Filed: April 8, 2016

Filed on behalf of: AbbVie Biotechnology Ltd.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM INTERNATIONAL GMBH AND
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner.

Case IPR2016-00408
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 CFR § 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 1141-71)
2002	Declaration of Michael E. Weinblatt, MD, Under 37 CFR § 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 1173-99)
2003	Declaration of Diane R. Mould Under 37 CFR § 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 1201-33)
2004	Declaration of Mr. Medgar Williams Under 37 CFR § 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 1240-51)
2005	Declaration Under 37 C.F.R. § 1.132 of Hartmut 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 600-04)
2006	Declaration Under 37 C.F.R. § 1.132 by Dr. Hartmut 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 808-18)
2007	Rituximab/RITUXAN® label (Nov. 1997)
2008	Trastuzumab/HERCEPTIN® label (Sept. 1998)
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2010	Daclizumab/ZENAPAX® label (Dec. 1997)
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I. INTRODUCTION

Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively "BI" or "Petitioner") seek *inter partes* review of U.S. Patent No. 8,889,135 ("the '135 patent"), contending that claims 1-5 are rendered obvious by van de Putte 2000 in view of Rau 2000. 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.

At the outset, the Board should deny the Petition pursuant to 35 U.S.C. § 325(d) because Petitioner makes the same arguments that are presented in a petition for *inter partes* review filed by Coherus BioSciences Inc. ("Coherus") against the '135 patent. *See* Ex. 2033. The art relied on by BI is wholly cumulative to the art raised by Coherus. The single ground of this Petition is also redundant of both grounds of BI's companion petition, IPR2016-00409.

Moreover, like Coherus, Petitioner rehashes arguments thoroughly considered by the Examiner during prosecution. The references that form the basis of Petitioner's single ground of obviousness were considered by the Examiner, and the issues raised by Petitioner and its declarants correspond directly to issues that were raised by the Examiner during prosecution and overcome by Patent Owner.

The expert declarations submitted by Petitioner do not present any persuasive new evidence that was not before the Examiner. The Petition is therefore cumulative, and the Board should decline to institute trial.

As summarized here and discussed in more detail in the sections that follow, the Petition also fails on the merits.

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 references relied on by Petitioner 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 the van de Putte 2000 abstract as the centerpiece of its single ground is pure hindsight. Moreover, Petitioner offers no rationale why a person of ordinary skill in the art ("POSA") would have viewed the reference's 20 mg dose, which was inferior to the 40 and 80 mg doses, as a logical starting point.

Second, Petitioner's argument that a POSA would have been motivated to stretch a weekly dose to a purportedly equivalent every-other-week 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. Prior art 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 a touchstone for its arguments regarding motivation, lack scientific merit. Petitioner bases its theory largely on a single sentence from Rau 2000, but this sentence does not suggest the claimed 40 mg dose nor every-other-week, subcutaneous administration. Moreover, the crux of Petitioner's theory is the assumption that serum half-life can meaningfully inform the choice of a dosing interval in the absence of other pharmacokinetic data. 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, which were not available.

Fourth, Petitioner's contention that allegedly being "obvious to try" renders the claims obvious is legally erroneous. The number of potential dosing regimens at the time of the invention was not "finite" and the efficacy and safety of different regimens was not "predictable." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421

(2007). The prior art showed different routes of administration, different drug amounts, and different dosing intervals. From these variables, an almost limitless number of dosing regimens could have been tried by a POSA. Moreover, in the absence of critical data on how D2E7 behaved in the body, there was no information that would have led a POSA to reasonably predict success. Petitioner cannot avoid its burden of showing a reasonable expectation of success by relying on the contention that the claimed invention would have been obvious to try.

Fifth, 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, concluding that the Patent Owner's showing of commercial success was "convincing and considered to be commensurate in scope with the breadth of the now claimed invention." *See* Ex. 1002 (File History), 1586 (Notice of Allowance).

Finally, the expert declarations submitted by Petitioner rely on conclusory opinions and irrelevant contentions, but do not contradict the scientific facts relevant to obviousness. Indeed, outside of the context of this proceeding, each of Petitioner's declarants has made statements consistent with Patent Owner's positions. For example, in evaluating the 20, 40, and 80 mg doses from van de Putte 2000, Dr. Weisman argues in this proceeding that it is "essential to have statistical information regarding clinical responses" before "making any dose-to-

dose comparisons . . . ." Ex. 1003 (Weisman Decl.) ¶ 38. Yet in his publications, he routinely draws conclusions comparing doses based on numeric trends even in the absence of statistics. *See, e.g.*, Ex. 2026 (Mason), 5; Ex. 2034 (Moreland), 9; Ex. 2035 (Kavanaugh), 4-6.

In short, Petitioner's arguments are duplicative of the issues set forth in the petition filed by Coherus and considered thoroughly by the Examiner during prosecution. Petitioner also fails to demonstrate a reasonable likelihood that it will prevail. The Board should therefore refuse to institute trial.

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; *see also* labeling information for those antibodies, including Ex. 2014, 13; Ex. 2008, 2; Ex. 2029, 9; Ex. 2009, 17; Ex. 2007, 2; Ex. 2011, 7; Ex. 2012, 1; Ex. 2010, 2; and Ex. 2028, 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. 1024 (HUMIRA® label), 1.

Rheumatoid Arthritis. RA is a life-long, inflammatory disease of the joints and surrounding tissue. Left untreated, the 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 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. 1011 (Kempeni), 3. 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. *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. 1022 (FDA Guidance), 4. The search for new treatments focused on inhibiting tumor necrosis factor alpha ("TNFα"). Ex. 2030 (Furst 2001), 2-3.

[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 also be found in Petitioner's Ex. 1002.

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, were a new class of drugs with promise for treating RA. Ex. 1011 (Kempeni), 3; Ex. 2003 (Mould Decl.) ¶ 17.

These drugs presented unique safety and efficacy concerns. Ex. 1011 (Kempeni), 3; *see also* Ex. 1022 (FDA Guidance), 17. By targeting TNFα, anti-TNFα biologics ***suppress*** the patient's immune system, creating a risk of infection. Ex. 2001 (Pope Decl.) ¶ 55; Ex. 2003 (Mould Decl.) ¶¶ 52-53. 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. 1022 (FDA Guidance), 14.

Anti-drug antibodies can also reduce 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. 1022, 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 REMICADE®, the only anti-TNFα antibody approved by the FDA as of 2001. 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. 2029 (REMICADE® label), 6, 8. 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 7; *see also* Ex. 2001 (Pope Decl.) ¶ 55; Ex. 2003 (Mould Decl.) ¶ 52. 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. 2029 (REMICADE® label), 7; *see also* Ex. 2002 (Weinblatt Decl.) ¶ 37; Ex. 2003 (Mould Decl.) ¶ 57.

