Filed: January 5, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD,
Patent Owner.

Case IPR2017-02105
Patent No. 9,090,689

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Federal Cases

Patent Trial and Appeal Board Cases

Federal Statutes

Regulations

PATENT OWNER'S EXHIBIT LIST

EXHIBIT	DESCRIPTION
2001	Information Disclosure Statement, Form SB08, submitted May 2015, during prosecution of U.S. Application No. 14/681,704
2002	List of References Cited by Examiner dated May 13, 2015 during prosecution of U.S. Application No. 14/681,704
2003	Information Disclosure Statement dated May 4, 2015, submitted during prosecution of U.S. Application No. 14/681,704
2004	*Reserved*
2005	S. R. Feldman & G. G. Krueger, *Psoriasis assessment tools in clinical trials*, 64 ANN RHEUM DIS (Suppl II), ii65, ii65-ii68 (2005)
2006	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*, 50 J. AM. ACAD. DERMATOLOGY, 859, 859-866 (June 2004)
2007	Irwin M. Freedberg et al. (eds.), FITZPATRICK'S DERMATOLOGY IN GENERAL MEDICINE (6th edition, 2003)
2008	John Brockbank & Dafna Gladman, *Diagnosis and Management of Psoriatic Arthritis*, 62 DRUGS 2447-57 (2002)
2009	John Brockbank & Dafna Gladman, *Psoriatic Arthritis*, 9 EXPERT OPINION ON INV. DRUGS 1511-22 (2000)
2010	AMEVIVE® (alefacept) Package Insert (May 2012)
2011	RAPTIVA™ (efalizumab) Package Insert (March 2009)
2012	REMICADE® (infliximab) Package Insert (Nov. 2013)
2013	William J. Sandborn et al., *A Randomized, Double-Blind, Placebo-Controlled Trial Of Subcutaneous Etanercept (p75 Soluble Tumor Necrosis Factor:FC Fusion Protein) ln The Treatment Of Moderate To Severe Crohn's Disease*, 120 GASTROENTEROLOGY, A-20 (April 2001)
2014	*Will Onercept failure derail similar biologics?*, FROST & SULLIVAN (May 5, 2005), http://www.frost.com/sublib/display-market-insight.do?id=37506280
2015	Lisa M. Sedger et al., *Therapeutic Antibody-Based Drugs in the Treatment of Human Inflammatory Disorders*, IMMUNOLOGY AND MICROBIOLOGY (Krassimir Metodiev, ed. April 26, 2017)
2016	*Pegsunercept*, ADIS R&D INSIGHT (Dec. 21, 2010) *downloaded* on December 14, 2017

EXHIBIT	DESCRIPTION
2017	Siba Prasad Raychudhuri, M.D. et al., *Psoriasis Risk Factors: Role of Lifestyle Practices*, 66 CUTIS 348, 348-352 (Nov. 2000)
2018	R.D. Mosteller, M.D., *Simplified Calculation of Body-Surface Area*, 317 NEW ENG. J. MED 1098, 1098 (Oct. 22, 1987)
2019	R. Munro & H. Capell, *Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response*, 56 ANN. RHEUMATIC DISEASES 326, 326-329 (1997)
2020	G. Steiner et al., *Cytokine production by synovial T cells in rheumatoid arthritis*, 38 RHEUMATOLOGY 202, 202-213 (1999)
2021	A. Mussi et al., *Serum TNF-alpha levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis*, 11 J. BIOLOGICAL REG. & HOMEOSTATIC AGENTS 115, 115-118 (1997).
2022	AMEVIVE® (alefacept) Package Insert (Feb. 2003), downloaded from https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/alefbio013003LB.htm on August 18, 2017
2023	RAPTIVA™ (efalizumab) Package Insert (Oct. 2003)
2024	*Reserved*
2025	Kim A. Papp et al., *Efalizumab for the Treatment of Psoriatic Arthritis*, 11 J. CUTANEOUS MED. & SURGERY 57, 57-66 (2007).
2026	Charles Camisa, M.D., HANDBOOK OF PSORIASIS 2ND EDITION, Blackwell Publishing, Inc. (MA) (2004)

I. Introduction

U.S. Patent No. 9,090,689 discloses a specific dosing regimen for adalimumab to treat a specific condition: moderate-to-severe chronic plaque psoriasis. Patients with this condition constitute a small subset of a broader class of psoriasis patients that exhibit a range of clinical manifestations and severities.

