ¶ 44; Ex. 2003 (Mould Decl.) ¶ 44. Thus, regardless of whether clinicians routinely experiment with the dosing indicated on an FDA label, here there was no approved dose for clinicians to stretch.

Second, Dr. O'Dell fails to explain why "dose-stretching" would have focused on a 40 mg dose, subcutaneous administration, or an every-other-week schedule. If a clinician felt free to experiment with different doses, routes of administration, and dosing frequencies (*see* Ex. 1007 (O'Dell Decl.) ¶ 20), there would be innumerable possible combinations. Only hindsight would lead one to the claimed invention.

Third, the inventors discovered a "one size fits all" method of administering D2E7 for RA. The challenged claims recite this discovery, i.e., a method of treating RA involving administering to a patient a fixed dose ("a total body dose") of 40 mg of antibody. Ex. 1001, 45:14. The claims do not recite weight-based dosing or open-ended D2E7 dosing intervals individualized to a particular patient. Dr. O'Dell's "stretching" theory, which seeks to provide optimal treatment regimens for individual patients, is the antithesis of the claimed invention. Ex. 1007 ¶¶ 21, 33. Accordingly, it is irrelevant whether, in June 2001, Dr. O'Dell and his colleagues were custom-tailoring anti-TNFα dosing regimens for the benefit of individual patients.[4] *See* Ex. 1007 ¶¶ 20-21.

Fourth, Petitioner ignores the significant risks a POSA would have understood to be associated with dose-stretching. As discussed in § II.A above, there was a serious concern about potential adverse consequences of under-dosing,

[4] Like Dr. O'Dell, the Salfeld patent cited by Petitioner discusses individualized dosing, stating that "for any particular subject, specific dosage regimens should be adjusted over time . . . ." Ex. 1008, 23:18-19. The Salfeld patent further states that dosing "may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual." *Id*. at 22:47-50.

including the formation of anti-drug antibodies that could negatively impact both safety and efficacy of treatment. *See* Ex. 2001 (Pope Decl.) ¶ 47; Ex. 2002 (Weinblatt Decl.) ¶ 40; Ex. 2003 (Mould Decl.) ¶ 60. In alleging that a POSA would have selected a 40 mg every-other-week dose as the "most conservative choice" (Pet. 37), Petitioner completely glosses over the risks that a POSA would have perceived with respect to lengthening the interval over which the dose would be administered.

Notably, Petitioner's declarants acknowledge the existence of concerns with anti-drug antibodies but dismiss them in their analyses. For example, Dr. Baughman admits that "[p]eople working in the field knew that developing anti-drug antibodies was a possibility," but she dismisses this concern given the lack of mention of such antibodies in the D2E7 publications. Ex. 1006 ¶ 71; *see also* Ex. 1007 (O'Dell Decl.) ¶ 42. In June 2001, however, the prior art consisted of only a handful of abstracts and reviews providing preliminary information on early studies designed by Patent Owner. A POSA would ***not*** have assumed from this meager record that anti-drug antibodies did not pose a risk. Ex. 2001 (Pope Decl.) ¶¶ 46-48; Ex. 2002 (Weinblatt Decl.) ¶¶ 37-40; Ex. 2003 (Mould Decl.) ¶¶ 57-59. To the contrary, the FDA specifically identified the development over time of anti-drug antibodies "following repeated courses of treatment" as a "particular concern with biological agents." Ex. 1016 (FDA Guidance), 14.

Absent information firmly establishing that D2E7 was not associated with anti-drug antibodies, a POSA would not have disregarded this concern.

Subsequent literature confirms the development of anti-D2E7 antibodies and their link to sub-therapeutic serum drug levels. *E.g.*, Ex. 2021 (van de Putte 2004), 9 (12% of patients tested positive for antibodies against D2E7); Ex. 2022 (Vincent) (reporting incidence of anti-drug antibodies); Ex. 2023 (Schouwenburg), 5 (anti-D2E7 antibody "strongly linked" to sub-therapeutic serum drug levels). As stated in an AbbVie study report, "[every-other-week] administration of adalimumab [D2E7] resulted in a higher incidence of [anti-drug antibody] positivity than weekly administration, and [anti-drug antibody]-positivity was associated with a reduced frequency of ACR20 responses." Ex. 2016, 29; *see id.* at Tables 10 and 11. Despite this, 40 mg every-other-week D2E7 works at least as well as, if not better, than 20 mg weekly. *Id.* at 29, Table 9.