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. 2029 (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 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 allergic reactions. 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 abstracts and review articles. These include three abstracts from van de Putte reporting on the DE007 clinical trial (van de Putte 1999 (Ex. 1008), van de Putte 2000 (Ex. 1009), and van de Putte 2000b (Ex. 1010)), as well as the Rau 2000 (Ex. 1012) review. 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 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.

Rau 2000 discusses several early D2E7 trials, including the DE001/DE003, DE004, DE007, and DE010 studies. Ex. 1012 (Rau 2000). 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 5; *see also* Ex. 1011 (Kempeni), 4; Ex. 2006 (Kupper II Decl.) ¶ 12. Rau 2000 reported that while "improvement persisted at

the higher dose for four weeks; after the lower doses (0.5 or 1 mg per kg of body weight), the number of swollen joints gradually increased again." Ex. 1012 (Rau 2000), 6. For one measure (the erythrocyte sedimentation rate "ESR"), "[i]n the 0.5 mg group there was a worsening again already after one week." *Id.* (internal citation omitted).

The DE003 study discussed in Rau 2000 was an open-label continuation of the DE001 study. *Id.*; Ex. 1011 (Kempeni), 4; Ex. 2006 (Kupper II Decl.) ¶ 13. D2E7 was administered intravenously based on body weight. *Id.* Patients received a first dose identical to the dose received in the DE001 study a minimum of 4 weeks after the DE001 dose, and only after losing response status. Thereafter, patients received D2E7 every 2 weeks "until responses could be rated as 'good', defined as an absolute DAS [Disease Activity Score] of <2.4," and were then retreated upon disease flare-up. Ex. 1011 (Kempeni), 4; Ex. 1012 (Rau 2000), 5-6. The mean dosing interval was reported as 2.5 weeks. Ex. 1011 (Kempeni), 4; Ex. 1006 (Rau 1998), 5. Patients in DE003 "who did not respond well after 0.5 or 1 mg/kg ***received higher doses*** . . . ." Ex. 1011 (Kempeni), 4 (emphasis added); Ex. 1006 (Rau 1998), 5; Ex. 2006 (Kupper II Decl.) ¶ 13.

The DE004 trial reported in Rau 2000 evaluated weekly, subcutaneous administration of a weight-based dose of 0.5 mg/kg D2E7 for three months. Ex. 1012 (Rau 2000), 7; Ex. 1011 (Kempeni), 4-5; Ex. 2006 (Kupper II Decl.)

¶ 17. "[N]on-responders or those losing their responder status" were up-dosed to 1 mg/kg weekly. Ex. 1011 (Kempeni), 5; Ex. 2006 (Kupper II Decl.) ¶ 17.

The DE010 trial reported in Rau 2000 compared head-to-head a 1 mg/kg dose administered subcutaneously to a 1 mg/kg dose administered intravenously. Ex. 1012 (Rau 2000), 8; Ex. 1011 (Kempeni), 5; Ex. 2006 (Kupper II Decl.) ¶ 20. Intravenously administered D2E7 showed better efficacy than subcutaneously administered D2E7 for every reported metric, leading Rau 2000 to conclude that "[i]ntravenous administration gives advantages in terms of joints painful to pressure, ESR, and C-reactive protein." Ex. 1012 (Rau 2000), 8; *see also* Ex. 1011 (Kempeni), 5; Ex. 2003 (Mould Decl.) ¶ 32.

Preliminary data from the first phase II trial of D2E7, called DE007, were reported in Rau 2000 and an abstract by van de Putte. Ex. 1008 (van de Putte 1999). This trial featured a three-month placebo-controlled study in which patients received a fixed dose of 20, 40, or 80 mg D2E7 administered subcutaneously on a weekly schedule. *Id.* at 7. The data reported for the 40 and 80 mg doses are on their face superior to the 20 mg dose, but van de Putte 1999 reported that all doses "were statistically significantly superior to placebo ($p < 0.001$)." *Id.* Consistent with this data showing superiority of the higher doses as compared to the 20 mg dose, Rau 2000 focused on these doses in its discussion of the data. Ex. 1012 (Rau 2000), 7 ("[A]n improvement by > 60% in the CRP (C-reactive protein) and in the

number of swollen joints was attained in the patient groups treated with 40 mg or 80 mg, while no change appeared in the placebo group.").

Following the placebo-controlled portion of the DE007 trial, patients formerly in the placebo group received 40 mg D2E7 subcutaneously on a weekly basis. Ex. 1009 (van de Putte 2000), 2. The van de Putte 2000 (relied on by Petitioner) and van de Putte 2000b abstracts are updates of the van de Putte 1999 abstract, reproducing the 3-month placebo controlled data and showing efficacy data for the continuation phase at 6 months and 1 year, respectively. Ex. 1009 (van de Putte 2000); Ex. 1010 (van de Putte 2000b). The weekly 40 mg and 80 mg doses again produced numerically superior results to the weekly 20 mg dose, with the higher doses showing superior results for every reported metric following one year of treatment. Ex. 1010 (van de Putte 2000b), 5.

Finally, the Weisman 2000 abstract (Ex. 1014) reports on the DE005 trial. In that study, patients received weight-based intravenous injections every-other-week at doses ranging from 0.25 mg/kg to 5 mg/kg. Ex. 1014, 5. 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, the Examiner considered each of the references relied on by Petitioner and made the same arguments Petitioner now advances.

The Examiner cited the van de Putte 1999 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 (File History), 1094 (emphasis omitted). The Examiner further considered the 6-month and 1-year updates to the 1999 report (*id*. at 1110-11, 1535), ultimately explaining in the Notice of Allowance that the teachings of the van de Putte 1999 (3-month placebo controlled data) and van de Putte 2000b (1-year update) abstracts were “considered to be of primary

importance." *Id*. at 1584. The Examiner cited Rau 2000, focusing on the statement in Rau that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." Ex. 1002 (File History), 632; Ex. 1012 (Rau 2000), 8; *see also* Ex. 1002, 761, 1002, 1098. Petitioner's single ground is focused on the very same data from van de Putte 2000 and the very same excerpt from Rau 2000. Pet. 22-28, 32, 34-37.

The Examiner argued that a POSA would have been motivated to modify the dosing regimen of van de Putte 1999 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 (File History), 1095. The identical argument is made by Petitioner. Pet. 31-33.

The Examiner also argued that a POSA would have had a reasonable expectation of success in achieving an effective treatment of RA from every-other-week dosing based on Rau 2000's disclosure of the intravenous half-life of D2E7 combined with the teaching of "nearly equal efficacy of 20, 40, and 80 mg weekly treatments as taught by Van de Putte." Ex. 1002 (File History), 761-62. Petitioner also relies on the intravenous half-life from Rau 2000 and the dosing regimens disclosed in the van de Putte abstracts. Pet. 2, 22-23, 27-31.

