UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD,
Patent Owner.

Case IPR2018-00002
Patent No. 9,512,216

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Federal Cases

Board Authority

Federal Statutes

Federal Regulations

PATENT OWNER'S EXHIBIT LIST

EXHIBIT	DESCRIPTION
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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)
2015	Petition for Inter Partes Review in *Sandoz Inc. v. AbbVie Biotechnology Ltd*, IPR2017-01824, Paper 1 (July 20, 2017) ("First Petition")
2016	Comparison of Summary of Argument section in IPR2017-01824 (First Petition) to Summary of Argument section in IPR2018-0002 (Current Petition) (generated via Word's Comparison function)
2017	Ex. 1002, Declaration of Simon M. Helfgott, M.D., C.M. in *Sandoz Inc. v. AbbVie Biotechnology Ltd*, IPR2017-01824 (July 20, 2017) ("First Helfgott Declaration")
2018	Ex. 1050, Declaration of John Posner, Ph.D., MB.BS., FRCP in *Sandoz Inc. v. AbbVie Biotechnology Ltd*, IPR2017-01824 (July 20, 2017) ("First Posner Declaration")
2019	Ex. 1070, Transcript of November 30, 2017 Conference Call in *Sandoz Inc. v. AbbVie Biotechnology Ltd*, IPR2017-01824 (filed December 11, 2017)

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, or experimental anti-TNFα biologics tested for psoriasis, used an initial dose of drug that was greater than subsequent doses. The claimed treatment method is strikingly different from earlier regimens.

Petitioner nevertheless asserts that one 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 invention's unexpected results.

The Board should deny institution for several reasons:

First, the Petition presents substantially the same references and arguments as a prior petition that Petitioner filed challenging the same claims of the '216 patent. (*See Sandoz Inc. v. AbbVie Biotechnology Ltd*, IPR2017-01824, Paper 1 ("First Petition"; provided as Ex. 2015).) Four of the five references in the proposed obviousness ground are the same in both petitions, and the fifth reference in the Second Petition was discussed as background art in the First Petition. Moreover, essentially all of the background art cited in the Second Petition was also cited in the First Petition. Further, the Second Petition presents nearly identical arguments as the First Petition. Petitioner offers no justification for filing a Second Petition challenging the same claims based on the same references and arguments. The Board should therefore deny institution under 35 U.S.C. § 325(d) or § 314(a).

Second, 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.

Third, 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.

Fourth, Petitioner fails to establish that three of the references in its five-reference obviousness combination were publicly accessible before the critical date and thus qualify as prior art. This alone defeats the Petition.

For the reasons detailed below, Petitioner has failed to show a reasonable likelihood of prevailing as to any challenged claim. The Board should therefore deny institution.

II. BACKGROUND

A. Chronic Plaque Psoriasis

Psoriasis is an immunological skin disorder with a range of clinical manifestations. (Ex. 1003, 10.)[1] Psoriatic skin lesions vary 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 varies in severity. (Ex. 1003, 23.) The extent of skin involvement can range from discrete, localized areas to generalized body involvement. (*Id*., 11.) Today, as in 2004 when the earliest priority application was filed, the pathogenesis of the disease is poorly understood, as several factors, including genetic, immune, and environmental elements, play a role. (Ex. 2001, 27-33; Ex. 1003, 14-18, 25, 47.)

Chronic plaque psoriasis, the most common form of the disease, 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. (Ex. 1008, 11; Ex.

[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.

1003, 19.) 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 based on the body surface area affected: less than 5% body surface area for mild, 5-15% for moderate, and 15-20% for severe. (Ex. 1003, 14.)

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 body regions and assigning each an area score and severity score. (Ex. 1036, 5; Ex. 1001, 28:24-29.) "PASI 75," which refers to a 75% reduction of the PASI score from start of treatment, was considered the treatment goal for many clinical trials. (Ex. 2004, ii65.) PASI 75 efficacy is difficult to achieve, and some practitioners have argued that the FDA should therefore use a PASI 50 score as a clinical endpoint instead. (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, 4.) 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, 4.) 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, 49.)

C. Prior Art Treatments Investigated for Psoriasis

Treatments for plaque psoriasis were mostly "developed empirically . . . as with all other diseases of unknown cause." (Ex. 2001, 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, 27.) 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, 26-27, 30.) Systemic

treatments were typically used for moderate-to-severe chronic plaque psoriasis. (*Id*., 27; 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, 13 (Table 3); *see also* Pet., 32-33 (Table 4).) 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, no anti-TNFα biologic had been approved to treat psoriasis. Infliximab and etanercept were under investigation for treatment of psoriasis but there were no clinical trials for either of these biologic drugs investigating an initial dose greater than the treatment dose. (Ex. 1003, 38; Pet., 30-31.)

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 is administered via intravenous infusion with a weight-based dosing regimen. (*Id*., 4) 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, 49.) The initial dose 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, 6-7.) 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 dosing regimens tested for these biologics are summarized below.

