UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD,
Patent Owner.

Case IPR2017-01824
Patent No. 9,512,216

PATENT OWNER'S PRELIMINARY RESPONSE

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PATENT OWNER'S EXHIBIT LIST

EXHIBIT	DESCRIPTION
2001	Fitzpatrick's Dermatology in General Medicine, 407-444 (6th ed. 2003)
2002	Christopher S. Carlin, et al., *A 50% Reduction in the Psoriasis Area and Severity Index (PASI 50) is a Clinically Significant Endpoint in the Assessment of Psoriasis*, J. AM. ACAD. DERMATOLOGY, 859, 859-66 (June 2004)
2003	Craig L. Leonardi, M.D. et al., *Etanercept as Monotherapy in Patients with Psoriasis*, 349 NEW ENG. J. MED. 2014, 2014-22 (2003)
2004	S. R. Feldman & G. G. Krueger, *Psoriasis Assessment Tools in Clinical Trials*, 64 ANN RHEUM DIS (Suppl II), ii65, ii65-ii68 (2005)
2005	Miriam Richter Cohen et al., *Baseline Relationships Between Psoriasis and Psoriatic Arthritis: Analysis of 221 Patients with Active Psoriatic Arthritis*, 26 J. RHEUMATOLOGY, 1752, 1752-56 (1999)
2006	AMEVIVE® (alefacept) Package Insert (Feb. 2003)
2007	RAPTIVA™ (efalizumab) Package Insert (Oct. 2003)
2008	Noemi Busquets-Pérez et al., *Relationship Between Psoriatic Arthritis and Moderate-Severe Psoriasis: Analysis of a Series of 166 Psoriatic Arthritis Patients Selected from a Hospital Population*, 31 CLIN. RHEUMATOLOGY 139, 139-43 (2012)
2009	Alexa B. Kimball et al., *Approved Adalimumab Dosing Regimen Associated With Greater Efficacy and Lower Cost per Responder Compared With 40-mg Every Other Week Dosing Without Initial 80-mg Dose: Analysis of Outcomes From Adalimumab Psoriasis Clinical Trial Database*, Presented at the 20th Congress of the European Academy of Dermatology and Venereology, Lisbon, Portugal (Oct. 20-24, 2011)
2010	Chris Fellner, *More Biologic Therapies Expected To Treat Advanced Plaque Psoriasis*, 41 P&T 388, 388-90 (2016)
2011	Information Disclosure Statement dated August 12, 2016, submitted during prosecution of U.S. Application No. 15/173,191 (U.S. Patent No. 9,512,216)

EXHIBIT	DESCRIPTION
2012	Dror Mevorach & Stephen A. Paget, *Rheumatoid Arthritis*, *in* Manual of Rheumatology and Outpatient Orthopedic Disorders: Diagnosis and Therapy 192-229 (4th ed. 2000)
2013	W. Wang et al., *Monoclonal Antibody Pharmacokinetics and Pharmacodynamics*, 84 CLINICAL PHARMACOLOGY & THERAPEUTICS 548, 548-58 (2008)
2014	Applicant Arguments/Remarks Made in an Amendment dated January 12, 2015, submitted during prosecution of U.S. Application No. 14/510,821 (U.S. Patent No. 8,986,693)

I. INTRODUCTION

U.S. Patent No. 9,512,216 ("the '216 patent") reflects the innovative work of AbbVie scientists to develop a novel method of treating moderate-to-severe chronic plaque psoriasis with the biologic drug HUMIRA® (adalimumab). The claimed dosing regimen uses an initial dose of 80 mg of adalimumab followed by 40 mg of adalimumab every other week, beginning one week after the initial dose. Surprisingly, this regimen provides greater long-term improvements in treating moderate-to-severe chronic plaque psoriasis than a 40 mg every-other-week adalimumab regimen *without* an 80 mg initial dose.

As of the priority date, no clinical evaluation of adalimumab in psoriasis patients had been published, and the drug was only approved to treat a materially different disease (rheumatoid arthritis). Further, *none* of the biologics or small molecules approved to treat psoriasis and *none* of the experimental anti-TNFα biologics tested for psoriasis used an initial dose of drug that was greater than subsequent doses. The claimed psoriasis treatment method is thus strikingly different from all of these earlier regimens.

In challenging the '216 patent claims, Petitioner nevertheless asserts that a person of ordinary skill in the art ("POSA") would have found it obvious to treat moderate-to-severe chronic plaque psoriasis using the approved dosing regimen of HUMIRA® for rheumatoid arthritis (40 mg of adalimumab every other week) after

modifying that regimen (1) to add an 80 mg initial dose of adalimumab; and (2) to wait just one week before starting the 40 mg every-other-week regimen. Petitioner relies on *five* references to piece together this argument, without addressing the unexpected results provided by the invention.

The Board should deny institution for three principal reasons:

First, Petitioner fails to establish that the asserted references disclose all of the claim elements, expressly or inherently. The cited references, for example, do not suggest administering an 80 mg initial dose of adalimumab *one week* before starting a 40 mg every-other-week regimen. Further, for claims 1-8, Petitioner fails to establish that the cited art discloses or suggests the claimed Psoriasis Area and Severity Index (PASI) 75 efficacy requirement at week 12 of treatment. Petitioner's inability to identify all of the claim elements in the five asserted references renders its obviousness theory legally deficient.

Second, even accepting Petitioner's contention that a POSA would have started with the approved dosing regimen for HUMIRA® for rheumatoid arthritis, the asserted references provide no reason or motivation to modify that regimen by adding an *80 mg initial dose* of adalimumab just *one week* before starting the 40 mg every-other-week regimen. Nothing in the cited references, or Petitioner's conclusory expert testimony, supports these proposed modifications of the HUMIRA® rheumatoid arthritis dosing regimen. Moreover, Petitioner fails to

address the unexpectedly superior long-term efficacy achieved by the claimed dosing regimen.

Third, Petitioner fails to establish that three of the references cited in its five-reference obviousness combination are prior art because it does not show they were publicly accessible before the critical date. This alone defeats the Petition.

For the reasons detailed below, Petitioner has failed to meet its burden of showing a reasonable likelihood that it will prevail as to any challenged claim. The Board should therefore deny institution of the Petition.

II. BACKGROUND

A. Chronic Plaque Psoriasis

Psoriasis is an immunological skin disorder with a range of clinical manifestations. (Ex. 1003, 1.)[1] The appearance of psoriatic skin lesions varies considerably. (Ex. 2001, 22.) They may appear as thick, circular red patches covered with silvery scales (plaque psoriasis), eruptions of small dot-like lesions (guttate psoriasis), or white pustules surrounded by red skin (pustular psoriasis). (*Id.*, 24-26.) Psoriasis is a chronic condition that often varies in severity. (Ex. 1003,

[1] Citations refer to the original page numbering of each exhibit except for references that have been stamped with page numbers. Citations to such references refer to the stamped-on page numbers.

14.) The extent of skin involvement can range from discrete, localized areas to generalized body involvement. (*Id*., 2.) Today, as in 2004, the pathogenesis of the disease is not completely understood, as several factors, including genetic, immune, and environmental elements, play a role. (Ex. 2001, 27-33; Ex. 1003, 5-9, 16, 248.)

Chronic plaque psoriasis is the most common form of the disease. (Ex. 1008, 21.) It is characterized by red, scaly lesions that may range in size from small coin-sized plaques to larger ones that may coalesce to cover large areas. (*Id*.; Ex. 1003, 10.) The Physician's Global Assessment categorizes "moderate to severe" psoriasis based on "marked plaque elevation, scaling, and/or erythema." (Ex. 1001, 41:65-66.) The severity of psoriasis has also been classified on the basis of percentage of body surface area affected: less than 5% body surface area for mild, 5-15% for moderate, and 15-20% for severe. (Ex. 1003, 5.) Other factors, such as patient quality of life and location of the disease on the body, are also considered in determining severity. (*Id*.) Approximately 20-25% of psoriasis patients have moderate-to-severe chronic plaque psoriasis, which is physically and psychologically debilitating and often affects daily activities and ability to work. (Ex. 1036, 1842; Ex. 1003, 19, 4; Ex. 1053, 700.)

The Psoriasis Area and Severity Index (PASI) is the most widely used objective method to assess psoriasis severity in clinical trials. (Ex. 2004, ii65.) The

score is a multi-factorial calculation generated by examining four different body regions and assigning an area score and a severity score for each. (Ex. 1036, 1843; Ex. 1001, 28:24-29.) The term "PASI 75" is shorthand for a 75% reduction of the PASI score from start of treatment, and PASI 75 was considered the treatment goal for many clinical trials. (Ex. 2004, ii65.) It is a difficult target to achieve, with some practitioners in the field arguing that the U.S. Food and Drug Administration (FDA) should instead use a lower PASI 50 score as a clinical endpoint. (Ex. 2002, 860.)