The Examiner further argued 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 (File History), 1095. The identical argument is made by Petitioner. Pet. 2, 7-8, 22, 26, 39.

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 (File History), 1269-330. 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. Patent Owner also rebutted the obviousness rejection with evidence demonstrating HUMIRA®'s commercial success. Ex. 1002 (File History), 1282-90; Ex. 2004 (Williams Decl.).

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 (File History), 1584-85 (Notice of Allowance). 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

The Petition should be denied regardless of the definition of a POSA or whether the Board chooses to construe any claim term. However, Patent Owner responds below to Petitioner's proposals.

A. Level of Ordinary Skill in the Art

Petitioner defines the POSA as a practicing rheumatologist with, among other things, "familiarity with basic pharmacokinetic concepts such as half-life." Pet. 18. This differs from the proposed definition of prior petitioner Coherus, which argued that a POSA would have the understanding of both a rheumatologist ***and*** a Ph.D. pharmacokineticist with at least three years of experience working with biologic agents. Ex. 2033 (Coherus Pet.), 27.

The understanding of a pharmacokineticist with a Ph.D. in pharmacokinetics (or a related discipline) and experience with biologic agents should be included in defining the POSA. During prosecution, Patent Owner submitted declarations of both rheumatologists (Drs. Pope and Weinblatt) and a pharmacokineticist (Dr. Mould), and the Examiner quoted favorably from each in the Notice of

Allowance. Ex. 1002 (File History), 1184, 1208, 1584-85. The Examiner also emphasized pharmacokinetic principles in evaluating the claimed invention. *E.g.*, *id*. at 1099.

B. Claim Construction

Petitioner proposes that no term requires construction and that the ordinary and customary meaning should apply to all claim terms. Pet. 19. Patent Owner submits, consistent with its preliminary response filed in IPR2016-00172, that the Board should construe the term "for a time period sufficient to treat the rheumatoid arthritis" to mean "for a time period sufficient to reduce significantly the signs and symptoms of rheumatoid arthritis." This construction is consistent with the patent specification, which discloses that the claimed dosing regimen results in a "significant[]" reduction in both "the signs and symptoms of RA at twenty-four weeks." Ex. 1001 ('135 patent), 30:25-28. The specification further 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)." *Id*. at 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.

IV. THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER VAN DE PUTTE 2000 IN VIEW OF RAU 2000

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. Like prior petitioner Coherus, which made substantially similar arguments, Petitioner uses the claims as a road map to arrive at the claimed dosing regimen. This is evidenced by Petitioner's limitation-by-limitation analysis, which permits it to use the claim as a guide to selectively pick through the maze of prior art to arrive at the claimed invention. The result is a textbook example of hindsight that fails to carry Petitioner's burden of demonstrating that the claims are obvious.

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 2000 rather than the intravenous, weight-based dosing that predominated in the art and which Rau 2000 itself said was more efficacious. *E.g.*, Pet. 22-27; Ex. 1012 (Rau 2000), 8. 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.

- Other than the DE007 trial described in the van de Putte abstracts, ***all*** of the other D2E7 clinical trials reported in the prior art utilized body-weight-based dosing. Ex. 1012 (Rau 2000); Ex. 1011 (Kempeni); Ex. 1014 (Weisman 2000).
- REMICADE®, the only anti-TNFα antibody approved for treating RA as of 2001, was approved only for intravenous, weight-based dosing. Ex. 2029 (REMICADE® label), 6, 8; 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.
- 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 Rau 2000, indicated that weight-based doses administered intravenously provided ***better*** efficacy than weight-based doses administered subcutaneously. Ex. 1012 (Rau 2000), 8; Ex. 1011 (Kempeni), 5; Ex. 2001 (Pope Decl.) ¶ 34.

Petitioner's argument ignores these aspects of the art and fails to provide evidence for why a POSA would have acted in a contrary manner.

Instead, Petitioner cites the "Summary of the Invention" from the '135 patent as evidence of the "many advantages" of the claimed invention. Pet. 13. The '135 patent is not prior art and cannot be relied upon by Petitioner as part of its obviousness challenge. Petitioner also cites to six paragraphs of Dr. Weisman's declaration, without providing any contemporaneous evidence, for the proposition that these advantages were "were well known to a person of ordinary skill in the art." Pet. 13-14 (citing Ex. 1003 (Weisman Decl.) ¶¶ 42-47). But the '135 patent is the only document discussed in these paragraphs that addresses the advantages of a subcutaneous, fixed-dose regimen. *See* Ex. 1003 (Weisman Decl.) ¶ 45 (citing ¶ 41, which cites Ex. 1001 ('135 patent), 2:60-3:2 (describing the advantages of the instant invention)).

Petitioner's improper reliance on the '135 patent reflects an incorrect understanding of the state of the art. The issue raised by Petitioner's argument is not whether a subcutaneous, fixed dose might have been considered generally advantageous. The issue is whether a POSA in June 2001, confronted with the nascent state of the art and what it taught about D2E7, would have been motivated to pursue a dosing regimen based on "patient compliance" and "convenience." Pet. 2, 31-33, 46. Prior to first marketing 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 considering the art as a whole would have considered intravenous, weight-based dosing the best alternative for addressing those concerns.

B. A POSA Would Not Have Been Drawn Toward the 20 mg Weekly Dose in van de Putte 2000

Assuming a preference for a subcutaneous, fixed-dose regimen such as that disclosed in van de Putte 2000, Petitioner posits that a POSA would have been drawn toward the 20 mg weekly dose in van de Putte 2000 and, based on half-life, clinical considerations, or routine experimentation, would have arrived at 40 mg every-other-week dosing because it is purportedly "equivalent to" 20 mg weekly dosing. Pet. 25, 28. As explained below, a POSA would not have pursued an every-other-week dosing schedule "equivalent to" 20 mg weekly because the 20 mg weekly dose was inferior to the 40 mg and 80 mg doses reported in van de Putte 2000.

1. van de Putte 2000 suggested the superiority of a 40 mg weekly dose

Petitioner contends that a POSA would have been attracted to the 20 mg weekly dose in van de Putte 2000 because it was shown to be efficacious versus placebo and because the abstract states that the experimental doses are "statistically equally efficacious." Pet. 22-27, 33-34. Petitioner's premise requires a POSA to

ignore data in van de Putte 2000 showing that the 40 mg and 80 mg weekly doses were clinically superior to the 20 mg dose.

All three van de Putte abstracts report the same data from the three-month placebo-controlled portion of the DE007 trial. Ex. 1008 (van de Putte 1999), 7; Ex. 1009 (van de Putte 2000), 2; Ex. 1010 (van de Putte 2000b), 5. 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 to the 80 mg dose in 3 out of 4 outcome measures during the placebo-controlled portion of the trial. Ex. 1008 (van de Putte 1999), 7 (data reproduced below); Ex. 1009 (van de Putte 2000), 2; Ex. 1010 (van de Putte 2000b), 5; 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 (File History), 1585-86 (quoting Ex. 2002 (Weinblatt Decl.) ¶ 20).