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, provide tables purporting to compare prior art rheumatoid arthritis and plaque psoriasis dosing regimens. (Pet., 30-33 (Tables 3-4); Ex. 1002, 33-37 (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., 30 (Table 3) (citing Ex. 1060, 6)), 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, 6). Regardless, *none* of the "psoriasis" dosing regimens Petitioner identifies include an initial dose greater than the subsequent doses. (Pet., 30-33 (Tables 3, 4); Ex. 1002, 33-37 (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 by 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 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.) 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 '216 patent claims. 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., 18-19.) Petitioner defines a POSA developing a treatment as "an M.D. with at least 3 years' experience post-residency treating patients for psoriasis." (*Id*., 18.) 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*., 19.)

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, 23 (Table 6), 29-33.) Indeed, the psoriasis references relied on by Petitioner characterize the treating physician as a "dermatologist." (*Id.*, 23, 29.) Weinstein, for example, classifies treatment agents based on what percentage of "dermatologists" use that agent. (*Id.*, 29 (Table 12); *see also* Ex. 1008 (Textbook of Psoriasis), 30, 33, 46 (stating that dermatologists

[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.)

prescribe and determine the dosage of drugs for treating psoriasis patients).) For the reasons set forth below, the Board should deny institution regardless of the definition of a 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. (Pet., 19.) But Patent Owner disputes Petitioner's contention that the "wherein" clause of claim 1 does not limit the claim. (*Id*.)

Claims 1-8 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 specification supports this interpretation. It describes a clinical study 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 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 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., 19, 52-54.) Instead, Petitioner relies solely on *Minton v. National Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373 (Fed. Cir. 2003). (Pet., 19, 52.) This reliance is misplaced. The patent at issue there 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 "efficiently" was 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 laudatory term "efficiently" in *Minton*. The Board should reject Petitioner's position because the PASI 75 language limits the claims by requiring 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 show that three of its asserted references qualify as prior art—the Humira® 2003/2002 Label (Ex. 1026/Ex. 1075), the Press Release (Ex. 1052), and Weinstein (Ex. 1003). (*See infra* Section VI.D.) This failure requires denial of institution. Nonetheless, Patent Owner addresses these references below.

A. The Humira® 2003/2002 Label (Ex. 1026/Ex. 1075)

The Humira® 2002 Label and Humira® 2003 Label, neither of which Petitioner has established as prior art, concern Humira®, AbbVie's adalimumab product. Petitioner asserted the Humira® 2002 Label in its First Petition challenging the '216 patent claims (Ex. 2015, 22-24), but now also relies on the Humira® 2003 Label (Pet., 9-11). Petitioner refers to them as "the Humira® 2003/2002 Label," and states that the labels "are substantively similar and provide the same information pertinent to this Petition." (Pet., 4 n.9, 11.)

The Humira® 2003/2002 Label 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. (Ex. 1026, 1-2; Ex. 1075, 1-2.) Humira® was initially approved for treating *rheumatoid arthritis* (Ex. 1026, 4; Ex. 1075, 6), which 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). Rheumatoid arthritis is an "aggressive disorder [that] demands the early institution of an equally aggressive therapeutic approach." (Ex. 2012, 4.)

The Humira® 2003/2002 Label states that the approved dose "for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection." (Ex. 1026, 9; Ex. 1075, 14.) It 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 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 relied on the Press Release in the proposed obviousness ground in the First Petition (Ex. 2015, 22-24), and still has not established it as prior art. It 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, 1-2.) 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*., 1.) 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)

Petitioner relied on Weinstein in the proposed obviousness ground in the First Petition (Ex. 2015, 22-24), and still has not established it as prior art. Weinstein consists of chapter excerpts from a textbook on psoriasis and its 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, 6-7.) Weinstein reports that the "moderate/severe [psoriasis] patient population comprises 20-25% of all the psoriatics seen in the average practice." (*Id*., 28.)

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. Mease 2002 (Ex. 1009)

Petitioner cited Mease 2002 as a background reference in its First Petition. (Ex. 2015, 34, 42.) The reference discusses the role of TNFα in PsA, not psoriasis. (Ex. 1009, 4.) It states that the TNFα inhibitors infliximab and etanercept have proven effective in treating rheumatoid arthritis and that these agents "may have therapeutic benefit in patients with PsA." (*Id*., 7.)

Mease 2002 discloses results from a study treating 60 PsA patients with 25 mg of etanercept twice weekly. (*Id*.) It states that 38 of these patients had psoriasis with the minimum amount of affected skin required to evaluate skin response. (*Id*., 8.) Of these patients, only 26% of those treated with etanercept achieved a PASI 75 response, with a median PASI response of 50%. (*Id*.)