Finally, Petitioner's attempt to rely on half-life as providing a motivation to develop every-other-week dosing (and a reasonable expectation of success) is flawed in numerous respects, as explained below.

D. Petitioner Cannot Establish that a POSA Would Have Reasonably Expected Success

Petitioner argues that a POSA would have reasonably expected a 40 mg, subcutaneous, every-other-week regimen "to be safe and effective in treating RA" based upon "the known half-life of 11.6 to 13.7 days for D2E7." Pet. 31.

Petitioner fails to carry its burden of proving this contention, and it is incorrect, as demonstrated during prosecution.

1. The known data on D2E7 half-life would not have led to a reasonable expectation of success

As of June 2001, it was known that half-life could not be used as a surrogate or predictor for establishing dosing interval in any periodic dosing regimen. Ex. 2003 (Mould Decl.) ¶¶ 76-78. The lack of correlation between half-life and dosing interval, ignored entirely by Petitioner and its experts, cannot legitimately be disputed in view of these prior art FDA-approved antibodies:

- REMICADE® is dosed about once every 3 to 6 half-lives (Ex. 1012, 2);
- RITUXAN® is dosed about once every 0.3 half-lives (Ex. 2007, 1);
- MYLOTARG® is dosed about once every 5 half-lives (Ex. 2013, 3); and
- ZENAPAX® is dosed about once every 0.6 half-lives (Ex. 2010, 1).

See also Ex. 2002 (Weinblatt Decl.) ¶ 57. Thus, prior art antibody therapeutics were dosed both more frequently and less frequently than their serum half-lives, indicating that other factors must be considered when determining dosing intervals for antibodies such as D2E7.

There are many reasons why serum half-life alone cannot meaningfully inform the choice of dosing interval. As explained by Dr. Harmut Kupper, the AbbVie Study Director who approved the final study reports for the DE001, DE003, DE004, DE007, and DE010 clinical trials:

> ***Drug half-life*** relates to how fast the drug is cleared from a patient's system. It ***is merely one of many factors – many of which are unpredictable and may or may not be inter-related – that ultimately contribute to the choice of dosing frequency***. Other medical factors, such as the maximum tolerable / non-toxic dose load, the minimum effective drug concentration, any associated severe adverse events (SAEs), immunogenicity (especially important for antibody-based drugs), and binding kinetics of the drug molecule to its target, all play just as important, if not more important roles in determining final dosing frequency. ***One of skill in the art would not have, at the time of the invention (and in fact still will not today), chosen dosing frequency based on drug half-life alone.***

Ex. 2006 (Kupper II Decl.) ¶ 5 (emphases added); *see also* Ex. 2003 (Mould Decl.) ¶ 78 (explaining that half-life "correlates so poorly with dosing interval" for biologic therapeutics that it "cannot be used to reasonably predict whether a dosing interval will be safe and efficacious").

To form any expectation about an untested dosing interval, a POSA would have required more: at a minimum patient-specific data (rather than aggregate data) on ***both*** therapeutic response and drug serum concentrations, e.g., peak concentration (C_{max}), trough concentration (C_{min}), and total concentration over time (AUC). Ex. 2003 (Mould Decl.) ¶¶ 64, 68. Dr. Baughman, Petitioner's pharmacokineticist, agrees, explaining that "many in the industry" believed that C_{min} "might be the best parameter to indicate the threshold of efficacy." Ex. 1006

¶ 62. Yet, Dr. Baughman admits this important information was not available for D2E7 in June 2001. *Id*.

Having admitted the need for, and lack of, this important information, Petitioner and Dr. Baughman nonetheless argue that a POSA would have relied on half-life alone to arrive at the claimed dosing interval. *See* Pet. 34-35; Ex. 1006 (Baughman Decl.) ¶ 66. But arguments submitted to the Office in support of one of Dr. Baughman's own patent applications indicate the situation is far more complex. There the applicant argued:

> ***The determination of the dosing schedule of a drug, such as a therapeutic antibody, including the effective dose, efficacy of single or repeated administration, route(s) and frequency of administration, and the order and relationship of these steps is very complex going far beyond routine optimization***. Thus, for example, the feasibility of a particular route of administration, such as subcutaneous delivery, ***depends on a number of factors***, such as pharmacokinetic profile (including half-life and clearance mechanism), bioavailability, local reaction, and immunogenicity, just to mention a few.