The later van de Putte abstracts show that the superiority of the 40 mg and 80 mg weekly subcutaneous doses as compared to the 20 mg dose was ***maintained over time***. van de Putte 2000 shows that at 6 months, ACR20 (the primary measure of efficacy for the DE007 trial) and SJC (swollen joint count) were superior for the 40 and 80 mg doses versus the 20 mg dose. Ex. 1009 (van de Putte 2000), 2. In fact, van de Putte 2000 reveals that patients switched from placebo to the 40 mg dose showed greater improvement based on ACR20, SJC, and CRP (C-reactive protein) after just 3 months of treatment than patients treated with the 20 mg dose weekly for 6 months. *Id*.

Moreover, although ignored by Petitioner, the one-year results from the DE007 trial reported in van de Putte 2000b show that 40 mg and 80 mg weekly D2E7 ***produced numerically superior results to 20 mg weekly D2E7 for every metric tested***, including ACR20, ACR50, TJC (tender joint count), SJC (swollen joint count), and CRP (C-reactive protein). Ex. 1010 (van de Putte 2000b), 5. 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.

Despite this demonstrated inferiority, Petitioner argues (with the benefit of hindsight) 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. 24-25. 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.) ¶¶ 18-23; Ex. 2002 (Weinblatt Decl.) ¶¶ 18-22; Ex. 2003 (Mould Decl.) ¶¶ 21-25.

It is not just the Patent Owner's declarants whose testimony shows this. Petitioner's own declarant, Dr. Weisman, has relied on numerical differences in data to support his conclusions, even if not statistically significant. *See, e.g.*, Ex. 2026 (Mason), 5 (reporting "a dose-response ***trend in efficacy***" although "the differences ***failed to reach statistical significance***" (emphases added)); Ex. 2034 (Moreland), 9 (reporting data that "reveal a dose response with the ***highest dose tested demonstrating the largest improvement*** in swollen joint counts," although the trial "was not designed to provide formal significance testing of efficacy endpoints" (emphasis added)); Ex. 2035 (Kavanaugh), 4-6 (reporting Paulus 20 efficacy data at Day 28 that only "trended toward clinical significance (p =

0.107)," but concluding that the "study allowed some evaluation of therapeutic benefit . . . [in] the highest dose group, 67% of patients appeared to have achieved a Paulus 20 response by Day 28").

Although ignored by Petitioner, Rau 2000 itself demonstrates how a POSA would have interpreted the significance of van de Putte's results. In reporting on the DE007 study, Rau 2000 disclosed clinical data for the 40 mg and 80 mg doses but ***ignored*** the 20 mg dose. Ex. 1012 (Rau 2000), 7. Another contemporaneous report of the DE007 trial likewise failed to report 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. Moreover, the full-length peer-reviewed article reporting the results of the DE007 trial stated that "[i]n most measures of efficacy at week 12, ***adalimumab [D2E7] 40 mg was associated with better results than the other doses***." Ex. 2041 (van de Putte 2003), 9 (emphasis added). Similarly, Example 2 of the '135 patent, which discloses the results of the DE007 study, focuses on the 40 mg/week dose, stating that "subcutaneous D2E7, ***particularly at a dose of 40 mg/week***, generates a good response." Ex. 1001, 29:8-10 (emphasis added). This 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.

2. The degree of efficacy required by the claims is irrelevant to the issue of motivation

In support of its motivation argument, Petitioner also argues that even if the 20 mg dose was viewed as inferior, its superiority to placebo is evidence of "clinical effectiveness" and that the claims require only a dose "sufficient to treat," not "the most effective dose." Pet. 26-27, 34-35, 37. This argument is a red herring.

Motivation is a function of the goal that a POSA would seek to achieve. *See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (a POSA would not have been motivated to modify a compound expected to exhibit merely a "baseline level" of activity). The goal of a POSA engaged in the design of a D2E7 dosing regimen would have been to achieve the highest level of efficacy possible while maintaining patient safety. Ex. 2025 (Wolfe), 3 ("the fundamental goal" of treating RA was to treat "disease activity to the fullest extent possible"); Ex. 2001 (Pope Decl.) ¶ 44; Ex. 2003 (Mould Decl.) ¶¶ 44-45. Petitioner's declarants do not suggest otherwise. In light of this goal, a POSA would not have been motivated to modify the 20 mg weekly dosing regimen in van de Putte 2000 when more promising data are reported in the very same reference. *See Yamanouchi*, 231 F.3d at 1345 (no motivation to modify a compound where the prior art showed other compounds with higher activity levels).

Petitioner also argues that a POSA would have considered the 20 mg dose sufficiently efficacious by comparing it to data from the trial resulting in FDA approval of REMICADE®. Pet. 24. This cross-drug, cross-study comparison is wholly inconsistent with Petitioner's argument that, absent statistics, one cannot compare results among different dosing groups in the same clinical trial. *See* Pet. 25. Moreover, even if the comparison was appropriate, it fails to explain why a POSA would have selected the 20 mg weekly regimen when more promising data are reported in the same reference for the higher doses.

The cases cited by Petitioner do not support its assertion that a POSA would have been drawn to the 20 mg dose, even understanding that it was "less effective than the 40 or 80 mg doses." Pet. 26. In those cases, the prior art identified solutions for overcoming the disadvantages of the prior art under consideration and therefore provided the motivation for modifying it. *See Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1381 (Fed. Cir. 2015) (despite one reference disclosing potential disadvantages with a particular chemical composition, "other prior art references disclose[d] roadmaps on how to offset the disadvantages"); *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197 (Fed. Cir. 2014) (known disadvantages with a particular formulation could be addressed with prior art solution of reducing particle size). Here, the "problem" with the 20 mg D2E7 dosing regimen in van de Putte 2000 was that it was facially inferior to the 40 and 80 mg dosing regimens.

The solution would not have been to modify the 20 mg dose. If one was motivated to modify the existing regimens at all, the solution would have been to modify the demonstrably more efficacious 40 or 80 mg weekly dosing regimens or the myriad of weight-based dosing regimens reported in the prior art.

C. A POSA Would Not Have Been Motivated to Stretch the 20 mg Weekly van de Putte 2000 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 2000 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 stretch the 20 mg weekly dose into a 40 mg every-other-week dose as recited in the claims. Petitioner fails to discharge this burden as well.

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

Petitioner points to the DE003 study described in Rau 2000 as disclosing an every-other-week dosing regimen, and argues that a POSA would have understood that Rau 2000 proposed every-other-week subcutaneous administration. Pet. 27-28. This argument is based on a misreading of Rau 2000 and the DE001/DE003 study it describes.