Mease 2002 also discusses two studies treating patients with infliximab, administered at 5 mg/kg at weeks 0, 2, and 6. (*Id*.) The first study involved PsA patients and the second involved patients with spondyloarthropathy, nine of whom also had PsA. (*Id*., 8-9) Mease 2002 does not disclose whether these patients had psoriasis or report any PASI efficacy results.

None of the patients in Mease 2002 are reported to have moderate-to-severe chronic plaque psoriasis. Nor does Mease 2002 suggest using adalimumab to treat

moderate-to-severe chronic plaque psoriasis or any dosing regimen for adalimumab.

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

This textbook chapter by Stuart Proudfoot and John Collett (Aulton) was asserted in the First Petition. (Ex. 2015, 22-24.) It 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, 12-13.) 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., 35 (citing Ex. 1056).)

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, 13 (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

[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."

describe or suggest the claimed dosing regimen for adalimumab or suggest any need to use an initial dose of adalimumab higher than subsequent doses.

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. THE BOARD SHOULD DENY INSTITUTION UNDER 35 U.S.C. § 314(a) AND § 325(d)

A. The Board Should Deny Sandoz's Second Petition Under § 325(d) Because It Presents Substantially the Same References and Arguments as Sandoz's First Petition

The Board may deny institution where "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). Here, the Board should deny institution because Sandoz's Second Petition challenging the '216 patent claims presents nearly identical references and arguments as its First Petition. Indeed, much of the Second Petition is word-for-word identical to the First Petition. (*See, e.g.*, Ex. 2016.)

Sandoz filed its First Petition challenging claims 1-16 of the '216 patent on July 20, 2017, asserting a single obviousness ground based on a combination of five references: the Humira® 2002 Label, the Press Release, Aulton, Weinstein, and Marzo-Ortega. (Ex. 2015, 21-24.) The First Petition also cited over 50 other

references as background art, including the Mease 2002 reference asserted in this proceeding. (*See, e.g.*, Ex. 2015, 34, 42.)

Sandoz filed this petition on October 2, 2017, its second challenge to claims 1-16 of the '216 patent. This Second Petition proposes one obviousness ground based on essentially the same references as the First Petition, only substituting Marzo-Ortega with the previously cited Mease 2002, and adding a 2003 version of the Humira® label as a joint reference with the Humira® 2002 Label. The ground is still based on the same Humira® 2002 Label, Press Release, Aulton, and Weinstein that were asserted in the First Petition. The addition of the Humira® 2003 Label in combination with the Humira® 2002 Label (referred to jointly as "the Humira® 2003/2002 Label") does not distinguish the Second Petition in any meaningful way, as Petitioner concedes that these labels "are substantively similar and provide the same information pertinent to this Petition." (Pet., 4 n.9.)

Aside from the Humira® 2003 Label, every reference cited in the Second Petition was also cited in the First Petition. (*Compare* Pet., vii-xvii, *with* Ex. 2015, 7-13.) The only difference is that the Second Petition moves Mease 2002 into the proposed obviousness ground rather than citing it as a background reference and cites Marzo-Ortega as a background reference rather than including it in the

proposed ground.[4] (Pet., 4.)

Petitioner does not explain how these changes justify a follow-on petition. Instead, Petitioner states only that Mease 2002 discusses both infliximab and etanercept, while Marzo-Ortega discusses only infliximab. (Pet., 4.) But Mease 2002 is not a new reference. On the contrary, Petitioner addressed its disclosures regarding etanercept in the First Petition, and the Second Petition relies on those same disclosures to support the same arguments made in the First Petition. (*Compare* Pet., 21, *with* Ex. 2015, 34; *compare* Pet., 27 n.18, *with* Ex. 2015, 40 n.15; *compare* Pet., 30-31 (Table 3), *with* Ex. 2015, 42 (Table 3).) In addition, Mease 2002 discloses studies that administered 5 mg/kg of infliximab at weeks 0, 2, and 6 to treat PsA, which is the *same* infliximab dosing regimen disclosed in several other references cited and discussed in the First Petition, including Marzo-Ortega. (*Compare* Ex. 1009, 8-9, *with* Ex. 1060, 6 (5 mg/kg at weeks 0, 2, and 6 for psoriasis); *see also* Ex. 1003, 49 (5 mg/kg at weeks 0, 2, and 6 for moderate-to-severe plaque psoriasis); Ex. 1036, 5 (5 mg/kg at weeks 0, 2, and 6 for moderate-to-severe plaque psoriasis).) Mease 2002's disclosure of this same dosing regimen thus is cumulative of other references cited in the First Petition.

Petitioner relies on both Mease 2002 and Marzo-Ortega for substantially the

[4] In both petitions, Mease 2002 is Exhibit 1009 and Marzo-Ortega is Exhibit 1060.

same disclosures in both petitions, and thus moving Mease 2002 into the proposed obviousness ground in the Second Petition is not a substantive change. *See, e.g.*, *Toyota Motor Corp. v. Cellport Sys., Inc.*, IPR2015-01423, Paper 7 at 7 (P.T.A.B. Oct. 28, 2015) (denying institution under § 325(d) where Petitioner did not explain why a reference cited in the first petition was "substantively and meaningfully different" from a reference cited in the second petition).