In challenging the '689 patent claims, Petitioner asserts that a person of ordinary skill in the art ("POSA") would have found it obvious to treat moderate-to-severe chronic plaque psoriasis using adalimumab's approved rheumatoid arthritis dosing regimen (40 mg of subcutaneous adalimumab every-other-week). As of the priority date, however, no pre-clinical or clinical evaluation of adalimumab in psoriasis or any other skin disease had been published. Further the asserted references taught the use of *higher* doses for treating moderate-to-severe chronic plaque psoriasis than those approved for rheumatoid arthritis for other TNFα inhibitors. Indeed, *none* of Petitioner's cited references discloses that the approved rheumatoid arthritis dose of a biologic would treat moderate-to-severe chronic plaque psoriasis. The Board should deny institution for three principal reasons:

First, Petitioner fails to establish any reasonable expectation of success in using adalimumab to treat moderate-to-severe chronic plaque psoriasis. Rather, the cited references merely express a hope that adalimumab would work to treat

psoriasis. *None* of these references discloses or suggests adalimumab's efficacy in treating any form of psoriasis, much less the claimed moderate-to-severe chronic plaque psoriasis. The cited art also specifically refutes the idea that adalimumab's efficacy could be presumed, stating that "long-term observations" were "*required* concerning side effects and efficacy" of agents including adalimumab. (Ex. 1028 at S18 (emphasis added).) [1]

Second, Petitioner fails to establish that a POSA would have been motivated to use, or would have had a reasonable expectation of success in using, the approved rheumatoid arthritis dosing regimen of adalimumab (40 mg every-other-week) to treat moderate-to-severe chronic plaque psoriasis. Petitioner's only asserted prior art reference directed to the treatment of moderate-to-severe chronic plaque psoriasis, Chaudhari (Ex. 1036), used a *higher dose* of infliximab than approved for rheumatoid arthritis, contradicting any motivation or expectation of success in using the *same dosing regimen* as approved for rheumatoid arthritis. Using higher doses for moderate-to-severe chronic plaque psoriasis than for rheumatoid arthritis is consistent with the differences between the two diseases,

[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.

which Petitioner fails to address. Petitioner's "background" references also disclose using higher doses of TNFα inhibitors to treat moderate-to-severe chronic plaque psoriasis than those approved for rheumatoid arthritis.

Third, with respect to dependent claims 16 and 19, Petitioner fails to establish that the recited efficacy limitations and patient population are inherent or that the claims as a whole would have been obvious. These claims are directed to treating patients with both moderate-to-severe chronic plaque psoriasis *and* psoriatic arthritis, wherein the patients achieve at least a 75% reduction in the Psoriasis Area and Severity Index (PASI) score at week 12 (claim 16) or a Physician's Global Assessment (PGA) score of clear or almost clear at week 12 (claim 19). None of the cited references discloses or suggests treating this patient population with adalimumab or achieving the claimed efficacy limitations. Nor do the references render these limitations inherent, and Petitioner's argument improperly applies inherency on top of obviousness to supply the limitations missing from the cited references.

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

II. The Patented Invention

The ’689 patent discloses and claims novel methods for preparing adalimumab for treating moderate-to-severe chronic plaque psoriasis. The patent explains that psoriasis is a form of skin inflammation characterized by frequent episodes of redness, itching, and silvery scales on the skin. (Ex. 1001 at 25:64-67.) The patent also explains that, in contrast to psoriasis, rheumatoid arthritis is characterized by swollen and tender joints. (Ex. 1001 at 27:53-55.) The patent describes the use of PASI and PGA to measure improvements in psoriasis. (Ex. 1001 at 27:58-28:3, 41:4-23.) The specification details the use of D2E7 (adalimumab) in treating human patients with moderate-to-severe chronic plaque psoriasis by filling adalimumab into vessels and subcutaneously administering to those patients 40 mg of adalimumab every-other-week with a primary endpoint of achieving at least a 75% reduction in PASI score at week 12. (Ex. 1001 at 40:1-16.)