The DE001/DE003 dosing schedules would not have motivated a POSA to pursue a 40 mg, every-other-week, subcutaneous dose. The patients in those

studies received drug according to a variety of different dosing schedules, not an every-other-week schedule (even the "biweekly" phase of the DE003 study involved a mean dosing interval of 2.5 weeks). And contrary to Petitioner's suggestion, the 2.5 week mean dosing interval would not have pointed in the direction of an every-other-week, subcutaneous dosing regimen. Patients in the DE001/DE003 studies received D2E7 intravenously, not subcutaneously. Ex. 1012 (Rau 2000), 5; Ex. 1011 (Kempeni), 4. Patients received weight-based doses, not fixed doses. *Id*. A POSA would not have considered the DE003 dosing schedules to be equivalent to a subcutaneous, fixed, every-other-week dosing regimen. Ex. 2005 (Kupper I Decl.) ¶ 4. Petitioner errs by minimizing these distinctions, and, as discussed below, ignores entirely the evidence of up-dosing that occurred in the DE003 trial as well as other prior art D2E7 trials.

Petitioner nevertheless argues that "[n]othing in Rau 2000 indicates that subcutaneous dosing would have produced different results when administered every other week." Pet. 27. But Rau 2000 expressly discloses that, as compared to subcutaneous administration, "intravenous administration gives advantages in terms of joints painful to pressure, ESR [erythrocyte sedimentation rate], and C-reactive protein." Ex. 1012, 8. Rau 2000 further states that, as compared to subcutaneous administration, intravenous injection results in "***somewhat better efficacy*** . . . [as] reflected in the DAS and ACR-20 response criteria . . . ." *Id*.

(emphasis added). Indeed, 72% of patients receiving an intravenous dose achieved a response in the DAS (Disease Activity Score) composite index, while only 45% of patients receiving a subcutaneous dose achieved a response. *Id.*

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), 8-9. Petitioner and its declarant Dr. Jusko gloss over the differences between intravenous and subcutaneous dosing. But in his own prior work, Dr. Jusko has acknowledged these differences and their significance. Ex. 2036 (Radwanski), 2 (reporting that "***the major concern for SC [subcutaneous]*** or any extravascular ***dosing is bioavailability***") (emphases added); *see also id*. at 5 ("C_{max} [peak concentration] for the SC [subcutaneous] route was more than an order of magnitude lower than that observed after IV [intravenous] administration.").

Petitioner compounds its error by equating the 0.5 mg/kg weight-based intravenous dose disclosed in Rau 2000 to a 40 mg subcutaneous dose (Petitioner multiplies the 0.5 mg/kg dose by an assumed 80 kg patient). *See* Ex. 1004 (Jusko Decl.) ¶ 23; Ex. 1003 (Weisman Decl.) ¶ 51; *see also* BI's concurrently filed petition in IPR2016-00409, Paper 3, 44 (stating that the "0.5 mg/kg weight-based

dose . . . would have been understood to correspond roughly to a 40 mg fixed dose," assuming an 80 kg patient). But a POSA would have understood that the weight-based doses reported in Rau 2000 are of limited relevance to a fixed-dose schedule 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 have known the distribution of patient weights, or 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 (File History), 1299-304; Ex. 2003 (Mould Decl.) ¶¶ 33-41), yet Petitioner and its declarants apply the same flawed reasoning. Pet. 2, 27-28, 30-32, 37-38, 46; Ex. 1004 (Jusko Decl.) ¶ 23; Ex. 1003 (Weisman Decl.) ¶ 51.

But even assuming for the sake of argument that Petitioner is correct, a POSA would still not have viewed the DE003 study as suggesting that 0.5 mg/kg every-other-week dosing is effective to treat RA. Petitioner ignores the fact that patients failing to respond to the lower 0.5 mg/kg dose 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. 1011 (Kempeni), 4; *see also* Ex. 2006 (Kupper II Decl.) ¶ 13. The inadequacy of these lower doses is consistent with Rau 2000's report that swollen joints increased for the lower doses (0.5 and 1 mg/kg) but not the higher doses, as well its conclusion that ESR values worsened "already after one week" for the 0.5 mg/kg group. Ex. 1012 (Rau 2000), 6.

In fact, D2E7 up-dosing was consistently reported in the prior art—***all trials that evaluated the 0.5 mg/kg dose*** (DE001/DE003, DE004, and DE005) ***had to increase to greater doses due to inadequate clinical response***. *See* § II.B, *supra*; Ex. 1011 (Kempeni), 4-5; Ex. 2002 (Weinblatt Decl.) ¶¶ 68-70; Ex. 2001 (Pope Decl.) ¶ 68; Ex. 2003 (Mould Decl.) ¶¶ 35, 81; Ex. 1014 (Weisman 2000), 5. If a 0.5 mg/kg dose was the equivalent of a 40 mg fixed dose (as Petitioner's expert argues), then both Rau 2000 alone and the art as a whole taught that a 40 mg every-other-week dose was too low to serve as a "one-size-fits-all" fixed dose and instead favored higher doses.

2. Petitioner minimizes the risks associated with stretching the 20 mg weekly dose to a purportedly equivalent every-other-week dose

In alleging that a POSA would have selected a 40 mg every-other-week dose, Petitioner glosses over the significant risks a POSA would have understood to be associated with lengthening van de Putte's 20 mg weekly dosing to 40 mg

every-other-week. As discussed in § II.A, above, there was a serious concern about potential adverse consequences of under-dosing, 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.

Petitioner's declarants acknowledge the existence of concerns with anti-drug antibodies, but dismiss them in their analyses because they are not aware of contemporaneous reports of anti-D2E7 antibodies. *E.g.*, Ex. 1003 (Weisman Decl.) ¶ 47 n.7 ("when anti-drug antibodies develop, they are typically reported in the literature"). But Rau 2000 reports that allergic reactions were observed in five patients following D2E7 administration, warning that this could result from "idiotypical epitopes" in D2E7. Ex. 1012 (Rau 2000), 8. The FDA had also specifically identified the development of anti-drug antibodies "following repeated courses of treatment" as a "particular concern with biological agents" used to treat RA. Ex. 1022 (FDA Guidance), 14.

Moreover, in June 2001, the D2E7 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. As explained by

Petitioner's declarant Dr. Weisman, abstracts are "Category D evidence" (the lowest form) because "they are not complete and may change by the time the data are published, or may not be published as full papers at all." Ex. 2038 (Furst 2003), 7. Given the limited public knowledge about D2E7 at the time, 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. 1020 (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. 1017 (FDA Clinical Review), 29; *see id*. at Tables 10-11.