B. Psoriatic Arthritis

Psoriatic arthritis (PsA) is an autoimmune inflammatory disease that affects the ligaments, tendons, fascia, and spinal or peripheral joints. (Ex. 2001, 42.) In 2003, about 10% of patients with established psoriasis were diagnosed with PsA. (*Id*.) The relationship between the skin disease and joint disease is unclear, and they often appear separately. (*Id.*; Ex. 1009, 298.) Further, the relationship between the severity of psoriasis and PsA has not been fully established. (Ex. 2005, 1752; Ex. 2008, 139.) In one study, only about 31% of patients with PsA also had moderate-to-severe psoriasis. (Ex. 2008, 141.) Other studies have noted that PsA patients had "generally mild skin disease" and that "clinical patterns of psoriasis were not significantly different from the general population with psoriasis . . . ." (Ex. 2005, 1755.)

PsA can precede or follow psoriasis by many years. (Ex. 2001, 45; Ex. 1009, 298.) Further, remissions and exacerbations of PsA, a joint disease, do not correlate with similar changes in psoriasis, a skin disease. (Ex. 2001, 45.) Like psoriasis, PsA's cause and pathogenesis are unknown. (*Id.*, 44; Ex. 1025, 1071.)

C. Prior Art Treatments Investigated for Psoriasis

Treatments for plaque psoriasis were mostly "developed empirically . . . as with all other diseases of unknown cause." (*Id*., 36.) Developing treatments for psoriasis was unpredictable, as shown by the great variety of dosing regimens used for different active agents. (*Id*., 36-40.)

Prior art treatments included topical medications, phototherapeutic therapies, and systemic drugs. (*Id.*; Ex. 1003, 18.) Topical therapies were of limited value because they were impractical for patients with high affected body surface area and ineffective at preventing relapse of the disease. (Ex. 1003, 17-18, 21.) Systemic treatments were typically used for moderate-to-severe chronic plaque psoriasis (when topical treatments were ineffective or impractical). (*Id*., 18; Ex. 2001, 37-40.)

1. No approved non-biologic systemic treatment for plaque psoriasis used an initial dose greater than the treatment dose

In 2004, approved non-biologic systemic treatments for chronic plaque psoriasis included methotrexate, cyclosporine, and retinoids. (Ex. 2001, 38-39.)

The table below summarizes the dosing regimens for these treatments. Notably, *none* of the approved non-biologic systemic treatments for psoriasis used an initial dose greater than the treatment dose despite the known severity of the disease and negative impact on quality of life. (Ex. 1003, 4 (Table 3).) Indeed, the dosing regimens for these agents started with a *lower* dose and increased the dose, as needed, over time.

Non-Biologic Systemic Psoriasis Treatments	
Treatment	**Dosing Regimen**
Methotrexate	10-25 mg per week. (Ex. 2001, 38; Ex. 1024, 10.) The dose may be increased to achieve optimal clinical response; 30 mg per week should not ordinarily be exceeded. (Ex. 1024, 10.)
Cyclosporine	2.5-3 mg/kg per day divided into two daily doses. This can be increased up to 5 mg/kg per day. (Ex. 2001, 38-39.)
Retinoids (Acitretin)	0.3-0.5 mg/kg per day initially, which is increased at 3- to 4-week intervals to 0.75 mg/kg per day. (*Id.*, 39.)

2. No approved biologic treatment for plaque psoriasis used an initial dose greater than the treatment dose

Before the April 9, 2004 priority date, alefacept and efalizumab were the only FDA-approved biologic treatments for chronic plaque psoriasis. (*See* Ex. 2006; Ex. 2007.) The table below summarizes the dosing regimens for these treatments. Again, neither treatment regimen used an initial dose that was higher

than subsequent doses. Indeed, like the non-biologic treatments, the initial dose for efalizumab was *lower* than the subsequent doses.

FDA-Approved Biologic Treatments for Psoriasis	
Treatment	**Dosing Regimen**
Amevive (Alefacept) (anti-CD-4 fusion protein)	7.5 mg weekly for 12 weeks via intravenous bolus or 15 mg weekly for 12 weeks via intramuscular injection. (Ex. 2006, 11-12.)
Raptiva (Efalizumab) (anti-CD11a)	0.7 mg/kg as a single dose, then 1 mg/kg weekly via subcutaneous injection. (Ex. 2007, 3.)

3. No experimental anti-TNFα biologic used an initial dose greater than the treatment dose

Before the April 9, 2004 priority date, the anti-TNFα biologics infliximab and etanercept were under investigation for treatment of psoriasis but had not yet been approved by the FDA. (Ex. 1003, 239.) Infliximab, which had been approved for the treatment of rheumatoid arthritis and Crohn's disease, is a chimeric anti-TNFα monoclonal antibody. (Ex. 1027, 1-2.) It was administered via intravenous infusion with a weight-based dosing regimen. (*Id*.) During trials for moderate-to-severe chronic plaque psoriasis, infliximab was dosed at 5 or 10 mg/kg at weeks 0, 2, and 6. (Ex. 1003, 250.) The initial dose of infliximab did not exceed subsequent doses. (*Id*.)

Etanercept, which in 2004 had been approved for the treatment of rheumatoid arthritis and PsA, is a fusion protein of two TNFα receptor p75

extracellular domains with one IgG1 Fc region. (Ex. 1006, 1, 12.) During the PsA trials, etanercept was administered via subcutaneous injection at a fixed dose of 25 mg twice weekly. (Ex. 1009, 300-01.) For the moderate-to-severe chronic plaque psoriasis trials, etanercept was administered at 25 mg weekly, 25 mg twice weekly, or 50 mg twice weekly. (Ex. 2003, 2014.) The higher 50 mg twice weekly dose achieved better efficacy than the other regimens. (*Id.*, 2021.)

The following table summarizes the dosing regimens tested for these biologics.

Anti-TNFα Biologics Investigated for Psoriasis	
Treatment	**Dosing Regimen**
Remicade (Infliximab)	5 mg/kg at weeks 0, 2, and 6 by intravenous infusion; or 10 mg/kg at weeks 0, 2, and 6 by intravenous infusion. (Ex. 1036, 1843.)
Enbrel (Etanercept)	25 mg weekly subcutaneously; 25 mg twice weekly subcutaneously; or 50 mg twice weekly subcutaneously. (Ex. 2003, 2014.)

Petitioner and its declarant, Dr. Helfgott, also provide tables purporting to compare prior art rheumatoid arthritis and plaque psoriasis dosing regimens. (Pet., 28 (Table 3); Ex. 1002, 31-35 (Tables 1-3).) But their tables conflate moderate-to-severe chronic plaque psoriasis and PsA, and include other significant errors. For example, Petitioner cites Marzo-Ortega as allegedly showing the psoriasis dosing

regimen for infliximab (Pet., 28 (Table 3) (citing Ex. 1060, 1)), but this reference only discusses the use of infliximab for PsA patients without disclosing whether those patients had moderate-to-severe chronic plaque psoriasis (Ex. 1060, 1).

Regardless, *none* of the "psoriasis" dosing regimens Petitioner identifies include an initial dose greater than the subsequent doses. (Pet., 28 (Table 3); Ex. 1002, 31-35 (Tables 1-3).)

III. THE INVENTION OF THE '216 PATENT

A. The Patent Claims a Novel Dosing Regimen with Unexpected Efficacy for Treating Moderate-to-Severe Chronic Plaque Psoriasis

The '216 patent discloses and claims novel methods for treating moderate-to-severe chronic plaque psoriasis. These methods comprise subcutaneously administering to a patient an initial dose of 80 mg of adalimumab, followed by 40 mg of adalimumab every other week, starting one week after the initial dose. (*See, e.g.*, Ex. 1001, 57:36-43.)

The '216 patent specification discloses a study discussing this multiple-variable dose treatment, where the initial dose was larger than subsequent doses. (*Id*., 40:44-42:58.) In this study, one of the treatment groups received an initial dose of 80 mg of adalimumab at week 0, followed by 40 mg every other week starting at week 1 and continuing through week 11. (*Id*., 41:17-45.) The treatment was administered subcutaneously with pre-filled syringes. (*Id*., 41:26-28.) At week

12, 53% of patients achieved PASI 75, which was a significant improvement compared to the placebo group. (*Id*., 42:5-9, Fig. 5.) Further, patients continued to show improvements through week 24. (*Id*., 42:44-46, Figs. 7-8.)