Independent claims 1 and 7 of the ’689 patent recite:

> 1. A method of administering adalimumab for treatment of moderate to severe chronic plaque psoriasis, comprising filling adalimumab into vessels and subcutaneously administering 40 mg of said adalimumab to a patient having moderate to severe chronic plaque psoriasis every other week.

> 7. A method of preparing adalimumab for treating moderate to severe chronic plaque psoriasis, comprising filling adalimumab into vessels and providing said adalimumab for treatment, wherein said treatment comprises subcutaneously administering 40 mg of said adalimumab to a patient having moderate to severe chronic plaque psoriasis every other week.

(Ex. 1001 at 57:15-35.)

Claims 16 and 19, which depend from claim 7, recite:

> 16. The method of claim 7, wherein said patient has both psoriasis and psoriatic arthritis and achieves at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score at week 12 of the treatment.
>
> 19. The method of claim 7, wherein said patient has both psoriasis and psoriatic arthritis and achieves at least a Physician Global Assessment (PGA) score of clear or almost clear at week 12 of the treatment.

(Ex. 1001 at 58:24-36.)

During prosecution, Patent Owner submitted to the Examiner an Information Disclosure Statement citing all of the references asserted by Petitioner, including Keystone, Lorenz, Mease 2000, and Chaudhari. (Ex. 2001 at 9, 14-16; Ex. 2003.)

The Examiner considered the references, as indicated on the May 13, 2015 List of References Considered. (Ex. 2002 at 9, 14-16.)

III. Background

A. Psoriasis Is a Disease That Encompasses a Range of Clinical Types and Severities

Psoriasis is a chronic, inflammatory skin disorder with a range of clinical manifestations.[2] (Ex. 1031 at 8-9.) The appearance of psoriatic skin lesions varies considerably, ranging from 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*. at 9; Ex. 1008 at 3-4, 11-17.) The extent of skin involvement can also range from discrete, localized areas, to generalized body involvement. (Ex. 1008 at 8-9, 11-12; Ex. 1031 at 9-12.) Chronic plaque psoriasis is characterized by red, scaly lesions that may range in size from small coin-sized lesions to larger ones that may coalesce to cover large areas. (Ex. 1008 at 11.) Today, as in 2002, the pathogenesis and etiology of the disease is not completely understood, as several factors including genetic, immune, and environmental elements play a role. (*Id.* at 6-11; Ex. 1031 at 12-13.)

[2] Unless otherwise specified, references herein to "psoriasis" encompass the broader disorder including its various clinical manifestations and severities.

Psoriasis is traditionally classified by severity. Most patients with psoriasis have mild psoriasis, which the Physician's Global Assessment (PGA) categorizes as only "slight plaque elevation, scaling, and/or erythema." (Ex. 1001 at 41:21-22.) In contrast, moderate-to-severe chronic plaque psoriasis is physically and psychologically debilitating and often affects daily activities and ability to work. (*See* Ex. 1036 at 4.) The PGA categorizes this severity as one of "marked plaque elevation, scaling, and/or erythema." (Ex. 1001 at 41:17-20.)

The Psoriasis Area and Severity Index (PASI) represents a widely-used method to assess psoriasis in clinical trials. (Ex. 2005 at ii65.) The score is a multi-factorial calculation generated by examining four body regions and assigning an area score and a severity score (based on redness, thickness, and scaling) for each. (Ex. 1036 at 5; Ex. 1001 at 27:64-28:3.) The term "PASI 75" is shorthand for a 75% reduction of the PASI score from the start of treatment, and PASI 75 has been used as the treatment goal for many clinical trials. (Ex. 1001 at 41:7-10.) It is a difficult target to achieve, prompting some practitioners to propose that the FDA should instead use a lower PASI 50 score as a clinical endpoint. (*See* Ex. 2006 at 860.)