3. The known data on D2E7 half-life would not have motivated a POSA to pursue the claimed invention

According to Petitioner, motivation to convert van de Putte's weekly dosing regimen into an every-other-week regimen comes from Rau 2000, which purportedly "explains that D2E7 can be administered every other week because

D2E7 has a 'half-life of 12 days' . . . ." Pet. 27. Petitioner's argument is premised largely on a single statement from Rau 2000: "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." Ex. 1012 (Rau 2000), 8; Pet. 12, 27-28. Neither this statement nor anything else in Rau 2000 suggests administering 40 mg every-other-week. Rau 2000 reports administering D2E7 as "an intravenous injection over 3-5 minutes" over a "minimum interval . . . [of] two weeks." Ex. 1012 (Rau 2000), 5, 8. It reports administering D2E7 subcutaneously (which takes only seconds; Ex. 1019 (CDER/CBER Review), 13) on a ***weekly*** interval for both the DE004 and DE007 studies. *Id.* A POSA would not reasonably have understood Rau 2000 to suggest administering D2E7 subcutaneously on an every-other-week interval as this interpretation requires ignoring the disclosure in Rau 2000 of how D2E7 was actually administered.

Petitioner nevertheless alleges that this statement would have suggested to a POSA "that D2E7 concentrations would have remained high enough to achieve clinical results over two weeks." Pet. 28. But Petitioner's half-life argument is at odds with what was known in the art. 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. 2029, 6);
- 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. Hartmut 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).

Petitioner nevertheless maintains that half-life would provide a POSA with the necessary motivation to dose once every-other-week, twice alleging that "even Dr. Mould admitted that half-life 'is of course a necessary parameter in any model.'" Pet. 38 (quoting Ex. 2003 (Mould Decl.) ¶ 78); *see also id*. at 15 n.8. This selective quote misrepresents her declaration, as Dr. Mould actually emphasized that half-life correlated ***poorly*** with dosing interval:

> The fact that ***half-life correlates so poorly with dosing interval*** for these biological therapeutics is *not* to say that half-life is irrelevant; it is of course a necessary parameter in any model. ***It just cannot be used to reasonably predict whether a dosing interval will be safe and efficacious, which are the two fundamental criteria that drive the ultimate selection of dosing regimen***, including dose amount, dosing approach (whether flat, weight-based, surface area-based, tiered), route of administration, and dosing schedule.

Ex. 2003 (Mould Decl.) ¶ 78 (bold-italic emphases added).

To support its half-life argument (Pet. 38-39), Petitioner also cites to its declarant Dr. Jusko, who states that "in the late 1990s, text books taught that half-

life is an important factor in designing multiple dosing regimens" (Ex. 1004 (Jusko Decl.) ¶ 18). The issue is not whether a POSA would have viewed half-life as "important," but whether a POSA would have been motivated to pursue a 40 mg, every-other-week dosing regimen based on the minimal pharmacokinetic information available in the prior art.

As both the textbook cited by Dr. Jusko and Dr. Mould confirm, 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, 70; *see* Ex. 1027 (Shargel & Yu), 7-8 (emphasizing the importance of C_{min}, $C_{max,}$, and AUC in determining drug efficacy and safety when developing multiple-dose regimens). Moreover, in this case, Dr. Jusko relies on half-life values determined following a ***single***, intravenous administration of D2E7 even though the claims require multiple doses on an every-other-week interval. Ex. 1004 (Jusko Decl.) ¶ 20. This is inconsistent with Dr. Jusko's published recommendation that multiple-dose pharmacokinetic experiments are necessary for therapeutic drugs intended to be administered in multiple doses. Ex. 2037 (Jusko), 7 ("***[m]ultiple-dose*** and steady-state [pharmacokinetic] experiments ***are necessary*** if this is the mode of therapeutic use of the drug" (emphases added)).

Both the Federal Circuit and the Board have recognized the unpredictability of dosing with inadequate pharmacokinetic information. In *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 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 1063, 1070 (Fed. Cir. 2012) (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 Pharm., Inc. v. Actavis S. Atl., LLC*, 36 F. Supp. 3d 475, 487, 506 (D. Del. 2014) (holding non-obviousness claims that recited two ranges of components where efficacy could not be predicted "based on in vivo or in vitro pharmacokinetic studies when the dose-effect relationship was unknown"), *aff'd*, *Avanir Pharm. Inc. v. Par Pharm., Inc.*, 612 F. App'x 613 (Fed. Cir. 2015). Similarly, 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 D2E7 pharmacokinetic information available (Ex. 1012 (Rau 2000), 8), and there was no known correlation between half-life and dosing interval for therapeutic antibodies. As such, the evidence regarding

D2E7's half-life does not carry Petitioner's burden of providing a motivation to modify van de Putte's 20 mg weekly dose into a 40 mg every-other-week dose.

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

Even if the available intravenous terminal half-life estimate from Rau 2000 would have had predictive value, it would not have pointed to a 40 mg every-other-week schedule where the dose is administered subcutaneously.

According to Petitioner, "the approximate amount of D2E7 circulating in the body two weeks after administering a 40 mg dose would have been roughly one half of that dose (*i.e.*, approximately 20 mg)." Pet. 28. Petitioner is simply wrong in asserting that roughly 20 mg would be circulating two weeks after subcutaneously administering a 40 mg dose—it would be significantly less. Petitioner ignores that the delivery of a drug subcutaneously was known to cause a variable, frequently significant reduction in the amount of drug absorbed into the bloodstream. Ex. 2018 (Porter), 8-9; 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% for D2E7).

Petitioner's claim that the pharmacokinetics of D2E7 are supposedly "linear" (Pet. at 29-30; Ex. 1004 (Jusko Decl.) ¶ 24) misses the point. The study

upon which Petitioner and Dr. Jusko rely involved a single, ***intravenous*** administration (Ex. 1004 (Jusko Decl.) ¶ 24 n.7; Pet. 30 (referencing an observation in Kempeni 1999 concerning AUC from the DE001 study)), and therefore reveals nothing about how much D2E7 would be available in the blood after ***subcutaneous*** administration where an unpredictable amount of drug loss is expected. *See* Ex. 2017 (Rowland), 13, 29, 31; Ex. 2003 (Mould Decl.) ¶¶ 40, 82-83; Ex. 2018 (Porter), 9-11. Moreover, total systemic drug exposure amounts (AUC) were not reported in Kempeni 1999 nor any other prior art reference, nor were other critical pharmacokinetic parameters such as C_{max} and C_{min}. Ex. 1011 (Kempeni 1999), 4; Ex. 2003 (Mould Decl.) ¶¶ 64, 68; *see also* Ex. 1027 (Shargel & Yu), 7-8. It is undisputed that none of this information was available in the prior art.[2]

Subsequent studies confirm the error in Petitioner's logic. In Petitioner's oversimplified construct, dosing 80 mg of D2E7 once per month should be equivalent to dosing 40 mg every-other-week (or 20 mg weekly). But in an actual

[2] Petitioner contends it "relies only on van de Putte 2000 and Rau 2000 in its proposed ground" (Pet. 8), but relies exclusively on Kempeni 1999 to support this argument concerning purportedly linear pharmacokinetics. *See* Pet. 30-31; Ex. 1004 (Jusko Decl.) ¶ 24 n.7; Ex. 1003 (Weisman Decl.) ¶ 26.