Remarkably, this regimen also showed significantly greater long-term improvement in treating moderate-to-severe chronic plaque psoriasis than a 40 mg every-other-week regimen without an 80 mg initial dose. (*See* Ex. 2009, 1.) Specifically, analysis of data from multiple clinical trials showed that the PASI 75 rates for patients who received the 80 mg initial dose were statistically superior at both 12 weeks and 24 weeks compared to those who did not. (*Id*.) As the study authors stated, "[a]dalimumab treatment with [the] approved dosing regimen is associated with *significantly greater improvement in psoriasis severity symptoms* compared with adalimumab treatment of 40 mg every other week dosing without [the] initial 80 mg dose." (*Id*. (emphasis added).)

This invention is reflected in the claims of the '216 patent. Independent claims 1 and 9 recite:

> 1. A method for treating moderate to severe chronic plaque psoriasis, comprising subcutaneously administering to an adult patient having moderate to severe chronic plaque psoriasis an initial dose of 80 mg of adalimumab, followed by 40 mg of adalimumab every other week starting one week after said first dosing, wherein the patient achieves at least Psoriasis Area and Severity Index (PASI) 75 response at week 12 of the treatment.

> 9. A method for treating moderate to severe chronic plaque psoriasis, comprising subcutaneously administering to an adult patient having moderate to severe chronic plaque psoriasis an initial dose of 80 mg of adalimumab, followed by 40 mg of adalimumab every other week starting one week after said first dosing.

(Ex. 1001, 57:36-43, 58:35-40.)

The claims cover the approved method of treating patients with moderate-to-severe chronic plaque psoriasis using HUMIRA® (adalimumab). Tens of thousands of patients have benefitted from the claimed treatment methods. (*See* Ex. 2010, 388.)

B. The Person of Ordinary Skill in the Art

Petitioner provides definitions for two POSAs: one for developing a treatment for plaque psoriasis and another for developing a dosing regimen. (Pet., 17-18.) Petitioner defines a POSA developing a treatment as "an M.D. with at least 3 years' experience post-residency treating patients with psoriasis." (*Id*., 17.) And it defines a POSA developing a dosing regimen as "a Ph.D. in pharmacology, pharmacokinetics, or a related field and at least 3 years of experience working on the pharmacokinetics/pharmacodynamics of biologic drugs." (*Id*., 17-18.)

Patent Owner contests Petitioner's definition of "a POSA developing a treatment" because the '216 patent claims methods of treating moderate-to-severe plaque psoriasis, which predominately manifests itself on the skin and thus would generally have been treated not just by an M.D., but specifically by a

dermatologist.[2] (*See* Ex. 1003, 14 (Table 6), 20-24.) Indeed, the psoriasis references relied on by Petitioner characterize the treating physician as a "dermatologist." (*Id.*, 14, 20.) Weinstein, for example, classifies different treatment agents based on what percentage of "dermatologists" use that agent. (*Id.*, 20 (Table 12); *see also* Ex. 1008 (Textbook of Psoriasis), 233, 236, 249 (stating that dermatologists prescribe and determine the dosage of drugs for treating psoriasis patients).) For the reasons set forth below, the Board should deny institution of the Petition regardless of the definition it selects for the POSA.

C. Claim Construction

For the limited purposes of this preliminary response, Patent Owner does not contest Petitioner's assertion that no claim term requires a special meaning.

[2] Because Petitioner's expert, Dr. Helfgott, is a rheumatologist, not a dermatologist, his testimony should be given little weight. *See Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007) (where claimed invention related to a method for treating ear infections, the POSA would be someone with experience with ear treatments, not simply a general practitioner). While a rheumatologist might have treated PsA, it is separate condition from plaque psoriasis and was only recognized in about 10% of patients with psoriasis. (Ex. 2001, 42.)

(Pet., 18.) But Patent Owner disputes Petitioner's contention that the "wherein" clause of claim 1 does not limit the claim. (*Id*.)

Claims 1-8 of the '216 patent recite methods of treating moderate-to-severe chronic plaque psoriasis, "wherein the patient achieves at least Psoriasis Area and Severity Index (PASI) 75 response at week 12 of the treatment." (Ex. 1001, 57:36-61.) The PASI 75 claim language substantively limits claims 1-8 in at least two ways. First, by referring to "week 12 of the treatment," the claim language expressly requires at least a 12-week treatment duration. Otherwise, the reference to "week 12 of the treatment" would be superfluous. *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006) ("[C]laims are interpreted with an eye toward giving effect to all terms in the claim."). Second, requiring that the patient achieve at least a PASI 75 response at week 12 introduces an efficacy requirement not otherwise found in the claim. This express limitation should be given meaning.

The '216 patent specification supports this claim interpretation. It describes a clinical study performed to determine the efficacy of the claimed methods for treating moderate-to-severe chronic plaque psoriasis. (Ex. 1001, 41:3-42:59.) Patients were treated for 12 weeks (*id.*, 42:49-50), and the study's primary efficacy endpoint was the percentage of subjects achieving at least a 75% reduction in the PASI score (≥PASI 75) at week 12 (*id.*, 41:55-58). At week 12, 53% of patients on the claimed dosing regimen (an initial 80 mg dose, followed one week later by

40 mg administered every other week) achieved a PASI 75 response. (*Id.*, 41:17-48, Fig. 5, 42:5-12.) The specification thus supports an interpretation of the PASI 75 limitations as requiring a method of treatment persisting for at least 12 weeks and achieving at least a PASI 75 efficacy score at week 12.

Petitioner's argument that the PASI 75 language does not limit the claims fails to address any intrinsic evidence, including the claim language, specification, or prosecution history. (Pet., 48-49.) Instead, Petitioner relies solely on *Minton v. National Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373 (Fed. Cir. 2003). (Pet., 18, 22, 48.) This reliance is misplaced. The patent at issue in *Minton* claimed a method for trading securities "efficiently" on a computerized system. *Minton*, 336 F.3d at 1375, 1380 (citation omitted). The Federal Circuit determined that the term "efficiently" was simply a "laudatory" term that did not limit how trades were executed, and that nothing in the specification or prosecution history suggested otherwise. *Id*. at 1381.

The quantitative PASI 75 limitation here is not analogous to the qualitative term "efficiently" in *Minton*. The Board should reject Petitioner's proposed claim construction because the PASI 75 language limits claims 1-8 by requiring both that the patient be treated for at least 12 weeks and achieve at least a PASI 75 level of treatment efficacy at week 12.

IV. THE ASSERTED REFERENCES

Petitioner failed to meet its burden to show that three of its five asserted obviousness references qualify as prior art—the Humira Insert (Ex. 1026), the Press Release (Ex. 1052), and Weinstein (Ex. 1003). (*See infra* Section V.D.) This failure requires denial of institution. Nonetheless, Patent Owner addresses these references below.

A. Humira Insert (Ex. 1026)

The Humira Insert, which Petitioner has not established as prior art, concerns HUMIRA®, AbbVie's adalimumab product, which was initially approved for treating *rheumatoid arthritis*. (Ex. 1026, 6.) The Humira Insert states that adalimumab is a fully human monoclonal antibody that binds specifically to TNFα and blocks its interaction with the p55 and p75 cell surface TNF receptors. (*Id*., 1-2.)

Rheumatoid arthritis was understood as a "chronic disease that leads to joint damage within the first 2 years, causes marked functional limitation and a 30% loss of work within the first 5 years, and shortens life by 5 to 7 years." (Ex. 2012, 4). According to the prior art, rheumatoid arthritis is an "aggressive disorder [that] demands the early institution of an equally aggressive therapeutic approach." (*Id*.)

The Humira Insert states that the approved dose "for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous

injection." (Ex. 1026, 14.) The Humira Insert does not suggest using adalimumab for psoriasis, much less for moderate-to-severe chronic plaque psoriasis. It contains no information about adalimumab's distribution from the bloodstream to the psoriatic skin following subcutaneous administration, the drug's pharmacokinetics in the skin, or how the drug's concentration in blood serum correlates to its concentration in psoriatic skin. Moreover, it does not suggest using a higher initial dose, much less an initial dose of 80 mg. It also does not suggest administering lower subsequent doses starting one week after an initial 80 mg dose.