The petitions' similarities are summarized below:

	IPR2017-01824	**IPR2018-00002**
Petitioner	Sandoz	Sandoz
Challenged Patent	9,512,216	9,512,216
Challenged Claims	Claims 1-16	Claims 1-16
Asserted Grounds	Obviousness over: Humira® 2002 Label Press Release Aulton Weinstein Marzo-Ortega (Mease 2002 is background art)	Obviousness over: Humira® 2002 Label/ Humira® 2003 Label Press Release Aulton Weinstein Mease 2002 (Marzo-Ortega is background art)
Cited art	Exs. 1001-1025 Ex. 1026 Exs. 1027-1068	Same Same (as Ex. 1075) Same Exs. 1069-1074, 1076 (none of which is cited in the Petition)

The Second Petition also advances substantially the same arguments as the First Petition. Indeed, they present nearly identical arguments. (*Compare* Pet., i-iii, *with* Ex. 2015, 2-4; *see* Ex. 2016.) Further, Petitioner relies on the same two experts, whose declarations are substantially the same as those submitted with the First Petition. (*Compare* Ex. 1002, *with* Ex. 2017, *and* Ex. 1050, *with* Ex. 2018.)

The only discernible difference is the Second Petition's addition of an argument concerning the PASI 75 term in claims 1-8. As in the First Petition, Petitioner contends that this element is not a claim limitation or that it is inherent because *some* patients would achieve PASI 75 efficacy using the claimed dosing regimen. (Pet., 52-53; Ex. 2015, 62-63.) The Second Petition adds one paragraph contending that achieving PASI 75 efficacy at week 12 of treatment would have been obvious. (Pet., 53-54.) But Petitioner does not explain why it failed to include this argument in the First Petition and, moreover, this single paragraph is not a substantial change that would merit adjudication of a second, nearly identical petition. (*See infra* Section VI.A.)

Where, as here, a petitioner fails to "provide a compelling reason why [the Board] should readjudicate substantially the same prior art and arguments as those presented" in a prior proceeding before the Office, instituting the petition "would not be an efficient use of Board resources." *Unified Patents Inc. v. Berman*, IPR2016-01571, Paper 10 at 12 (P.T.A.B. Dec. 14, 2016). This is particularly true

here because Petitioner previously challenged the same claims based on substantially the same references without presenting any new arguments or evidence or providing any justification for filing a second petition. *Toyota Motor Corp.*, IPR2015-01423, Paper 7 at 8. The Board should therefore deny the Second Petition under § 325(d).

B. The *General Plastics* Factors Strongly Favor Denial of Institution Under § 314(a)

Even where the Board declines to deny a petition under § 325(d), institution remains discretionary, and the Board may decline to institute under § 314(a). In *General Plastic Industrial Co. vs. Canon Kabushiki Kaisha*, an expanded panel identified a nonexhaustive set of factors that the Board may consider when deciding whether to deny institution of follow-on petitions. IPR2016-01357, Paper 19 at 8-10 (P.T.A.B. Sept. 6, 2017). The factors take into account the inequity and undue prejudice that may arise when patent owners face follow-on petitions. *Id.* at 17. As discussed below, the Board should also deny the Second Petition under § 314(a) because five of the seven factors strongly favor denying institution.[5]

[5] Factors 3 and 7 are neutral and far outweighed by the other factors. Although Petitioner filed the Second Petition before receiving AbbVie's preliminary

1. Factor 1: Petitioner filed an earlier petition challenging the same claims

Factor 1 addresses "whether the same petitioner previously filed a petition directed to the claims of the same patent." *Id*. at 9. Here, the same petitioner challenges the same claims of the same patent using substantially the same references and arguments. This factor thus weighs heavily in favor of denial.

2. Factors 2 and 4: Petitioner knew of all the asserted art, and cited it in the First Petition

Factor 2 concerns "whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it." *Id*. at 9. Here, the only reference cited in the Second Petition that was not cited in the First Petition is the Humira® 2003 Label, which Petitioner states is "substantively similar and provide[s] the same information pertinent to this Petition" as the Humira® 2002 Label. (Pet., 4 n.9.) Petitioner does not explain why it did not cite the Humira® 2003 Label in the First Petition or assert that it was unaware of the reference or could not have cited it. Nor does Petitioner contend that it could not have asserted Mease 2002 in the proposed ground in the First Petition rather than using it as a background reference. Further, every reference in

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response to the First Petition, Petitioner fails to explain its delay in filing a substantially duplicative Second Petition.

the proposed grounds of both petitions was submitted during prosecution of the '216 patent, as were many of the cited background references. (Ex. 2011, 13-32[6]; Pet., 11 n.11; Ex. 2015, 24 n.5.) Factor 2 thus strongly favors denial.