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 (emphases added).

5. A POSA would have faced innumerable possible combinations for a D2E7 dosing regimen

Assuming that a POSA would have focused on a fixed, subcutaneous dosing regimen, Petitioner contends that "40 mg every 13-15 days to treat RA would have been obvious to try in view of the finite number of fixed dosing options (20, 40, and 80 mg) employed in van de Putte 2000 . . . ." Pet. 31. But the obvious-to-try test described in *KSR* requires "a design need or market pressure to solve a problem," a "good reason to pursue the known options," a "finite" number of options, and "predictable solutions" expected to be successful. *KSR*, 550 U.S. at 421.

Based on the D2E7 clinical trials in the prior art, which tested different doses, routes of administration, and dosing frequencies (Ex. 1012 (Rau 2000); Ex. 1014 (Weisman 2000)), a POSA would have been faced with innumerable possible combinations in a notoriously unpredictable field. Even putting aside the teachings in favor of intravenous, weight-based dosing discussed above, the amount of the dose and the dosing interval alone present an almost unlimited range

of possibilities, undermining Petitioner's obvious-to-try argument. *See In re Cyclobenzaprine*, 676 F.3d at 1072-73 ("in the absence of a known PK/PD relationship," a POSA "would not have encountered finite, small, or easily traversed options in developing a therapeutically effective [drug]").

Moreover, Petitioner and its declarants provide ***no contemporaneous evidence*** supporting a design need or market pressure to solve a problem presented by the prior art. *See* Pet. 31; Ex. 1003 (Weisman Decl.) ¶¶ 41-44. Such evidence is required. 37 C.F.R. § 42.65(a); *Commerce Bancshares, Inc. v. Intellectual Ventures II LLC*, IPR2014-00793, Paper 7, 13-14 (Dec. 1, 2014) (rejecting obvious-to-try argument where expert did "not refer to evidence explaining how many solutions were available, what those solutions were, or specifically why a skilled artisan would have chosen the solutions disclosed in [the cited references] to solve the relevant problem"); *Coalition for Affordable Drugs XI LLC v. Insys Pharma, Inc*., IPR2015-01799, Paper 9, 11 (Mar. 10, 2016) (declining to institute review "[b]ecause the Petition rests on opinion testimony [that patient discomfort was a concern in the art] untethered to adequate objective proof—for example, ***disclosures in the art*** . . . .") (emphasis added). There was no clamor for an every-other-week dose or a fixed dose of 40 mg. The "market pressure" was to develop a safe and efficacious dosing regimen for D2E7. Ex. 2001 (Pope Decl.) ¶ 44; Ex. 2025 (Wolfe), 3.

Instead of citing actual evidence, Petitioner relies on *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014), for the general proposition that "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance." Pet. 2; *see also* Pet. 31-32. But Petitioner crops the actual case quote, which concludes the preceding sentence by clarifying that the identified problem of patient non-compliance stems "from the inconvenience of oral bisphosphonate regimens." *Hoffman-LaRoche*, 748 F.3d at 1329. No analogous evidence is of record for RA or anti-TNFα biologics, and, unlike the oral bisphosphonates at issue in *Hoffman-LaRoche*, *id.* at 1331, there was no approved D2E7 dose at all.

D. Petitioner Fails to Establish that a POSA Would Have Reasonably Expected Success

A mere motivation to try without a corresponding reasonable expectation of success is not sufficient to show obviousness. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Petitioner fails to establish that a POSA would have had a reasonable expectation of success in applying the teachings of van de Putte 2000 and Rau 2000 to achieve the claimed invention. Petitioner's one cursory statement concerning expectation of success focuses narrowly on specific claim terms rather than each claim as a whole in violation of Section 103 of the Patent Act and well-established precedent. The Petition is also deficient because Petitioner's statements are conclusory in nature,

lacking "articulated reasoning with rational underpinnings to support its assertion." *Torrent Pharm. Ltd. v. Novartis AG & Mitsubishi Pharma Corp.*, IPR2014-00784, Paper 11, 12 (Dec. 1, 2014).

Petitioner provides only one basis for expecting success from the combination of van de Putte 2000 and Rau 2000: at page 31, Petitioner alleges a reasonable expectation of success for "administering 40 mg every 13-15 days to treat RA" based on a POSA's "understanding of D2E7's properties, including its long half-life." Pet. 31.

Petitioner has failed to demonstrate, or even allege, that a POSA would have reasonably expected that 40 mg D2E7 administered every-other-week subcutaneously could be used to successfully treat RA based on the van de Putte 2000 abstract in view of Rau 2000. The statement at page 31 does not address the claim requirement of "administering subcutaneously," which is addressed in a different subsection of the Petition. Ex. 1001 ('135 patent), 45:12-17. Petitioner's failure to conduct a proper obviousness analysis of the claims ***as a whole*** warrants denial of institution. *Grain Processing Corp. v. Am. Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988); *see also Apple Inc. v. Memory Integrity, LLC*, IPR2015-00159, Paper 12, 27 (May 11, 2015) (finding obviousness challenge deficient where petition did not address reasonable expectation of success in combining the cited references to reach the claimed invention).

Petitioner's expectation of success argument is also conclusory, as the cursory reference at page 31 fails to articulate how or why a POSA would have had a reasonable expectation of success in combining the van de Putte 2000 abstract and Rau 2000 to achieve the claimed invention. Petitioner's statement ignores both the complexity of subcutaneous administration, addressed in § IV.A above, and the lack of correlation between half-life and dosing interval, addressed in § IV.C.3 above. Such conclusory assertions cannot establish a reasonable expectation of success. *Torrent Pharm.*, IPR2014-00784, Paper 11, 13 (petitioner "fails to explain adequately, or provide specific evidence to support," why a POSA would have combined or had a reasonable expectation of success); *see also 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).

In contrast to Petitioner's conclusory assertions, the evidence shows that as of June 2001, a POSA would ***not*** have had a reasonable expectation of success at least because:

- there was no known correlation between half-life and dosing interval for therapeutic antibodies (*see* § IV.C.3 above);

- a POSA would have had both safety and efficacy concerns about administering 40 mg every-other-week, including in particular the formation of anti-drug antibodies (*see* §§ IV.A, IV.C.2 above);
- all of the D2E7 clinical trials except DE007 utilized weight-based dosing, not a fixed dose, as did the only then-approved therapeutic antibody to treat RA (REMICADE®) (*see* § IV.A above); and
- every D2E7 trial that had tested 0.5 mg/kg (which, according to Petitioner, equates to a 40 mg fixed dose) reported that patients needed to be up-dosed (*see* § IV.C.1 above).