B. Psoriatic Arthritis Is a Joint Disease Distinct from Psoriasis

While sometimes associated, psoriatic arthritis (PsA) and psoriasis are distinct conditions affecting different anatomy. (Ex. 2008 at 2448-50; Ex. 2009 at

1511-12.) In contrast to psoriasis, which is a skin disorder, PsA affects the ligaments, tendons, fascia, and spinal or peripheral joints. (Ex. 2007 at 42.) In its most severe form, PsA can result in the destruction of a patient's joints. (Ex. 2009 at 1513.) PsA patients can also experience joint fusion (ankylosis), destruction of bone cells (bone lysis), and new bone formation, which are collectively "responsible for a large degree of the long-term loss of function and disability" and are "very particular to PsA." (*Id*. at 1519.) The cause and pathogenesis of PsA are not completely understood. (Ex. 2007 at 44; Ex. 1025 at 49.)

The relationship between the skin disease of psoriasis and the joint disease of PsA is unclear, and patients with psoriasis often do not have PsA. (Ex. 2008 at 2455; Ex. 1009 at 4.) In 2003, it was reported that only about 10% or less of patients with established psoriasis were diagnosed with PsA. (Ex. 2007 at 42; Ex. 1017 at 2.) PsA can precede or follow psoriasis by many years, and remissions and exacerbations of PsA do not correlate with similar changes in psoriasis. (Ex. 2007 at 45; Ex. 1009 at 4.) There is also no connection between the location, distribution, or pattern of psoriatic skin and which joints are affected by PsA. (*See* Ex. 2009 at 1513.) Further, while the relationship between the severity of psoriasis and PsA has not been fully established, PsA patients with psoriasis often do not have the moderate or severe form of the disease. (Ex. 2009 at 1515 (skin disease in

PsA patients "can often be very mild"); Ex. 2008 at 2455 ("some studies suggest skin disease is milder in patients with arthritis.").)

C. Prior Art Treatments Investigated for Moderate-to-Severe Chronic Plaque Psoriasis Used Higher Doses Than Approved for Rheumatoid Arthritis

Treatments for chronic plaque psoriasis were mostly "developed empirically . . . as with all other diseases of unknown cause." (Ex. 2007 at 36.) Although new biologic treatments were being investigated in 2002-03 to treat moderate-to-severe chronic plaque psoriasis, *none* of Petitioner's cited references discloses using the same dose to treat moderate-to-severe chronic plaque psoriasis as approved to treat rheumatoid arthritis.

Infliximab is a chimeric anti-TNFα monoclonal antibody administered via intravenous infusion with a weight-based dosing regimen. (Ex. 1027 at 2.) In 2002, the approved dose for treating rheumatoid arthritis was 3 mg/kg at weeks 0, 2, and 6 and then every 8 weeks thereafter. (*Id.* at 4.) Rather than using infliximab's approved dose for rheumatoid arthritis, however, trials in patients with moderate-to-severe chronic plaque psoriasis used *higher* doses of 5 or 10 mg/kg of infliximab at weeks 0, 2, and 6. (*Id.*; Ex. 1036 at 4.) The FDA later approved infliximab for the treatment of severe chronic plaque psoriasis at 5 mg/kg—not the rheumatoid arthritis dose of 3 mg/kg. (Ex. 2012 at 1.)

Etanercept is a fusion protein of two TNFα receptor p75 extracellular domains with one IgG1 Fc region. (Ex. 1005 at 1.) In 2002, the approved etanercept dosing regimen for treating rheumatoid arthritis was subcutaneous injection of 25 mg of drug twice weekly. (*Id*. at 23.) This 25 mg twice-weekly dosing regimen was studied in patients with PsA who also had psoriasis. (Ex. 1017 at 3, 6.) Notably, however, the publication reporting this trial did not disclose treating patients with moderate-to-severe chronic plaque psoriasis. (*Id*.) The FDA later approved etanercept for treating moderate-to-severe chronic plaque psoriasis at a *higher* dose of 50 mg twice weekly for three months (instead of the lower rheumatoid arthritis dose of 25 mg twice weekly). (Ex. 1005 at 5; Ex. 1048 at 1, 3.)