Ex 2029, 7-8 (emphases added).

The Federal Circuit has also recognized this complexity. In *In re Cyclobenzaprine*, the court found that without knowing the PK/PD relationship, a POSA would not have been able to "predict whether any particular PK profile . . .

would produce a therapeutically effective formulation." 676 F.3d at 1070 (reversing the district court and holding non-obvious claims to therapeutically effective dosage forms because of the lack of a known PK/PD relationship); *see also Avanir Pharms., Inc. v. Actavis S. Atl., LLC*, 36 F. Supp. 3d 475, 487, 506 (D. Del. 2014) (holding non-obviousness patent claims that recited two ranges of drug components and stating that efficacy cannot be predicted "based on in vivo or in vitro pharmacokinetic studies when the dose-effect relationship was unknown"), *aff'd*, *Avanir Pharms. Inc. v. Par Pharm, Inc.*, 612 F. App'x 613 (Fed. Cir. 2015) (affirmance via Rule 36).

The complexity of modifying dosing regimens has also been addressed by the Board. In *Dr. Reddy's Laboratories, Ltd. v. Galderma Laboratories, Inc*., IPR2015-01782, Paper 10, 20-21 (Feb. 16, 2016), although the drug half-life was disclosed in the prior art, the Board denied institution where Petitioner failed to address the relationship between peak drug levels and therapeutic effects.

Here, there was very limited pharmacokinetic information available for D2E7. And there was no known correlation between half-life and dosing interval for therapeutic antibodies. Dr. Baughman's assertions that half-life would have been "instructive" or would have created a reasonable expectation of success are utterly unsupported by citation to any prior art publication, and are nothing more than conclusory. As such, they do not carry Petitioner's burden of demonstrating a

key element of its obviousness case. *Integrated Global Concepts, Inc. v. Advanced Messaging Techs., Inc.*, IPR2014-01027, Paper 16, 8 (Dec. 22, 2014) (declining to institute IPR supported by "conclusory" expert declaration); *Gen. Elec. Co. v. Tas Energy Inc.*, IPR2014-00163, Paper 11, 11 (May 13, 2014) (discounting conclusory expert declaration).

2. Petitioner's analysis of the available half-life data is wrong

Even if the available intravenous half-life estimate would have had predictive value, it would not have pointed to a 40 mg every-other-week schedule.

According to Petitioner, a POSA "would have recognized that one week after administration of a 40 mg dose of D2E7, the amount circulating in the patient's blood would have been at least 30 mg, which is greater than the 20 mg dose that van de Putte 1999 already taught was efficacious relative to placebo when administered on a weekly basis." Pet. 36. To support this allegation, Petitioner cites to the following table from Dr. Baughman's declaration:

D2E7 Dose Administered	D2E7 Circulating One Week After Injection	D2E7 Circulating Two Weeks After Injection
20 mg	15 mg	10 mg
40 mg	30 mg	20 mg
80 mg	60 mg	40 mg

Ex. 1006, ¶ 67.

The numbers in Dr. Baughman's table are indisputably incorrect. Dr. Baughman's table ignores that the delivery of a drug subcutaneously, as described in van de Putte, was known to cause a variable, frequently significant reduction in the amount of drug absorbed into the bloodstream. Ex. 2018 (Porter), 8; Ex. 2003 (Mould Decl.) ¶ 40; Ex. 2006 (Kupper II Decl.) ¶ 18. This means that following administration of a subcutaneous dose, only a fraction of the total antibody administered reaches the blood and is available to contribute to efficacy. Ex. 2006 (Kupper II Decl.) ¶ 18 (now known to be about 64% in the case of D2E7). Even assuming a 14 day half-life, for each "D2E7 Dose Administered," the amount of D2E7 circulating "One Week" and "Two Weeks" after injection would be substantially lower than what is shown in Dr. Baughman's table. This is completely ignored in Petitioner's analysis.