E. The Alleged "Admissions" Are Irrelevant to Patentability

Petitioner asserts that Patent Owner "admissions" confirm the obviousness of administering 40 mg subcutaneously once every-other-week. Pet. 29. Like the cropped statement from Dr. Mould addressed in § IV.C.3 above, when viewed in context, these purported "admissions" are anything but.

For example, Petitioner suggests that Patent Owner conceded during a European opposition proceeding that it would have been obvious to move from 20 mg weekly dosing to 40 mg every-other-week. Pet. 29. Petitioner crops the actual statement, omitting the emphasized portion below:

> Over time, patients treated in accordance with the claimed invention with [a] 40mg flat dose, subcutaneously biweekly, receive the same amount of D2E7 as those treated in the DE007 trial with [a] 20 mg flat

> dose weekly. (***Note that we speak here of the amounts received by the patients. Except for the moments where the respective concentrations cross, for almost all of the time patients treated in the two different ways, 20 mg weekly versus 40 mg biweekly, have different amounts of bioavailable D2E7 remaining in their system.***)

Ex. 1023 (Applicant's Remarks), 45 (emphasis added). Patent Owner then explained that "[the pharmacokinetic profile] is ***completely different*** for 20 mg administered every week as compared to 40 mg administered biweekly." *Id.* at 47 (emphasis added). Read in context, it is clear that the alleged admission simply notes that over time, patients treated subcutaneously with a 40 mg every-other-week dose receive the same amount of drug as those treated subcutaneously with a 20 mg weekly dose. It is not an admission that anything else associated with the two regimens is the same, and it certainly is not an admission that it would have been obvious to move from 20 mg weekly to 40 mg every-other-week.

Petitioner also quotes from a table submitted to the FDA addressing the risk of tuberculosis and other opportunistic infections. Pet. 29; Ex. 1016 (Clinical Review), 2. To make comparisons across different clinical trials, Patent Owner "assumed" that every-other-week doses were "similar to one-half the same dose given weekly." *Id.* This was not an admission about the comparability of these doses, but rather a post-hoc assumption made for the limited purpose of comparing infection rates reported in different clinical trials involving different dosing

regimens. None of the statements attributed to Patent Owner is an "admission" that contradicts any statement made during prosecution. Nor do these post-filing date statements suggest that it would have been obvious to select a 40 mg, every-other-week, subcutaneous D2E7 dosing regimen in view of the prior art.[3]

F. Secondary Considerations Support the Non-obviousness of the Challenged Claims

1. Commercial success

Petitioner does not challenge HUMIRA®'s indisputable commercial success. 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.

Petitioner's suggestion that Patent Owner failed to demonstrate a nexus between the claimed invention and HUMIRA®'s commercial success is baseless.

[3] In addition, the statements by FDA (Ex. 1017) and the European Medicines Agency (Ex. 1018) cited by Petitioner (Pet. 29) are neither prior art nor admissions by Patent Owner.

During prosecution, Patent Owner demonstrated that the "combination of every other week dosing with subcutaneous, flat unit dosage forms" was an important feature that contributed to its success. Ex. 2004 (Williams Decl.) ¶ 28. The Examiner agreed. *See* Ex. 1002 (File History), 1586. 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. To the extent Petitioner contends that the claimed invention must be the only basis for commercial success, it is wrong. *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991).

Petitioner is also mistaken in relying on *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005), for the suggestion that commercial success has no probative value where there is another patent or regulatory barriers blocking market entry. In *Merck*, the claimed

inventions were modifications of already marketed dosages. 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.

Petitioner has not 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 (File History), 1586), which the Board should adopt. *See Omron Oilfield & Marine, Inc. v. MD/Totco*, IPR2013-00265, Paper 11, 12-13 (Oct. 31, 2013).

2. Unexpected results

Petitioner challenges the evidence of unexpected results furnished during prosecution. Pet. 45-49. Although Patent Owner disagrees with Petitioner's assertions, they are not addressed in this Preliminary Response because unexpected results were not relied upon by the Examiner in issuing the '135 patent and because Petitioner has failed to demonstrate a reasonable likelihood that it will prevail.

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." Section 325(d) serves to protect "the interests of patent owners, who seek to avoid harassment and enjoy quiet title to their rights." *Neil Ziegman, N.P.Z., Inc. v. Stephens*, IPR2015-01860, Paper 11, 12-13 (Feb. 24, 2016).

Here, Petitioner makes the same arguments that are presented by Coherus. *See* Ex. 2033 (Coherus Pet.). The only ground in BI's Petition (van de Putte 2000 combined with Rau 2000) discusses the same clinical trials and presents the same issues as those raised by Coherus. Because BI's Petition is wholly redundant to Coherus's petition, it should be denied. *Schrader-Bridgeport Int'l v. Wasica Fin. GMBH*, IPR2015-00272, Paper 17, 6 (June 1, 2015).

Moreover, like Coherus, the prior art BI relies on and the arguments it makes were thoroughly considered by the Examiner during prosecution. In these circumstances, the Board has repeatedly 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"). Indeed, even if the references relied on by the Petitioner were not identical to those considered by the Office, institution will be declined if the references presented in the Petition advance the same arguments considered during examination. *Ziegman*, IPR2015-01860, Paper 11, 13.

Application of § 325(d) to deny institution is particularly appropriate because Petitioner does not present persuasive new evidence to supplement the record that was before the Office during examination. *Integrated Global Concepts*, 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). 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 references 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. 32-33, 45-46; Ex. 1003

(Weisman Decl.) ¶¶ 41, 49-50. 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 2000 as equally efficacious. Pet. 22-27, 33-34; Ex. 1003 (Weisman Decl.) ¶¶ 28, 30, 39. The Examiner thoroughly considered this argument. Ex. 1002, 1094, 1535, 1584-1586.
- Petitioner contends that every-other-week dosing was established in the art and would have been perceived as advantageous. Pet. 31-33; Ex. 1003 (Weisman Decl.) ¶¶ 49-50. 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. 27-28, 30-31; Ex. 1003 (Weisman Decl.) ¶ 43; Ex. 1004 (Jusko Decl.) ¶¶ 19-20. 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. 22, 26; Ex. 1003 (Weisman Decl.) ¶¶ 34, 48. 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. 50-51. 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); 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.

In short, the Petitioner is simply asking the Board to "second-guess" the Office's extensively considered decision on the same issues. This request should be denied.

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: April 8, 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 the exhibits cited therein were served electronically via email on April 8, 2016, in their entirety on the following:

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