Although adalimumab, infliximab, and etanercept all function as TNFα inhibitors, Petitioner fails to adequately address fundamental differences in, for example, their dosing regimens, methods of administration, and efficacy (or lack thereof) in treating different diseases believed to involve TNFα. (Ex. 1027 at 2, 4; Ex. 1005 at 2, 5; Ex. 1026 at 1, 14; Ex. 2013 at 6 ("Subcutaneous etanercept at a dose of 25 mg twice weekly is not an effective therapy for patients with moderate to severe [Crohn's disease].").) Petitioner also fails to address the pharmacokinetic differences among these drugs (for example, differences in terminal half-lives, tissue distribution, and tissue absorption) or conduct any comparison of the drugs' pharmacokinetic/pharmacodynamic profiles in the skin to arguably justify

comparing their dosing regimens for treating skin diseases such as moderate-to-severe chronic plaque psoriasis. (Ex. 1027 at 2; Ex. 1005 at 3; Ex. 1026 at 2.)

IV. The Asserted References

Petitioner's asserted references concern the use of adalimumab to treat rheumatoid arthritis or the use of different drugs to treat different diseases, instead of the use of adalimumab to treat moderate-to-severe chronic plaque psoriasis, as claimed.

A. Keystone

The Keystone abstract discusses the use of 20, 40, or 80 mg of adalimumab every-other-week for treating *rheumatoid arthritis*. (*See* Ex. 1003.) Keystone does not discuss psoriasis or moderate-to-severe chronic plaque psoriasis, much less a dosing regimen for treating patients with those conditions. (*Id*.) Nor does it discuss adalimumab's distribution to or activity in skin affected by moderate-to-severe chronic plaque psoriasis. (*Id*.)

B. Lorenz

Lorenz provides an overview of clinical trials using infliximab or etanercept to treat different TNFα-mediated conditions, including rheumatoid arthritis, Crohn's disease, juvenile chronic arthritis, psoriasis, PsA, ankylosing spondylitis, adult-onset Still's disease, polymyositis, dermatomyositis, Behçet's disease, and Wegener's granulomatosis. (*See* Ex. 1028.) Lorenz discusses clinical trials using 5

or 10 mg/kg of infliximab or 25 mg twice a week of etanercept to treat PsA patients, a subset of whom had psoriasis of unspecified severity. (*Id.* at S18.) Lorenz does not disclose using the approved rheumatoid arthritis dose for infliximab or etanercept to treat moderate-to-severe chronic plaque psoriasis. (*Id.*)

Lorenz discusses adalimumab (also referred to as D2E7) *only* in its "Summary" and "Rheumatoid arthritis and Crohn's disease" sections but *never* in connection with moderate-to-severe chronic plaque psoriasis. (Ex. 1028 at S17-18.) It also does not disclose any clinical trials, dosage, or results for adalimumab in the treatment of moderate-to-severe chronic plaque psoriasis. (*See generally* Ex. 1028.) Nor does Lorenz discuss adalimumab's distribution to or activity in skin affected by moderate-to-severe chronic plaque psoriasis.

Lorenz speculates that "encouraging results might arise" if TNFα-directed agents, such as etanercept, onercept, PEG-TNFRI ("pegsunercept"), or adalimumab were used in trials for other TNFα-associated conditions. (*Id.* at S17-18.) Lorenz cautions, however, that further studies of the efficacy of these agents in these conditions were "required." (*Id.*at S18.) Indeed, the prior art confirmed that further studies were in fact required. Sandborn, for example, reported in 2001 that etanercept was *ineffective* in treating Crohn's disease. (Ex. 2013 at 6.) Further, Phase 3 trials of onercept in psoriasis were later discontinued and the drug was

never approved for this indication. (Ex. 2014; Ex. 2015 at 13.) Similarly, pegsunercept was never approved for psoriasis. (Ex. 2015 at 13; Ex. 2016 at 1.)