Subsequent studies confirm the lack of correlation between half-life and dosing frequency. Under Petitioner's theory, 80 mg of D2E7 administered once per month should be superior (or at least equivalent) to the claimed dosing regimen. Returning to the chart above, Dr. Baughman claims that an administration of 80 mg subcutaneous D2E7 will result in 40 mg circulating D2E7 at 14 days. Thus, in the Petitioner's oversimplified construct, dosing 80 mg once per month should be equivalent to dosing 40 mg every-other-week (or 20 mg

weekly). Dosing once a month presumably would be more convenient for patients because it would require less frequent injections and would involve a dosing interval that presumably would be easy to remember. *See* Ex. 2002 (Weinblatt Decl.) ¶ 58.

But in an actual clinical study, subcutaneous injection of 80 mg D2E7 on a monthly basis was found not to be superior to placebo. Ex. 2015 (Adalimumab Clinical Study Report), 6. Specifically, "***superiority*** of adalimumab [D2E7] 80 mg compared with placebo ***could not be claimed***," because no difference was observed in the primary efficacy endpoint (ACR 20). *Id.* at 5 (emphasis added).

E. *Boehringer* and *BioMarin* Are Inapposite

Petitioner's reliance on the Board's conclusions in *Boehringer Ingelheim Int'l GmbH v. Genentech, Inc*., IPR2015-00417, Paper 11 (July 14, 2015) and *BioMarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd.*, IPR2013-00534, Paper 81 (Feb. 23, 2015) is misplaced.

In *Boehringer*, the Board instituted trial on a patent claiming a dosing regimen for treating a particular subset of patients where the ***exact same dosing regimen*** was disclosed in the prior art for treating the patient population as a whole. IPR2015-00417, Paper 11, 17-18. Here, the dosing regimen was not disclosed in the prior art for any patient population.

In *BioMarin*, the Board found obvious claims drawn to a method of treating a particular lysosomal disorder (Pompe disease). IPR2013-00534, Paper 81, 11-17. The claimed dosing interval was characterized by the patent owner as a "novel element" but was used in the prior art for treating a different lysosomal storage disorder (Gaucher disease). *Id*. at 11, 17, 22. Testimony established that selecting the dosing interval for Pompe disease "would have been informed by the clinical experience with Gaucher disease." *Id*. at 17. On these facts, the Board determined that there were not "numerous parameters to try." *Id*. at 17.

Here, the claimed dosing regimen was ***not*** disclosed in the prior art. Rather, the prior art provided at best a general approach that seemed to be a promising field of exploration, whereas the claims at issue recite multiple parameters, including the route of injection, the dosing schedule, the amount dosed, and the period of time required.

F. Secondary Considerations Support the Nonobviousness of the Challenged Claims

HUMIRA® indisputably is a commercial success. Even Petitioner's declarant, Dr. Reisetter, acknowledges that HUMIRA® "has been ***commercially successful since its introduction in 2003***." Ex. 1025 ¶ 9 (emphasis added). RA was the only indication for which HUMIRA® was approved until October 2005. Ex. 2004 (Williams Decl.) ¶ 5. Despite competition from two previously-launched TNFα inhibitor biologics, ENBREL® and REMICADE®, HUMIRA® gained

significant U.S. market share in the first two years following launch, with revenue of about $250 million in 2003 and $550 million in 2004. *Id.* at ¶¶ 16-17. HUMIRA® achieved commercial success despite being the third anti-TNFα product to market. Ex. 2031 (Timmerman), 3.

During prosecution, Patent Owner demonstrated, and the Examiner agreed, that the commercial success of HUMIRA® bore a nexus to the challenged claims. *See* Ex. 1002, 1586 (Notice of Allowance). This nexus between HUMIRA®'s dosing regimen and its commercial success has been widely-recognized, with the dosing regimen identified as a "key design feature":

> ***There was one other key design feature, which many scientists didn't fully appreciate at the time***, but turned out to be a crucial advantage. [REMICADE®] had to be taken via an intravenous infusion, which meant regular trips to the doctor. [ENBREL®] had to be taken via self-administered injections under the skin twice a week. [HUMIRA®], by contrast, was designed to last longer in the bloodstream. ***Patients could inject themselves just under the skin, as little as once every two weeks***.

Ex. 2031 (Timmerman), 3 (emphases added); *see also* Ex. 2004 (Williams Decl.) ¶¶ 28-31.