For the same reasons, Factor 4 strongly favors denying the Second Petition. This factor considers "the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition." *General Plastic*, IPR2016-01357, Paper 19 at 9. Petitioner knew of the cited art at least as early as the filing date of the First Petition on July 20, 2017, but waited until October 2, 2017, to file a minimally revised Second Petition. Petitioner does not explain or justify this delay. The *General Plastic* factors are meant to curtail precisely this type of serial challenge. *Id.* at 17-18.

3. Factor 5: Petitioner provides no justification for filing the Second Petition challenging the same claims based on the same references and arguments

Factor 5 examines "whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent." *Id*. at 9. Here, Petitioner provides *no explanation or justification* for filing a second petition challenging the same claims of the same

[6] As noted above, not every page of Weinstein (Ex. 1003) was submitted during prosecution.

patent based on substantially the same references and arguments. (Pet., 4-5.) This failure weighs in favor of denying the Petition, particularly given that both petitions cite all the same art and do no more than shift Mease 2002 from a background reference into the proposed ground.

4. Factor 6: The Board's finite resources

Factor 6 weighs in favor of denying the Second Petition. Petitioner offers no reason for the Board to expend its resources to consider two substantially identical petitions. The Board should therefore deny institution under § 314(a).

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

A. The Asserted References, Even if Combined, Do Not Disclose Every Claim Element

1. The cited references do 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 (Pet., 10-11), it fails to identify any disclosure in these references of

the claimed one-week interval between a higher initial dose and a first every-other-week dose. Indeed, it cannot—none of the cited references, either alone or in combination, describes this aspect of the claimed dosing regimen.

Petitioner relies on Aulton to argue that the one-week interval was an "obvious choice." (Pet., 22-23, 48-49.) Aulton, however, is a general reference that only addresses the "concept of 'loading doses.'" (Ex. 1051, 12-13.) 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, 11-13.) Indeed, Aulton suggests using 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*., 13 (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® 2003/2002 Label, but again points to no disclosure of the claimed one-week interval between a higher initial dose and subsequent every-other-week dosing. (Pet., 20-21, 48-49.) Indeed, Petitioner cites the Humira® 2003/2002 Label for its administration of 40 mg of adalimumab *every-other-week* to treat rheumatoid arthritis. (*Id.*, 22-23 (citing Ex. 1075; Ex. 1026).) But the label 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, 9; Ex. 1075, 14.) Petitioner concedes that the Humira® 2003/2002 Label does not suggest this dosing regimen, stating instead that, based on adalimumab's roughly two-week half-life, a "POSA would

understand that one appropriate adalimumab induction dosing regimen is 80mg (twice the 40mg treatment dose) *two weeks prior* to beginning 40mg [every-other-week] treatment dosing." (Pet., 46 (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*., 51.) 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, 50; Pet. 37, 51.) 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. 37; Ex. 1050, ¶ 40; Ex. 1003, 50; *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 inaccurately implies, or indeed for any drug other than infliximab. (Pet., 51.) Moreover, the reported induction and maintenance doses 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.[7]

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 VI.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. *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 . . . .").

[7] 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 references do not disclose the PASI 75 efficacy element of claims 1-8, either expressly or inherently

a. Achieving PASI 75 is not inherent

Petitioner does not contend that any asserted reference discloses the PASI 75 efficacy limitation for adalimumab, much less for the claimed dosing regimen. Faced with the absence of this claim element in the prior art, Petitioner instead argues that the PASI 75 efficacy limitation is a natural result inherently achieved by at least *some* psoriasis patients receiving adalimumab in accordance with the claimed dosing regimen. (Pet., 52-53.) 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 VI.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, thus failing 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., 52-53; *see also* Ex. 1002, ¶ 110.) 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 inherency argument because it ignores the claimed PASI 75 efficacy at week 12. (Pet., 52-54.) The Federal Circuit has held that it is legal error to use inherency to ignore claim limitations. *See Par*, 773 F.3d at 1195-96. In *Par*, for example, the court 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., 53.) Here, Petitioner identifies no prior art disclosure where administering adalimumab achieved the PASI 75 limitation, admits that PASI 75 efficacy does not necessarily occur at week 12, and cites no expert testimony to support its contentions.

The 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 required providing a "*therapeutically effective* plasma concentration over a period of 24 hours to treat muscle spasm." *Id*. 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 fails to cite any prior art disclosing—or expert testimony addressing—a treatment lasting at least 12 weeks where a patient being treated with adalimumab achieves PASI 75 at week 12. (Pet., 52-54.) Indeed, Dr.