C. Chaudhari

Chaudhari discusses the use of 5 or 10 mg/kg of infliximab administered intravenously at 0, 2, and 6 weeks to treat moderate-to-severe chronic plaque psoriasis. (*See* Ex. 1036 at 4.) Notably, Chaudhari used a *higher* dose of infliximab for moderate-to-severe chronic plaque psoriasis than the 3 mg/kg dose approved for rheumatoid arthritis. (*Id.* at 4; Ex. 1027 at 4; *see infra* Section VIII.B.1.) Chaudhari does not disclose any clinical trials or results using adalimumab, any dosing regimen for adalimumab, or any connection between adalimumab and moderate-to-severe chronic plaque psoriasis. (*See* Ex. 1036.) Nor does Chaudhari discuss adalimumab's distribution or activity in skin affected by moderate-to-severe chronic plaque psoriasis. (*Id*.)

D. Mease 2000

Mease 2000 discusses twice-weekly administration of 25 mg of etanercept to treat patients with active psoriatic arthritis. (*See* Ex. 1017 at 2.) Some patients also exhibited "evaluable psoriasis" but Mease 2000 does not disclose treating any patients with moderate-to-severe chronic plaque psoriasis. (*See id*. at 2-3.) Mease 2000 does not disclose any clinical trials or results using adalimumab, any dosing regimen for adalimumab, or any connection between adalimumab and

moderate-to-severe chronic plaque psoriasis. (*Id*.) Nor does it discuss adalimumab's distribution or activity in skin affected by moderate-to-severe chronic plaque psoriasis. (*Id*.)

V. The Person of Ordinary Skill in the Art

Petitioner proposes that a POSA would "have an M.D. and at least 3 years' post-residency experience treating patients for psoriasis, PsA and RA, including with TNFα inhibitors, and would be familiar with dosing regimens for TNFα inhibitors that had been reported in the literature." (Pet. at 14.) The definition of a person of ordinary skill, however, necessarily depends on the art of the claimed invention. *See, e.g., Daiichi Sankyo Co. v. Apotex, Inc*., 501 F.3d 1254, 1257 (Fed. Cir. 2007) (holding that, where the claimed invention related to a method for treating ear infections, the POSA would be a specialist with training and knowledge with ear treatments, not simply a general practitioner).

Patent Owner disagrees with Petitioner's proposed definition. The '689 patent claims, for example, relate to treating moderate-to-severe chronic plaque psoriasis, which predominantly manifests on the skin and thus would typically have been treated by a dermatologist. (*See* Ex. 1008 at 30, 33, 46, 49; Ex. 2007 at 36.) Petitioner fails to support its expansion of the definition of a POSA to a person with training in rheumatoid arthritis—a condition separate and distinct from that claimed. Notably, Petitioner's psoriasis references characterize the treating

physician as a "dermatologist." (Ex. 1008 at 30, 33, 46, 49; Ex. 1036 at 5.) For example, the patients in Chaudhari with moderate-to-severe psoriasis were referred to the study by the "Divisions of Dermatology and Clinical Pharmacology." (Ex. 1036 at 5). Similarly, the *Textbook of Psoriasis* states that dermatologists are responsible for prescribing and determining the dosages of drugs for treating psoriasis patients. (Ex. 1008 at 30, 33, 46, 49.)

Petitioner's declarant, Dr. Helfgott, is a rheumatologist, not a dermatologist, and thus his testimony should be given little weight. *Daiichi Sankyo*, 501 F.3d at 1257. For the reasons set forth below, however, the Board should deny institution of the Petition *regardless* of the definition it applies for the POSA.

VI. Priority

For purposes of this preliminary response only, Patent Owner does not dispute Petitioner's alternative use of July 18, 2003 (Ground 1) or July 19, 2002 (Ground 2) as the priority dates for the challenged claims. (Pet. at 9.)