Relying on the declaration of Dr. Reisetter, Petitioner argues that HUMIRA®'s commercial success "is not due to the dosing regimen claimed in the

'135 patent," but instead is attributable to other factors. Pet. 29 (citing Ex. 1025 ¶ 9). Petitioner's arguments are flawed.

Petitioner argues that AbbVie's marketing strategies have contributed to HUMIRA®'s commercial success. Pet. 29 (citing Ex. 1025 ¶ 14). Petitioner's argument is based solely on the observations that, a ***decade after*** HUMIRA®'s launch, "[t]he HUMIRA® marketing team was named 2014 Marketing Team of the Year by Medical Marketing & Media" and that "in 2013, AbbVie spent $132.4 million on direct-to-consumer advertising," which allegedly is "the fourth highest amount among pharmaceutical brands." *Id*. That argument is irrelevant because HUMIRA®'s commercial success extends back to the date it was approved by the FDA. Ex. 2004 (Williams Decl.) ¶¶ 14-18.

Moreover, Petitioner's argument contradicts the testimony of its own expert, Dr. Reisetter. Dr. Reisetter testified in another proceeding that "[u]nlike in most other commercial markets, the primary decision-maker in a pharmaceutical market [i.e., the physician] neither uses the product or therapy chosen nor is financially responsible for the decision made." Ex. 2030 (Reisetter Direct Narrative), 3. "Because of these market dynamics . . . [m]arketing alone does not and cannot drive use in pharmaceutical markets . . . ." *Id.* at 4; *see also id.* at 12 ("marketing and promotion . . . cannot contribute to continued market growth"). In any event, the test for commercial success does not require that the patented feature be the

only reason for the product's success. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991).

Contrary to Petitioner's contention (Pet. 30-31), the Federal Circuit in *Galderma Laboratories* and *Merck Co.* did not broadly hold that commercial success has no probative value where there is another patent blocking market entry. Rather, in both *Galderma* and *Merck*, the claimed inventions were modifications of already-marketed dosages. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 735 (Fed. Cir. 2013); *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1366 (Fed. Cir. 2005). Here, there was no approved D2E7 dosage, there was fierce competition among competing anti-TNFα biologics, including prior market entrants, and HUMIRA® distinguished itself on the basis of a unique and superior dosing regimen. Ex. 2031 (Timmerman), 3; Ex. 2004 (Williams Decl.) ¶¶ 28-31.

Neither Petitioner nor Dr. Reisetter has provided any basis to question the Examiner's conclusion that "applicant's showing of commercial success is convincing and considered to be commensurate in scope with the breadth of the now claimed invention" (Ex. 1002, 1586 (Notice of Allowance)), which should be adopted by the Board. *See Omron Oilfield & Marine, Inc. v. MD/Totco, L.P.*, IPR 2013-00265, Paper 11, 12-13 (Oct. 31, 2013).

V. 35 U.S.C. § 325(d) SUPPORTS DENIAL OF THE PETITION

35 U.S.C. § 325(d) provides that "[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." Where the Petitioner presents the exact same references that were considered by the Examiner during prosecution in the same or substantially the same way, the Board has declined to institute trial. *See, e.g.*, *Funai Elec. Co. v. Gold Charm Ltd.*, IPR2015-01491, Paper 15, 19-20 (Dec. 28, 2015) (declining to institute ground under § 325(d) where "Petitioner disagrees with the Examiner's conclusion, but relies on the identical portions of the reference considered by the Examiner and does not present any persuasive evidence to supplement the record that was in front of the Office during the original prosecution."); *Microboards Tech., LLC v. Stratasys Inc.*, IPR2015-00287, Paper 13, 11-12 (May 28, 2015) (declining to institute ground under § 325(d) where same prior art was overcome during examination and discussed in Notice of Allowability); *Tiffany & Co. v. Lazare Kaplan Int'l, Inc.*, IPR2015-00024, Paper 7, 19 (Apr. 20, 2015) (declining to institute ground under § 325(d) where Examiner made similar arguments about the same reference identified in petition).