B. Press Release (Ex. 1052)

Petitioner has not established that the Press Release is prior art. The Press Release describes work by Patent Owner's predecessor, Abbott Laboratories, regarding the initiation of a psoriasis clinical trial and a PsA clinical trial using HUMIRA®. (Ex. 1052, 2-3.) It states that Dr. Gordon, a dermatologist at Loyola University Medical Center, was "hoping" that the psoriasis clinical trial would lead to a treatment option. (*Id*., 2.) But it does not describe any dosing regimen, let alone suggest using a higher initial dose of 80 mg one week before beginning every-other-week dosing of 40 mg.

C. Weinstein (Ex. 1003)

Weinstein, which Petitioner has not established as prior art, consists of chapter excerpts from a textbook on psoriasis and psoriasis treatment. It begins by

stating that "[n]o treatment is universally effective" and that "treating psoriasis successfully and instilling hope in patients seems impossible." (Ex. 1003, v-vi.) Weinstein reports that the "moderate/severe [psoriasis] patient population comprises 20-25% of all the psoriatics seen in the average practice." (*Id*., 19.)

Weinstein does not suggest using adalimumab to treat psoriasis or describe any dosing regimen for using adalimumab to treat moderate-to-severe chronic plaque psoriasis.

D. Marzo-Ortega (Ex. 1060)

Marzo-Ortega is an abstract that concerns the use of the drug infliximab for treating PsA, which is a disorder that affects joints and can affect the skin. (Ex. 1060, 1.) Marzo-Ortega describes intravenously administering 3 mg/kg of infliximab with methotrexate at weeks 0, 2, 6, and 14 for PsA, noting that 3 mg/kg of infliximab had been used for rheumatoid arthritis and 5 mg/kg of infliximab had been used for psoriasis. (*Id*.)

Marzo-Ortega describes measuring efficacy using PASI scores, but does not discuss the severity of any patients' psoriasis or indicate whether the patients had moderate-to-severe chronic plaque psoriasis. Nor does it suggest using adalimumab to treat moderate-to-severe chronic plaque psoriasis or any dosing regimen for adalimumab.

E. Proudfoot & Collett (Aulton) (Ex. 1051)

Petitioner cites a textbook chapter by Stuart Proudfoot and John Collett (Aulton), which discusses dosing regimens for orally administered, small-molecule drugs. Aulton describes the concept of "loading doses," which it states can reduce the time required to achieve steady-state plasma concentrations of drug.[3] (Ex. 1051, 284-85.) Petitioner, citing Goodman & Gilman, describes a "loading dose" as "one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly." (Pet., 31 (citing Ex. 1056, 27).)

If a loading dose is to be used, Aulton describes using "an initial loading dose followed by equal maintenance doses at *fixed intervals*." (Ex. 1051, 285 (emphasis added); *see also id.*, Fig. 19.8 (administering each dose, including the initial dose, at fixed intervals).) Nothing in Aulton suggests varying the intervals between doses, such as administering a higher initial dose followed one week later by a maintenance dose that is then given every other week. Aulton thus does not describe or suggest the claimed dosing regimen for adalimumab or suggest any need to use an initial dose of adalimumab higher than subsequent doses.

[3] For the limited purposes of this Response, Patent Owner does not dispute Petitioner's interchangeable use of the terms "loading dose" and "induction dose."

Indeed, Aulton does not suggest using adalimumab or suggest that the technical principles it discusses would apply to biologic drugs or to treating moderate-to-severe chronic plaque psoriasis. Even for small molecules, Aulton does not suggest that the dosing interval after the initial dose should differ from the dosing interval between subsequent doses.

V. PETITIONER HAS NOT ESTABLISHED A REASONABLE LIKELIHOOD OF PREVAILING AS TO ANY CHALLENGED CLAIM

A. Petitioner Fails to Show that the Asserted References, Even if Combined, Expressly or Inherently Disclose Every Claim Element

1. The cited art does not disclose administering a higher initial dose followed one week later by a lower dose

The claimed methods of treating moderate-to-severe chronic plaque psoriasis comprise administering an initial 80 mg dose of adalimumab, followed one week later by 40 mg every-other-week dosing. (Ex. 1001, 57:36-43.) This regimen thus requires a one-week interval between the higher initial dose and the first every-other-week dose.

Although Petitioner asserts obviousness based on a five-reference combination of the Humira Insert, the Press Release, Aulton, Weinstein, and Marzo-Ortega, it fails to identify any disclosure in these references of the claimed one-week interval between the higher initial dose and the first every-other-week

dose. (Pet., 9-10.) Indeed, it cannot—none of these references describes this aspect of the claimed dosing regimen.

Petitioner relies on Aulton to argue that the one-week interval was an "obvious choice." (Pet., 21-22, 44-55.) Aulton, however, is a general reference that only addresses the "concept of 'loading doses.'" (Ex. 1051, 284-85.) It is not directed to the dosing of adalimumab, or even biologics as a general class. (*Id*.) In fact, one of the reference's authors, Dr. Collett, stated in declarations submitted during prosecution of related patent applications that "the Aulton and Shargel dosing regimen principles are not applicable to therapeutic antibodies, such as adalimumab." (*See, e.g.*, Ex. 1045, ¶¶ 14-16.) He explained that, due to the differences in size and structure, the dosing recommendations for small-molecule drugs do not apply to large biological molecules. (*Id*., ¶ 19; *see also* Ex. 2013, 549 ("Antibody drugs often exhibit PK/PD properties that are much more complex than those typically associated with small-molecule drugs . . . .").)

Importantly, Aulton does not disclose the claimed one-week interval between a higher initial dose and subsequent every-other-week doses, nor does it provide any methodology to calculate or vary the interval after the higher initial dose. (Ex. 1051, 283-85.) Indeed, Aulton teaches use of the *same* "fixed" interval between *all* doses—e.g., a "loading dose" is administered 24 hours before the first "maintenance dose" and then maintenance doses are given every 24 hours.

(*Id*., 285 (Fig. 19.8).) In Aulton's example, this 24-hour period between doses corresponds to the drug's half-life. (*Id*.) Aulton thus does not describe the claimed dosing regimen's use of different (i.e., not fixed) dosing intervals, in which the initial 80 mg dose is administered just *one week* before the first 40 mg dose, but subsequent 40 mg doses are administered *every other week* (with every-other-week dosing corresponding approximately to adalimumab's roughly two-week half-life). (Ex. 1001, 57:36-43; Ex. 1026, 2.) Indeed, even Petitioner interprets Aulton as purportedly motivating a POSA to administer an initial dose "two weeks" before the subsequent dose (Pet., 42), not one week as claimed.

Petitioner also cites the Humira Insert, but again points to no disclosure of the claimed one-week interval between a higher initial dose and subsequent every-other-week dosing. (Pet., 21-22, 44-46.) Indeed, Petitioner cites the Humira Insert for its administration of 40 mg of adalimumab *every other week* to treat rheumatoid arthritis. (*Id.*, 21-22 (citing Ex. 1026, 14).) But this document does not disclose treating psoriasis, a higher 80 mg initial dose, or a one-week interval between this higher dose and subsequent 40 mg every-other-week doses. (Ex. 1026, 14.) Even Petitioner concedes that the Humira Insert does not suggest this dosing regimen, instead concluding that, based on adalimumab's roughly two-week half-life, a "POSA would understand that one appropriate adalimumab induction dosing

regimen is 80 mg (twice the 40 mg treatment dose) *two weeks prior* to beginning 40 mg [every-other-week] treatment dosing." (Pet., 42 (emphasis added).)

Petitioner further argues that Weinstein suggests a one-week interval between an 80 mg initial dose and subsequent 40 mg every-other-week dosing. (*Id*., 46-47.) Weinstein, however, discloses clinical trials using a different dosing regimen for a different drug (infliximab), administered by a different route (intravenously), on a very different schedule. (Ex. 1003, 251; Pet. 33, 46-47.) Those clinical trials did *not* include a one-week interval between doses. Instead, Weinstein describes a "three-dose induction regimen," in which the infliximab induction doses were separated by 2 to 4 weeks each (weeks 0, 2, and 6) and the maintenance doses were given only "as needed" at 4- or 8-week intervals thereafter. (Pet. 33; Ex. 1050, ¶ 40; Ex. 1003, 251; *see also* Ex. 1027, 3.) Weinstein thus does not "explicitly state[] that an appropriate dosing regimen would include both an induction dose and treatment dosing" *for adalimumab*, as the Petition implies, or indeed for any drug other than infliximab. (Pet., 47.) Moreover, the induction and maintenance doses reported in Weinstein used the *same* dose rather

than a higher initial dose. Weinstein thus fails to suggest the claimed *one-week* interval between a higher initial dose and subsequent every-other-week dosing.[4]

Petitioner's failure to identify these claim limitations in the prior art is legally significant. Even if there were a motivation to combine the cited references (which, as addressed in Section V.B, below, there was not), the combined references do not disclose the claimed one-week interval between a higher initial dose and subsequent every-other-week dosing. Accordingly, Petitioner cannot establish that the claims would have been obvious. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006) (stating that motivation and reasonable expectation of success are considered only "if all the elements of an invention are found in a combination of prior art references"). The Board should thus deny institution of the Petition. *See* 37 C.F.R. § 42.104(b)(4) ("The petition must specify where each element of the claim is found in the prior art patents or printed publications relied upon . . . .").