Helfgott cites only the ’216 patent itself to support his conclusion that achieving PASI 75 efficacy at week 12 is a “natural result inherently achieved by at least some [psoriasis] patents” (Ex. 1002, ¶ 110), 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.

b. Achieving PASI 75 would not have been obvious

In a single paragraph, Petitioner alternately argues that the claimed PASI 75 efficacy at week 12 of treatment would have been obvious over cited art that discusses infliximab or etanercept. (Pet., 53-54.) The Board should reject this argument for several reasons. First, the cited references fail to teach achieving PASI 75 efficacy at week 12 for patients with moderate-to-severe chronic plaque psoriasis using the rheumatoid arthritis dosing regimen for infliximab or etanercept, much less for adalimumab. The cited infliximab references disclose using *consistently higher* doses for treating chronic plaque psoriasis than rheumatoid arthritis. (Ex. 1003, 49; Ex. 1009, 8; *see also* Exs. 1033, 1036, 1037 (disclosing use of higher infliximab doses).) For example, Weinstein, Chaudhari, and Mease 2000 discuss using infliximab doses of either 5 mg/kg or 10 mg/kg,

both higher than the 3 mg/kg dose approved for rheumatoid arthritis. (Ex. 1003, 68; Ex. 1009, 8; Ex. 1036, 4.) With respect to etanercept, Mease 2002 does not discuss treating moderate-to-severe chronic plaque psoriasis at all. Instead, it reports an etanercept study for patients with PsA, and none of those PsA patients are reported to have moderate-to-severe chronic plaque psoriasis. (Ex. 1009, 8.) Many of the other references Petitioner cites similarly fail to disclose treating the claimed patient population. (*See, e.g.*, Ex. 1060, 6; Ex. 1033, 6; Ex. 1037, 429; Ex. 1006, 10) Petitioner's own cited references thus fail to establish that it would have been obvious to achieve PASI 75 efficacy at week 12 using the claimed methods or that a POSA would have had any reasonable expectation of success.

Further, Petitioner provides no basis for extrapolating from the dosing regimens of different drugs to arrive at the claimed dosing regimen for adalimumab. Infliximab and etanercept were known to have different structures and pharmacokinetic properties, and Petitioner fails to establish that a POSA would simply assume that PASI 75—a rigorous threshold (Ex. 2002, 860)—could be achieved at week 12 using adalimumab. Accordingly, Petitioner has not established a reasonable likelihood that claims 1-8 are unpatentable for obviousness.

B. No Motivation Existed 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 and chronic plaque psoriasis using the *same dose* and *similar dosing regimens*. (Pet., 1-2, 20-21, 25-33, 40-43.) 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*., 41-43.) 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*., 44-49.)

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 have modified 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., 22), 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*., 22, 37-39.) 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, 22.) 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, 8.)

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 infliximab or 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, 4; Ex. 1039, 66; Ex. 1040, 8; Ex. 1060, 6; Ex. 1061, 7; Ex. 1036, 5; Ex. 1037, 429; Ex. 1033, 6.)

Further, although infliximab was dosed more frequently early in the regimen (e.g., at weeks 0, 2, and 6, and then every 8 weeks as needed), 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, 1.) As stated in the Remicade label, "[n]o systemic accumulation of infliximab occurred upon continued repeated administration." (*Id*.) 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*., 4.)

Like infliximab, the etanercept dosing regimens identified by Petitioner did not use a larger initial dose. Regardless of indication, etanercept was *always* administered as 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 identifies no 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 statements 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, 36.) 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., 36-39 & n.24.) 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, 49; Ex. 1060, 6.)

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 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 VI.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 other evidence. (Pet., 48-49; 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., 22-23, 48-49; 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., 22-23, 48-49; 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., 48-49); *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., 21, 48-49.) 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., 22-23, 36, 46.) Dr. Posner, for example, states 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 assertion 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, Petitioner states 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., 46, 48-49; *see also* 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 Enterprise, 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., 49.) 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., 3, 21-23, 49.) 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, Petitioner's cited references provide no 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, 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 drug levels would be achieved by week 10 without the initial 80 mg dose. (Pet., 45.) 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 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., 18.) 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., 17-18.) 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 efficacy levels. (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., 17-18.) 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® 2003/2002 Label, the Press Release, and Weinstein qualify as prior art under 35 U.S.C. § 102(b). Yet despite this being its second petition, Petitioner provides no evidence establishing public accessibility of these references. (Pet., 10-11.) This deficiency is fatal. Petitioner's sole ground of unpatentability relies on these 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.[8] *Ford Motor Co. v. Versata Dev. Grp., Inc.*, IPR2016-01012, Paper 12 at 3, 11-12 (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® 2003/2002 Label was publicly available in December 2002

Petitioner refers to Exhibits 1026 and 1075 collectively as the "Humira 2003/2002 Label." (Pet., 11.) Petitioner asserts that the "Humira® 2003 Label" (Ex. 1026) has a "Publication Date" of "January 2003," but offers no evidence to support this assertion. (Pet., 10.) Petitioner previously relied on the "Humira® 2002 Label" (Ex. 1075) in the first petition, yet provides no additional evidence in this second petition to support the asserted "Publication Date" of "Dec. 2002." (Pet.,

[8] 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.) The 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).