Application of § 325(d) to deny institution is particularly appropriate where Petitioner does not present persuasive new evidence to supplement the record that

was before the Office during examination. *Funai Elec. Co.*, IPR2015-01491, Paper 15, 19-20; *Integrated Global Concepts, Inc.*, IPR2014-01027, Paper 16, 8 (declining to institute under § 325(d) where same arguments and art were presented to the Office and only additional evidence provided by petitioner was "conclusory" expert declaration); *see also Merial Ltd. v. Virbac*, IPR2014-01279, Paper 13, 23-26, 28 (Jan. 22, 2015) (declining to institute under § 325(d) where petitioner did not convincingly address Examiner's allowance rationale).

Here, Petitioner relies on the exact same references that were presented and thoroughly considered by the Examiner during prosecution, and Petitioner does not present any persuasive new evidence to supplement the record considered during examination. As set forth in detail above, neither Petitioner's arguments, nor the positions of its declarants, shed a substantially different light on the combination of van de Putte and Kempeni compared to what was contemplated by the Examiner during the original examination. The issues raised by Petitioner and its declarants directly correspond with the issues raised in prosecution. For example:

- Petitioner and its experts argue that a POSA would have perceived the advantages of fixed, subcutaneous dosing. Pet. 31-33; Ex. 1006 (Baughman Decl.) ¶¶ 51-55; Ex. 1007 (O'Dell Decl.) ¶¶ 23-33, 43-44. The Examiner addressed the very same issue. Ex. 1002, 1095, 1546-1547.

- Petitioner claims a POSA would have viewed the 20, 40, and 80 mg weekly doses from van de Putte as equally efficacious. Pet. 33-34; Ex. 1006 (Baughman Decl.) ¶¶ 56-62; Ex. 1007 (O'Dell Decl.) ¶¶ 25-33, 35-37. The Examiner thoroughly considered this argument. Ex. 1002, 1094, 1535, 1584-1586 (Notice of Allowance).
- Petitioner contends that every-other-week dosing was established in the art and would have been perceived as advantageous. Pet. 35; Ex. 1006 (Baughman Decl.) ¶¶ 63-65, 72-73; Ex. 1007 (O'Dell Decl.) ¶¶ 42-44. The Examiner considered these points as well. Ex. 1002, 1094-1095, 1538-1539.
- Petitioner asserts that the reported D2E7 half-life allegedly would have supported every-other-week dosing. Pet. 34-35; Ex. 1006 (Baughman Decl.) ¶¶ 65-68. The Examiner evaluated the same argument. Ex. 1002, 1098-1099.
- Petitioner contends that dose optimization would have led a POSA to the claimed method of administration. Pet. 35-37; Ex. 1006 (Baughman Decl.) ¶¶ 49, 55-56, 63-69; Ex. 1007 (O'Dell Decl.) ¶¶ 20-22, 33. The Examiner also took this into account. Ex. 1002, 1096-1097, 1538-1539.
- Petitioner argues that the commercial success of HUMIRA® is not attributable to the claimed invention. Pet. at 29-31; Ex. 1025 (Reisetter

Decl.) ¶¶ 10-17. The Examiner analyzed the same issue during prosecution. Ex. 1002, 1545, 1586 (Notice of Allowance).

Moreover, despite being addressed during prosecution, neither Petitioner nor its declarants address:

- the lack of correlation between half-life and dosing interval;
- the evidence of up-dosing, even though the Examiner highlighted it as convincing in the Notice of Allowability (Ex. 1002, 1586);
- the evidence that body-weight doses administered intravenously showed better efficacy than when administered subcutaneously; and
- the evidence that subcutaneous delivery causes an unpredictable loss in the amount of drug absorbed into the blood and accordingly lower serum concentrations than intravenous administration.

Accordingly, the Board should not grant Petitioner the opportunity to revisit the same issues by IPR. *See Funai Elec. Co.*, IPR2015-01491, Paper 15, 20; *Integrated Global Concepts, Inc.*, IPR2014-01027, Paper 16, 8.

VI. CONCLUSION

For these reasons, Petitioner has not shown that it is reasonably likely to succeed on its challenge to any of claims 1-5 of the ’135 patent. Petitioner also makes the same arguments that were thoroughly considered by the Examiner

during prosecution. The Board should therefore deny the Petition and not institute *inter partes* review.

Dated: February 18, 2016 Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and Exhibits 2001-2031 were served electronically via email on February 18, 2016, in their entirety on the following:

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