[4] Regardless of whether a POSA measured the intervals between doses in terms of weeks or drug half-life, the cited references do not disclose or suggest the one-week interval between the initial dose and subsequent every-other-week dosing.

2. The cited art does not disclose the PASI 75 efficacy element of claims 1-8, either expressly or inherently

After incorrectly arguing that the claim language requiring PASI 75 efficacy at week 12 of treatment does not limit claims 1-8 (*see supra* Section III.C), Petitioner alternatively argues that this limitation is a natural result inherently achieved by at least some psoriasis patients receiving adalimumab in accordance with the claimed dosing regimen. (Pet., 48.) But a party must "meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). Petitioner fails to meet this high standard.

First, the cited references do not explicitly disclose the combination of elements of the claimed dosing regimen, and thus Petitioner cannot argue that PASI 75 efficacy is the "natural result" of this undisclosed combination. *Id*. This is particularly true where, as here, Patent Owner established that it was unexpected that the claimed dosing regimen yielded the claimed long-term improvements in the PASI 75 score. (*See infra* Section V.C.) The Board therefore should reject Petitioner's reliance on inherency.

Further, even if Petitioner *had* identified all the elements of the claimed dosing regimen in the cited references, Petitioner fails to establish that PASI 75

efficacy at week 12 is "necessarily . . . present," and thus fails to prove inherency. On the contrary, Petitioner and Dr. Helfgott concede that the claimed PASI 75 efficacy results are *not* achieved by *every* patient, and thus that this efficacy does not necessarily result from the claimed dosing regimen. Petitioner states, for example, that this result is only achieved by "certain patients" or "some [psoriasis] patients." (Pet., 48; *see also* Ex. 1002, ¶ 108.) This is legally insufficient to establish a limitation by inherency. "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient" to establish inherency. *Par*, 773 F.3d at 1195 (quoting *In re Rijckaert*, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993)). Inherency "may not be established by probabilities or possibilities." *Id.* (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

The Board should also reject Petitioner's improper attempt to use inherency to ignore the claimed PASI 75 efficacy at week 12. (Pet., 49.) Indeed, it is legal error to use inherency to wholly ignore claim limitations. *See Par*, 773 F.3d at 1195-96. In *Par*, the Federal Circuit rejected the district court's inherency analysis, which "ignore[d] the claim limitations at issue" in the claimed methods, and remanded to determine if the claimed food effect *necessarily* occurred. *Id*. The court explained that, even if reducing particle size naturally results in *some* improvement in food effect, the district court failed to analyze whether this reduction inherently yielded the extent of improvement recited in the claims. *Id*. at

1196. Petitioner's reliance on *Par* is thus misplaced, as the decision supports *nonobviousness*, not obviousness. (Pet., 49.) Here, Petitioner identifies no prior art disclosure of the PASI 75 limitation, admits that PASI 75 efficacy does not necessarily occur at 12 weeks, and cites no expert testimony in support of its contentions.

The Federal Circuit's decision in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), further illustrates Petitioner's error. The claimed method of treatment in *Cyclobenzaprine* required providing a "*therapeutically effective* plasma concentration over a period of 24 hours to treat muscle spasm." 676 F.3d at 1066 (emphasis added) (citation omitted). The court gave effect to the "therapeutically effective" language, holding that the district court "could not find obviousness without finding that the prior art would have taught or suggested a therapeutically effective formulation to one of ordinary skill in the art." *Id*. at 1070. Because the record lacked such evidence, the Federal Circuit reversed the obviousness ruling. *Id*. at 1070, 1088.

Similarly, here, Petitioner failed to cite any prior art disclosing—or expert testimony addressing—a treatment lasting at least 12 weeks where the patient being treated achieves PASI 75 at week 12. (Pet., 48-49.) Indeed, Dr. Helfgott cites only the '216 patent itself in support of his conclusion that achieving PASI 75

efficacy at week 12 is a "natural result inherently achieved by at least some [psoriasis] patents" (Ex. 1002, ¶ 108), and Dr. Posner does not analyze this aspect of the claims at all. *See Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."). By conceding that not every patient achieves the recited efficacy at week 12, Petitioner fails to establish this limitation by inherency. The Board thus should rule that Petitioner has not established a reasonable likelihood that claims 1-8 are unpatentable for obviousness.[5]

B. There Was No Motivation to Treat Chronic Plaque Psoriasis by Administering an 80 mg Initial Dose One Week Before Starting 40 mg Every-Other-Week Dosing

Petitioner argues throughout the Petition that a POSA would have expected a TNFα inhibitor such as adalimumab to effectively treat both rheumatoid arthritis

[5] For the same reasons, Petitioner also fails to establish that a POSA would have reasonably expected that the claimed methods would achieve PASI 75 efficacy at week 12 of treatment. Petitioner's experts did not even address whether a POSA would have reasonably expected this level of efficacy. (*See* Ex. 1002, ¶ 108; Ex. 1050, ¶¶ 49, 76.) This failure separately mandates denial of institution. *See, e.g.*, *In re Cyclobenzaprine*, 676 F.3d at 1070 (holding that the claimed efficacy requirement must be considered in evaluating reasonable expectation of success).

and chronic plaque psoriasis using the *same dose* and *similar dosing regimens*. (Pet., 1, 19-20, 24-29, 36-39.) This argument is the basis for Petitioner's contention that it would have been obvious that the 40 mg every-other-week dosing regimen for rheumatoid arthritis would have worked for chronic plaque psoriasis. (*Id*., 37-39.) Yet Petitioner *also* argues that, despite expecting that the rheumatoid arthritis regimen would work for psoriasis, a POSA nonetheless would have *modified* that regimen by adding an 80 mg initial dose one week before 40 mg every-other-week dosing. (*Id*., 40-45.)

Even if Petitioner *had* established that a POSA would have reasonably expected the rheumatoid arthritis dosing regimen of 40 mg every other week to work for psoriasis (which Patent Owner contests), Petitioner does not suggest any problem or reason that would have motivated one to change the regimen by (1) adding a higher initial dose of 80 mg and (2) administering the higher initial dose one week before beginning every-other-week dosing. *See, e.g., Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (stating that "[t]he ordinary artisan would first have needed to recognize the problem" before seeking to improve a pharmaceutical formulation).

1. A POSA would not have been motivated to use a higher initial dose

Petitioner not only fails to establish any reason why a POSA would seek to modify the rheumatoid arthritis dosing regimen to add an initial dose, but also *fails*

to identify a single prior art psoriasis treatment that used an initial dose that was higher than the subsequent doses. Indeed, as discussed above, many prior psoriasis treatments used initial doses that were *lower* than the subsequent doses. (*See supra* Section II.C.) While Petitioner alleges that a POSA would have been motivated to administer a higher initial dose based on Aulton (Pet., 21), Petitioner fails to explain why adalimumab would be dosed differently from all of these known psoriasis treatments.

Without citing *any* prior art reference comparing the diseases, Petitioner nevertheless argues that a POSA would have been motivated to use a higher initial dose to achieve steady-state adalimumab plasma concentrations faster in psoriasis patients than in rheumatoid arthritis patients because psoriasis is a serious disease that requires rapid achievement of the full response. (*Id*., 21, 33-34.) But Petitioner cites no evidence that psoriasis is *more* serious than rheumatoid arthritis, which the prior art indicated required immediate, aggressive treatment to avoid irreversible bone and joint damage. (Ex. 2012, 4; *see also* Ex. 1003, 13.) Petitioner also cites no evidence that the rheumatoid arthritis dosing regimen for adalimumab was not aggressive enough or was too slow to achieve adequate steady-state plasma concentrations. Indeed, the prior art characterized rheumatoid arthritis as an "aggressive disorder" demanding the "early institution of an equally aggressive therapeutic approach." (Ex. 2012, 4.) Absent aggressive treatment, rheumatoid

arthritis was known to cause irreparable joint damage. (*Id*.) The symptoms of psoriasis, in contrast, were reversible and the right treatment could make it possible to achieve clearance (i.e., no skin symptoms). (Ex. 1003, vii.)