10.)[9] Petitioner has not met its threshold burden for either of these labels for several reasons.

First, the dates on Exhibits 1026 and 1075 alone do not prove public availability. No evidence connects the December 20, 2002, date on page 1 of Exhibit 1075 or the "Issued: December 2002" language on page 16 to public accessibility. (Ex. 1075, 1, 16.) Similarly, no evidence connects the "Revised: January, 2003" language on pages 10 and 13 of Exhibit 1026 to public accessibility. (Ex. 1026, 10, 13.) Notably, no evidence establishes what "Issued: December 2002" or "Revised: January, 2003" means or equates "Issued" or "Revised" 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).

Instead, Petitioner asserts that these labels are publications "on their face," as it argued before the Board in connection with the First Petition. (Ex. 2019, 5:7-8.) This ignores, however, that a date alone does not establish the public *accessibility* component of the printed publication inquiry. *See In re Lister*, 83 F.3d

[9] In this follow-on petition, Petitioner has renumbered the Humira® 2002 Label as Exhibit 1075 (it was Exhibit 1026 in the First Petition) and has now labeled the Humira 2003 Label as Exhibit 1026.

at 1311-12. The Board has repeatedly held that dates on a drug's package insert alone 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). Thus, these dates, without more, do not meet Petitioner's threshold burden of showing that Exhibits 1026 and 1075 are printed publications.

Second, Petitioner cites no support from any of its declarants for the public availability of Exhibits 1026 and 1075. Thus, any arguments or explanation contained in these declarations should be disregarded. 37 C.F.R. § 42.104(b)(5). This is especially so here because incorporating arguments from uncited declarations would allow Petitioner to circumvent the 14,000-word limit, this Petition purportedly being 13,968 words.[10] *See Conopco, Inc. v. Procter & Gamble*

[10] Petitioner certifies that the Second Petition is 13,968 words, but this total appears to omit the conclusion (40 words) and signature block (35 words), and significantly, the footnotes in the Exhibit list (106 words) that contain arguments regarding documents' publication status (Pet. at vii). To the extent Petitioner seeks to rely on these arguments or the exhibits cited therein (the exhibit list being the only place Exhibits 1065-1074 and 1076 are cited), the Petition violates both the

Co., IPR2013-00510, Paper No. 9, 8-9 (P.T.A.B. Feb. 12, 2014) (declining to consider expert's declaration testimony "nowhere discussed in the Petition" because, "among other reasons, doing so would encourage the use of declarations to circumvent the page limits that apply to petitions.").

Third, even if the Board considers Petitioner's declarations, they fail to establish the public accessibility of either Humira® label. Dr. Posner simply assumes the documents are prior art without addressing either label's public availability or offering any supporting evidence. (*See* Ex. 1050, 7, n.2.)

As to the 2002 label, Dr. Helfgott states that "the 2002 Humira® label would have been available on the date Humira® was approved in 2002 and FDA-approved labels are publicly available for use by physicians and the public on the date printed on the insert." (Ex. 1002, ¶ 15.) Petitioner omits this argument from the petition. (*See* Pet., 10-11.) Furthermore, Dr. Helfgott cites no evidence tying FDA approval of Humira® in December 2002 to public dissemination of the Humira® 2002 Label (Ex. 1075). Nor does he offer any personal knowledge establishing that the Humira® 2002 Label was publicly available in December 2002, how it became available, or on what date it was available. (*See generally* Ex. 1002, ¶15.) The

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word count limit and the prohibition against incorporation by reference. 37 C.F.R. § 42.24(a)(1)(i); 37 C.F.R. § 42.6(a)(3).

Board should give no weight to his assertions, which are unsupported by any facts, data, or analysis. 37 C.F.R. § 42.65(a); *see, e.g.*, *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).

As to the Humira® 2003 Label, Dr. Helfgott makes no assertion regarding its public availability. The Board should disregard Petitioner's submission of declarations by Victoria Reines (Ex. 1068) and Christopher Butler (Ex. 1076) and a screen capture from the WayBack Machine (Ex. 1072) because the Second Petition *neither cites nor discusses* these exhibits. Petitioner cannot meet its threshold burden by asking the Board to piece together the record on Petitioner's behalf. *See Stampa v. Jackson*, 78 U.S.P.Q. 2d 1567, 1571 (B.P.A.I. 2005) ("Appellant's Brief is at best an invitation to the court to scour the record, research any legal theory that comes to mind, and serve generally as an advocate for appellant. We decline the invitation." (quoting *Ernst Haas Studio, Inc. v. Palm Press, Inc.*, 164 F.3d 110, 111–12 (2d Cir. 1999))). Regardless, neither declaration establishes or even mentions a January 2003 publication date or, critically,

addresses the accessibility of the Humira® 2003 Label—the touchstone of the printed publication inquiry. *Celltrion, LLC v. Biogen, Inc.*, IPR2017-01230, Paper 10 at 13-15 (P.T.A.B. Oct. 12, 2017).