Moreover, Petitioner's conclusory theory that a POSA would have been motivated to use a higher initial dose conflicts with how biologic psoriasis treatments were administered as of the '216 patent's priority date. Neither efalizumab nor alefacept used an initial dose that was higher than the subsequent dose. (Ex. 2007, 20; Ex. 2006, 11-12.) To the contrary, the initial dose of efalizumab was *lower* than all subsequent doses. (Ex. 2007, 20 (initial dose of 0.7 mg/kg compared to subsequent doses of 1.0 mg/kg).)

Petitioner also provides no evidence that either of the two known anti-TNFα drugs—infliximab and etanercept—had even been tested with an initial dose that was higher than subsequent doses. Infliximab, regardless of indication, was always administered at the same dose during a treatment regimen or using a *lower* initial dose; no study identified by Petitioner for *any* indication used a larger initial dose. (*E.g.*, Ex. 1027, 21; Ex. 1039, 66; Ex. 1040, 2206; Ex. 1060, 1; Ex. 1061, 128; Ex. 1036, 1843; Ex. 1037, 429; Ex. 1033, 587.)

Further, although infliximab was dosed more frequently early in the regimen, this was not done to achieve steady-state concentrations earlier in the regimen. Infliximab has a half-life of roughly 8-10 days, so dosing once every

eight weeks meant that drug blood levels reset to near zero between each dose rather than achieving higher, steady-state concentrations. (Ex. 1027, 2-3.) As stated in the Remicade label, "[n]o systemic accumulation of infliximab occurred upon continued repeated administration." (*Id*., 3.) Moreover, contrary to Petitioner's assertion that moderate-to-severe chronic plaque psoriasis required a different initial dose than rheumatoid arthritis, infliximab was dosed with the same frequency *regardless* of the disease being treated. (*Id*., 21.)

Like infliximab, the etanercept dosing regimens identified by Petitioner did not use a larger initial dose. Regardless of indication, etanercept was *always* dosed at a fixed dose, with no suggestion that a higher initial dose should be used or that a different initial dose should be used for moderate-to-severe chronic plaque psoriasis versus rheumatoid arthritis. (Ex. 1006, 23.) Petitioner fails to identify any prior art suggesting that these dosing regimens for etanercept or infliximab were not aggressive enough or would fail to achieve steady-state plasma concentrations fast enough to effectively treat moderate-to-severe chronic plaque psoriasis.

Given these dosing regimens for other anti-TNFα drugs, Petitioner fails to explain why a POSA would have administered a higher *initial* dose exclusively for adalimumab. Petitioner's contention that a POSA would choose a higher initial dose also fails to address suggestions in the cited references of possible disadvantages of doing so. Petitioner relies on the Goodman & Gilman textbook,

for example, but that reference states that "if the drug involved has a long half-life, it will take a long time for the concentration to fall if the level achieved was excessive." (Ex. 1056, 27.) For this reason, and as Petitioner admits, Goodman & Gilman recommends that, if one were to use a loading dose, it is "usually advisable to divide the loading dose into a number of smaller fractional doses that are administered over a period of time" instead of using a single higher dose. (*Id*.; *see also* Pet., 32-34 & n.22.) Even if one characterized the infliximab dosing regimen as including a "loading dose," the regimen did not use a larger initial dose but instead administered the *same* doses at 0, 2, and 6 weeks, and thereafter every 8 weeks. (Ex. 1003, 250; Ex. 1060, 1.)

Because Petitioner fails to establish that a POSA would have used a higher initial dose in treating psoriasis, fails to support its motivation allegation with citations to the prior art, and disregards how psoriasis was actually treated at the relevant time, the Petition should be denied.

2. A POSA would not have been motivated to use a shortened, one-week interval between the higher initial dose and the second dose

Petitioner identifies no prior art disclosing administration of a higher initial dose followed one week later by a lower dose. (*See supra* Section V.A.) Petitioner also identifies no suggestion or motivation in the prior art for administering a higher initial dose one week before beginning every-other-week dosing. While

Petitioner points to Dr. Posner's assertion that a POSA would have been motivated to select this one-week interval, his conclusory, one-paragraph statement addressing this aspect of the claim does not cite any prior art or evidence. (Pet., 44; Ex. 1050, ¶ 69.) An unsupported expert opinion of this type is entitled to little or no weight. *Coal. for Affordable Drugs VI, LLC v. Celgene Corp.*, IPR2015-01096, Paper 76 at 6 (P.T.A.B. Sept. 8, 2017).

Citing no evidence, Dr. Posner first contends that a POSA would have expected that a one-week interval between a higher initial dose and the second dose would "simply result in slightly higher plasma concentrations at an earlier point in time" and would thus provide a "more rapid therapeutic effect." (Ex. 1050, ¶ 69.) But Dr. Posner provides no evidentiary support for this assertion, and thus his testimony fails to establish that a POSA would have understood that achieving higher plasma levels more rapidly would be desirable for treating moderate-to-severe chronic plaque psoriasis or that "slightly higher plasma concentrations at an earlier point in time" would even be able to achieve a "more rapid therapeutic effect." (*Id*.) The Board should give no weight to this conclusory testimony. *See Upjohn Co. v. MOVA Pharm. Corp*., 225 F.3d 1306, 1311 (Fed. Cir. 2000) (requiring factual support for an expert's conclusory opinion).

The Board should similarly reject Dr. Posner and Petitioner's unsupported contention that a POSA would have viewed a one-week interval between a higher

initial dose and subsequent every-other-week dosing as an "obvious choice." (Pet., 21-22, 44-45; Ex. 1050, ¶ 69.) Despite identifying no prior art that describes this one-week limitation, Petitioner and Dr. Posner imply that a POSA would have done so based on common sense. (Pet., 21-22, 44-45; Ex. 1050, ¶ 69.) This type of analysis is impermissible, however, because common sense "cannot be used as a wholesale substitute for reasoned analysis and evidentiary support." *In re Van Os*, 844 F.3d 1359, 1361 (Fed. Cir. 2017) (quoting *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1362 (Fed. Cir. 2016)). Similarly, conclusory assertions without explanation are inadequate to support a motivation to combine. *Id*.

Petitioner's argument that a POSA would have been motivated to use a one-week interval also fails because both Petitioner and Dr. Posner assert only that a POSA *could* adjust "the two-week induction regimen interval," not that a POSA *would have been motivated to do so*. (Ex. 1050, ¶ 69; Pet., 44-45); *see also Upjohn*, 225 F.3d at 1311. Again, Dr. Posner offers no evidentiary support for this opinion, and thus the Board should give it no weight. (Ex. 1050, ¶ 69; Pet., 20.) Additionally, focusing on what a POSA "could" do is legally insufficient to establish obviousness. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.").

Importantly, Petitioner's argument that a POSA "could" select a one-week interval is inconsistent with its contention that, based on Aulton, a POSA would have selected an 80 mg initial dose because adalimumab's 40 mg every-other-week dosing interval approximately corresponds to its half-life. (*See, e.g.*, Pet., 21, 32, 41-42.) Dr. Posner, for example, stated that "the induction dose should be about twice the amount of the treatment dose, when the interval between administration of the induction dose and the treatment dose corresponds to the half-life of the drug." (Ex. 1050, ¶ 38.) The two-week interval between the initial dose and the subsequent dose was therefore critical to Petitioner and Dr. Posner's argument that a POSA would have selected an 80 mg initial dose to quickly achieve steady state. Neither Petitioner nor Dr. Posner explains why a POSA would have chosen the same 80 mg initial dose when using a shortened, one-week interval that does not correspond to adalimumab's half-life.

Finally, both Petitioner and Dr. Posner state that the initial dose could have been given either one week *or* two weeks before starting every-other-week treatment and still allegedly would have achieved a more rapid therapeutic effect than the every-other-week regimen without an initial dose. (Pet., 42, 44-45; Ex. 1050, ¶ 69.) But Petitioner has not identified any need or problem that would have motivated a POSA to shift from a two-week interval to a one-week interval. Thus, Petitioner has not identified a "design need or market pressure to solve a problem,"

as required to establish that something would have been obvious to try. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007); *Axon Enter., Inc. v. Digital Ally, Inc.*, IPR2017-00515, Paper 10 at 19-20 (P.T.A.B. July 6, 2017).

The Board should also reject Petitioner's unsupported assertion that the one-week interval between an 80 mg initial dose and subsequent 40 mg every-other-week dosing would have been "one of a finite number of obvious choices a POSA would have considered." (Pet., 45.) The finite-options analysis is relevant only to "known options" in the prior art. *See In re Kubin*, 561 F.3d 1351, 1359-60 (Fed. Cir. 2009) (quoting *KSR*, 550 U.S. at 421). But Petitioner's conclusory assertion of a "finite number" cites no evidence that a one-week interval was one of a finite number of known options. (Pet., 2, 20, 45.) Petitioner's experts fail to even assert that there were a limited number of options in the art. (*See generally* Ex. 1050.) Instead, the cited references highlight the multitude of options for dosing intervals. (*See supra* Section II.C, disclosing twice-daily dosing, daily dosing, twice-weekly dosing, weekly dosing, every-other-week dosing, and dosing at weeks 0, 2, and 6.) Moreover, none of Petitioner's cited references provides any specific guidance on psoriasis dosing intervals *for adalimumab*. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (stating that a claim would not have been "obvious to try" where "the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it").

Petitioner's failure to cite evidentiary support for its obviousness analysis is particularly problematic where, as here, the one-week interval is an important claim limitation that "*is not evidently and indisputably* within the common knowledge of those skilled in the art." *Arendi*, 832 F.3d at 1363-64 (quoting *K/S HIMPP v. Hear-Wear Techs., LLC*, 751 F.3d 1362, 1365-66 (Fed. Cir. 2014)). Accordingly, the Board should conclude that Petitioner has not established that a POSA would have been motivated to give a higher initial dose one week before starting every-other-week treatment. *See FedEx Corp. v. Intellectual Ventures II LLC*, IPR2017-00750, Paper 9 at 5-7 (P.T.A.B. Sept. 5, 2017) (finding Petition to be conclusory and lacking in evidentiary support, and therefore insufficient based on *Arendi* and *K/S HIMPP* to supply the missing limitation).

C. The Claimed Dosing Regimen Achieves Unexpectedly Superior Long-Term Efficacy

The claimed dosing regimen unexpectedly leads to superior long-term efficacy in treating moderate-to-severe chronic plaque psoriasis. Data from multiple clinical trials showed that the claimed dosing regimen "is associated with significantly greater improvement in psoriasis severity symptoms compared with adalimumab treatment of 40 mg every other week dosing without [the] initial 80 mg dose." (Ex. 2009, 1.) Indeed, the claimed regimen was nearly *twice as likely* to achieve PASI 75 efficacy as the rheumatoid arthritis dosing regimen of 40 mg

every other week without the 80 mg initial dose one week before the first 40 mg dose. (*Id*., 4 (Table 2).)

Importantly, the claimed dosing regimen showed an unexpected improvement in efficacy in the long term, with a significant improvement over the rheumatoid arthritis dosing regimen at both 12 and 24 weeks. (*Id*.) This long-term effect at 12 and 24 weeks undercuts Petitioner's assertion that adding a higher 80 mg initial dose one week before starting every-other-week dosing is simply a means to reach steady-state concentrations more quickly. And it is particularly significant given Petitioner's admission that steady-state levels of the drug would be achieved by week 10 without the initial 80 mg dose. (Pet., 41.) It thus was unexpected that patients who received the higher initial dose would show significantly increased efficacy compared to those who did not, months after levels of adalimumab would have reached steady state for both groups.

During prosecution of a related patent application, Patent Owner cited the data in the Kimball reference showing the unexpected improvement in PASI 75 efficacy of the claimed regimen and argued that a POSA would not have reasonably expected this enhanced efficacy. (Ex. 2014, 5-6.) Petitioner fails to address this evidence. Instead, Petitioner cherry-picks data from two independent examples in the '216 patent to argue that patients "who did not receive an induction dose had a greater clinical response than those patients who did receive

an induction dose." (Pet., 16.) This, however, is an improper apples-to-oranges comparison because one of the two examples Petitioner cites was directed to a *different indication* (PsA) instead of moderate-to-severe chronic plaque psoriasis. (Ex. 1001, 37:49-55, 40:44-42:67; *see also* Pet., 16.) Although some participants in the PsA example also had plaque psoriasis, there is no indication of the severity of that disease, precluding any ability to compare respective levels of efficacy. (Ex. 1001, 37:49-55.) Further, Petitioner does not attempt a statistical analysis of the data, notwithstanding that the results were obtained from different patient populations afflicted with different diseases. (*See id*., 37:49-55, 40:44-42:67; *see also* Pet., 16.) Petitioner's analysis is therefore fundamentally flawed and insufficient to carry its burden of establishing a reasonable likelihood that the challenged claims would have been obvious.

D. Petitioner Fails to Show That Three of the Five Cited References Qualify as Prior Art Printed Publications

A Petitioner may only challenge patent claims on the basis of "prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). To qualify as a prior art printed publication, a reference must have been publicly accessible before the critical date. *In re Lister*, 583 F.3d 1307, 1311-12 (Fed. Cir. 2009). Petitioner bears the burden to make a threshold showing that an alleged prior art reference was available as a printed publication. *Coal. for Affordable Drugs IV LLC v. Pharmacyclics, Inc.*, IPR2015-01076, Paper 33 at 5-6 (P.T.A.B. Oct. 19, 2015).

Petitioner asserts that the Humira Insert, the Press Release, and Weinstein qualify as prior art under 35 U.S.C. § 102(b), but provides no evidence that they were publicly available. (Pet., 9.) This deficiency is fatal. Petitioner's sole ground of unpatentability relies on these three documents as § 102(b) prior art, and thus failure to demonstrate that any of them is a printed publication under § 102(b) (as opposed to § 102(a), for example) warrants denial of institution.[6] *Ford Motor Co. v. Versata Dev. Grp., Inc.*, IPR2016-01012, Paper 12 at 3, 12 (P.T.A.B. Nov. 4, 2016). Because institution decisions must be based on information in the petition, this deficiency cannot be remedied. 35 U.S.C. § 314(a); *Actavis, Inc. v. Research Corp. Techs., Inc.*, IPR2014-01126, Paper 22 at 13 (P.T.A.B. Jan. 9, 2015).

1. Petitioner fails to establish that the Humira Insert was publicly available in December 2002

Petitioner asserts that the Humira Insert (Ex. 1026) has a "Publication Date" of "Dec. 2002," but offers no evidence to support this assertion. (Pet., 9.) Petitioner has not met its threshold burden for several reasons.

[6] Patent Owner cited each of these exhibits on an information disclosure statement ("IDS") during prosecution of the '216 patent, but clarified that this was not an admission that they were available as prior art. (Ex. 2011, 3, 18, 24, 31.) Patent Owner's IDS is therefore not evidence of publication. *Synopsys, Inc. v. Mentor Graphics Corp.*, IPR2012-00042, Paper 16 at 35-36 (P.T.A.B. Feb. 22, 2013).

First, the dates on Exhibit 1026 alone do not prove public availability. Petitioner submits no evidence connecting the December 20, 2002, date on page 1 or the "Issued: December 2002" language on page 16 to public availability. (Ex. 1026, 1, 16.) For example, Petitioner offers no evidence showing what "Issued: December 2002" means or equating "Issued" with public accessibility. *See Coal. for Affordable Drugs IV*, IPR2015-01076, Paper 33 at 7-8 ("[u]pdated" date on document did not prove publication without evidence of what "[u]pdated" meant).

Thus, these dates, without more, do not meet Petitioner's threshold burden of showing that Exhibit 1026 is a printed publication. Indeed, the Board has repeatedly held that dates on a drug's package insert do not establish the insert as a printed publication. *See, e.g.*, *Frontier Therapeutics, LLC v. medac Gesellschaft für klinische Spezialpräparate mbH*, IPR2016-00649, Paper 10 at 22 (P.T.A.B. Sept. 1, 2016); *see also Mylan Pharm. Inc. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01565, Paper 17 at 19-20 (P.T.A.B. Feb. 9, 2017).