Finally, Petitioner provides no evidence showing the source of Exhibits 1026 and 1075, how one could have obtained a copy, or whether they were reasonably accessible to the interested public. *See Mylan Pharm.*, IPR2016-01563, Paper 16 at 14. Petitioner argued previously that "it is difficult to imagine" what evidence could prove the publication status of the Humira® 2002 Label without discovery from AbbVie. (Ex. 2019 at 33:8-11.) But this argument improperly shifts the burden to patent owner and disregards Petitioner's failure to show that it even attempted to establish the document's accessibility, such as through supported expert testimony, the FDA website, or the Physician's Desk Reference. Rather, Petitioner's failure to include any of this information compels a finding that it did not establish Exhibits 1026 and 1075 as printed publications. *See, e.g., Teva Pharm. USA, Inc. v. Indivior UK 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 as in its First Petition, Petitioner cites only the exhibit itself with no evidence as to the exhibit's source, publication, dissemination, or public availability. (Pet., 10, 24.) Dr. Helfgott's declaration adds nothing and should be disregarded because (1) it merely parrots the Petition's conclusory assertions (Ex. 1002, ¶¶ 51, 59), 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). Petitioner previously argued that the March 3, 2003, date means that "on its face" and "[b]y definition" the document was publicly accessible on this date. (Ex. 2019, 5:16-22.) This argument cannot be reconciled, however, with the two other dates listed on the exhibit—July 8, 2003, and August 25, 2017. (Ex. 1052, 1.) Petitioner's reliance only on one date listed on Exhibit 1052, without any additional evidence or explanation, fails to establish public accessibility.

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, 1-2.) Indeed, Petitioner admitted to the Board that this is a "third-party document" that "purports" to be an AbbVie press release. (Ex. 2019, 25:2-4.)

Petitioner also fails to address the webpage's public availability on March 3, 2003 or establish 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). As Petitioner has acknowledged, mere availability on a website is not enough to establish public accessibility, and the WayBack Machine does not indicate whether an interested person could have located the document. (Ex. 2019 at 26:5-20); *Celltrion*, IPR2017-01230, Paper 10 at 13-15. Petitioner thus has not shown that Exhibit 1052 was published on March 3, 2003.

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., 10), but again fails to establish the exhibit's public availability. This date does not appear in Weinstein, so Petitioner instead submits Exhibit 1065 (purportedly a website printout from the Copyright Office). As an initial matter, Petitioner's only citation to Exhibit 1065 is in a footnote to its exhibit list. (Pet., vii.) The exhibit is not cited or discussed in the body of the Petition. Further, Petitioner seems to have omitted this footnote from the word count. The Board should therefore disregard this citation and any arguments based thereon. *Conopco*, IPR2013-00510, Paper No. 9 at 8-9; 37 C.F.R. §42.24(a)(1)(i).

The Board should also disregard Exhibit 1065 because Petitioner fails to explain how it relates to Weinstein's alleged public availability as of March 19, 2003. 37 C.F.R. § 42.104(b)(5). Exhibit 1065 lists (without explanation) "Date of Publication: 2003-03-19." Crucially, Petitioner does not explain how this date was generated, what "publication" means to the copyright office, 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).

Petitioner's submission of the Reines Declaration (Ex. 1068), which

discusses Exhibit 1065, also does not establish public availability. (Ex. 1068 at ¶3.) Petitioner does not cite Exhibit 1068 or incorporate any of its arguments into the Petition, and the Board therefore should disregard it. Additionally, the Reines Declaration, which at most authenticates the *existence* of Exhibit 1065 *in 2017*, fails to establish that Ms. Reines has any personal knowledge regarding the publication of Exhibit 1003 as of March 19, 2003, or the meaning of information provided by the Copyright Office's public catalog or its publishing practices.

The unintelligible stamp on page 5 of Exhibit 1003 and "© 2003" text on page 2 also do not establish public availability. (Ex. 1003, 2, 5.) 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 stamp fails to establish a date of public availability because (1) it does not appear to match 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 source library's stamping, indexing, cataloging, and shelving practices. *See In re Hall*, 781 F.2d at 899. The copyright notice also does not establish public availability, as it relates only to the document's creation, not 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)). Accordingly, the Second Petition should be denied.

VII. CONCLUSION

The Board should deny institution under 35 U.S.C. § 325(d) or § 314(a) because Petitioner offers no explanation for filing a Second Petition challenging the same claims of the '216 patent based on nearly identical references and arguments. Alternatively, the Board should deny institution because 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; 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.

Respectfully submitted,

Date: February 5, 2018

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CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that the foregoing **Patent Owner's Preliminary Response** contains 13,753 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.

Date: February 5, 2018

By: /*William B. Raich* /
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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response and Exhibits 2001-2019** were served electronically via email on February 5, 2018, in its entirety on the following:

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