Petitioner's declarants similarly offer no support for the public availability of Exhibit 1026. Dr. Posner calls the exhibit the "Humira® 2002 Package Insert," but fails to address its public availability or offer any supporting evidence. (*See* Ex. 1050, ¶ 51.) Ms. Reines is silent regarding the Humira Insert's public availability or authenticity. (*See generally* Ex. 1068.) Dr. Helfgott states that "[i]n

December 2002, the FDA approved Humira® to treat rheumatoid arthritis," and refers to Exhibit 1026 as the "accompanying" package insert. (Ex. 1002, ¶¶ 31, 56.[7]) But he cites no evidence tying FDA approval of HUMIRA® in December 2002 to public dissemination of the Humira Insert, and he also offers no personal knowledge of the Humira Insert's publication. (*See generally* Ex. 1002.) The Board should give his conclusory assertion no weight. *See Mylan Pharm. Inc. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01563, Paper 16 at 14 (P.T.A.B. Feb. 3, 2017) (finding conclusory expert statements that a drug label was approved by the FDA to be insufficient to establish the label's public availability); *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01094, Paper 12 at 11 (P.T.A.B. Oct. 2, 2017) (rejecting petitioner's assertion that patent owner's Rituxan label was prior art when no evidence supported the label's public dissemination).

Finally, Petitioner provides no evidence of the source of Exhibit 1026, how one could have obtained a copy, or whether it was reasonably accessible to the interested public. *See Mylan Pharm.*, IPR2016-01563, Paper 16 at 14. Petitioner's failure to include any of this information compels a finding that it did not establish Exhibit 1026 as a printed publication. *See Teva Pharm. USA, Inc. v. Indivior UK*

[7] The Petition does not cite these paragraphs, and thus the Board should disregard them. 37 C.F.R. § 42.104(b)(5).

Ltd., IPR2016-00280, Paper 23 at 9-11 (P.T.A.B. June 10, 2016) (finding no "threshold evidence" of publication where the petition cited no information about how one could have obtained the drug label or whether it was "reasonably accessible through generally available means").

2. Petitioner fails to establish that the Press Release was publicly available on March 3, 2003

Petitioner characterizes Exhibit 1052 as an "AbbVie Press Release" published on March 3, 2003, but cites only the exhibit itself with no evidence as to its source, publication, dissemination, or public availability. (Pet., 9, 23.) Dr. Helfgott's declaration adds nothing and should be disregarded because (1) it merely parrots the Petition's conclusory assertions (Ex. 1002, ¶¶ 50, 58); and (2) Petitioner did not cite it for this issue. *Coal. for Affordable Drugs IV*, IPR2015-01076, Paper 33 at 7-8 (giving little weight to the conclusory testimony of Petitioner's expert that a document from www.ClinicalTrials.gov was prior art); 37 C.F.R. § 42.104(b)(5).

The March 3, 2003 date printed on Exhibit 1052, alone, is insufficient to establish public availability. *See LG Elecs., Inc. v. Advanced Micro Devices, Inc.*, IPR2015-00329, Paper 13 at 13 (P.T.A.B. July 10, 2015). Indeed, Petitioner fails to reconcile this date with two other dates listed on the exhibit—July 1, 2003, and July 5, 2017. (Ex. 1052, 2.) Nor does the "© 2002-3" copyright notice on the document establish public availability, as it relates only to the document's creation,

not to its publication. *See Mylan Pharm. Inc. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01565, Paper 23 at 6 (P.T.A.B. Aug. 1, 2017) ("[A] copyright date is associated with the creation of a document, but not necessarily its publication." (citing 17 U.S.C. §§ 408, 409)).

Compounding Petitioner's failure, Exhibit 1052 appears not to be a press release directly from AbbVie, as Petitioner implies, but rather an Internet Archive Wayback Machine search result for an "Immune Tolerance Network" webpage. (Ex. 1052, 2-3.) Petitioner does not address whether the webpage was available on March 3, 2003, and, moreover, mere availability on a website is not enough to establish public accessibility. *Celltrion, LLC v. Biogen, Inc.*, IPR2017-01230, Paper 10 at 13-15 (P.T.A.B. Oct. 12, 2017). Petitioner also provides no evidence establishing: whether the webpage was indexed; whether an interested person would have been aware of the web address; how the Wayback Machine archives webpages; or how archiving through this site relates to public availability. *See Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349-50 (Fed. Cir. 2016) (reference was not publicly accessible because no evidence showed that an interested person would be aware of the web address or that an Internet search would have located the reference). Petitioner thus has not shown that Exhibit 1052 was published on March 3, 2003.

Ms. Reines's declaration does not compel a different conclusion. She states that Exhibit 1052 is a true and correct copy of the press release available at the URL for the Internet Archive of the Immune Tolerance Network. (Ex. 1068, ¶ 2.) She does not, however, address public availability at the relevant time, establish any personal knowledge of the Immune Tolerance Network webpage or the Internet Archive, or establish whether the Immune Tolerance Network was "well-known to the community interested in the subject matter of the reference." *Celltrion*, IPR2017-01230, Paper 10 at 13-15 (noting the absence of testimony establishing that anyone had accessed or distributed a newsletter or that it was well-known to the community). Accordingly, her declaration is insufficient to authenticate the *content* (including the date) of the webpage. *See Neste Oil Oyj v. REG Synthetic Fuels, LLC*, IPR2013-00578, Paper 53 at 4 (P.T.A.B. Mar. 12, 2015) (requiring testimony from someone with knowledge of the website to prove the date on the printout of a website).

3. Petitioner fails to establish that Weinstein was publicly available on March 19, 2003

Petitioner asserts that Weinstein (Ex. 1003) was published on March 19, 2003 (Pet., 9), but again fails to establish public availability. This date does not appear in Weinstein, so Petitioner instead relies on Exhibits 1065 (purportedly a Website Printout from the Copyright Office) and 1068 (the Reines Declaration). But these exhibits, without more, are insufficient to establish that Weinstein is a

printed publication. 35 U.S.C. § 312(a)(3); 37 C.F.R. § 42.104(b)(5). Moreover, these exhibits fail to establish public availability as of March 19, 2003.

The Petition fails to explain how Exhibit 1065 relates to Weinstein's alleged public availability, and the Board should therefore disregard this exhibit. 37 C.F.R. § 42.104(b)(5). Exhibit 1065 lists (without explanation) "Date of Publication: 2003-03-19." Crucially, neither Petitioner nor its declarants explain how this date was generated or whether it has any bearing on when the public gained access to the reference. *See In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986) (requiring affidavits establishing a library's indexing, cataloging, and shelving practices to establish public accessibility).

The Reines Declaration (Ex. 1068) does not mention any asserted date of publication in connection with Exhibit 1065. Instead, Ms. Reines simply states that Exhibit 1065 is a "true and correct copy of the United States Copyright Office, Public Catalog Website Printout," for Weinstein. (Ex. 1068, ¶ 3.) But she does not explain Exhibit 1065's contents or how and when it was retrieved. (*Id*.) Nor does she assert personal knowledge of the Copyright Office's public catalog, and thus she cannot authenticate Exhibit 1065's content (e.g., any dates listed therein). *Neste Oil Oyj*, IPR2013-00578, Paper 53 at 4. Critically, Ms. Reines fails to explain how the catalog in Exhibit 1065 is relevant to Weinstein's purported public

availability. (Ex. 1068, ¶ 3.) The Board should therefore disregard her declaration (Ex. 1068). 37 C.F.R. § 42.104(b)(5).

The "Aug 13 2003" stamp and "© 2003" text on Exhibit 1003 also do not establish public availability. (Ex. 1003, Copyright Page.) First, the Board should not rely on these dates because Petitioner fails to cite or explain them. 37 C.F.R. § 42.104(b)(5). Additionally, the "Aug 13 2003" stamp fails to establish a date of public availability because (1) it contradicts Petitioner's asserted March 19, 2003 date; (2) would be hearsay if relied on to establish a date of public availability; and (3) cannot establish when Weinstein was publicly available absent evidence of the Library of Congress's stamping, indexing, cataloging, and shelving. *See In re Hall*, 781 F.2d at 899. As discussed above, the copyright date alone is also insufficient to support public availability. *See Mylan Pharm.*, IPR2016-01565, Paper 23 at 6.

VI. CONCLUSION

Petitioner fails to show (1) that the cited references, even if combined, disclose every limitation of the claims, either expressly or inherently; (2) that a POSA would have been motivated to modify the known dosing regimen for rheumatoid arthritis to arrive at the claimed dosing regimen for treating moderate-to-severe chronic plaque psoriasis with a reasonable expectation of success; and (3) that three of the five cited references qualify as prior art. In view of these failures, Petitioner has not shown a reasonable likelihood of establishing that any

challenged claim is unpatentable. The Board therefore should deny institution of the Petition.

Respectfully submitted,

Date: November 13, 2017

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CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that the foregoing **Patent Owner's Preliminary Response** contains 10,937 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and Exhibits 2001-2014 were served electronically via email on November 13, 2017, in its entirety on the following:

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