VII. Claim Construction

For the limited purposes of this preliminary response, Patent Owner does not contest Petitioner's assertion that the claim terms are presumed to have their ordinary and customary meaning. (Pet. at 15-16.) Patent Owner also does not contest Petitioner's claim construction of "treating" or "treatment," but reserves the right to propose an alternate construction. As discussed below, however, by failing

to construe "moderate-to-severe chronic plaque psoriasis," Petitioner has provided no framework for analyzing, for example, Lorenz and Mease 2000, which non-specifically refer to treating patients with "psoriasis." (*See infra* Section VIII.A.2.) Thus, Petitioner fails to establish any reasonable expectation of success for treating moderate-to-severe chronic plaque psoriasis based on these references. (*Id*.)

VIII. Petitioner Does Not Establish a Reasonable Likelihood of Prevailing as to Any Challenged Claim

Challenged claims 1, 4, 7, 10, 13, 16, and 19 require subcutaneous administration of 40 mg adalimumab every-other-week to patients having moderate-to-severe chronic plaque psoriasis. (Ex. 1001 at 57:15-58:36.) Petitioner asserts that these claims would have been obvious over Keystone, Chaudhari, and either Lorenz (Ground 1) or Mease 2000 (Ground 2). (Pet. at 9.) For both grounds, however, Petitioner fails to establish any a motivation or reasonable expectation of success.

A. Petitioner Fails to Establish Any Reasonable Expectation of Success of Treating Moderate-to-Severe Chronic Plaque Psoriasis with Adalimumab

Petitioner repeatedly asserts that the prior art taught that "[a]dalimumab would be useful in the treatment of PsO" and that "adalimumab would effectively treat PsO." (Pet. at 17, 18, 20, 41.) These assertions are incorrect because *none* of

Petitioner's references discloses or suggests use or efficacy of adalimumab to treat any form of psoriasis, much less moderate-to-severe chronic plaque psoriasis.

1. The Asserted Art Fails to Disclose That Adalimumab Would Treat Moderate-to-Severe Chronic Plaque Psoriasis

Keystone is directed to using adalimumab for rheumatoid arthritis. (Ex. 1003.) It is not directed to the treatment of moderate-to-severe chronic plaque psoriasis or any dosing regimen for treating moderate-to-severe chronic plaque psoriasis with adalimumab. (*See generally id*.) Keystone also does not disclose or suggest how adalimumab's distribution to the affected tissue of rheumatoid arthritis (a joint disease) would be predictive of the distribution of adalimumab to the affected tissues of moderate-to-severe chronic plaque psoriasis (a skin disease). Indeed, Keystone does not purport to extend the relevance of its results beyond treatment of rheumatoid arthritis. (*Id*.)

Chaudhari also fails to disclose use of adalimumab to treat moderate-to-severe chronic plaque psoriasis. Chaudhari is instead directed to use of *infliximab*. (Ex. 1036 at 4.) Chaudhari does not disclose that infliximab and adalimumab have comparable distribution to or pharmacokinetics in skin affected by moderate-to-severe chronic plaque psoriasis. Chaudhari's use of a different drug is no more than a disclosure of a "general approach that seemed to be a promising field of experimentation," which is legally insufficient to establish a reasonable expectation of success. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d

989, 996-97 (Fed. Cir. 2009) (finding no reasonable expectation of success "where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it").

Petitioner asserts that Lorenz (Ex. 1028) taught treatment of "PsO and PsA" with agents such as adalimumab. (Pet. at 20-22.) Not so. Lorenz does not discuss adalimumab in connection with moderate-to-severe chronic plaque psoriasis (*See generally*, Ex. 1028.) Rather, despite Lorenz having a section dedicated to PsA and psoriasis, this section discusses only anti-TNFα therapy with infliximab and etanercept—*not adalimumab*. (*Id*. at S18-19.)

Indeed, Lorenz mentions adalimumab *only* in its "Summary" and "Rheumatoid arthritis and Crohn's disease" sections. (*Id.* at S17-S18.) In the "Summary" section, Lorenz states that "[s]imilar encouraging results *might* arise" in *rheumatoid arthritis* if clinical trials were conducted with adalimumab. (*Id*. at S17 (emphasis added).) In the "Rheumatoid arthritis and Crohn's disease section," it states that developments in the treatment of other unidentified chronic inflammatory diseases "may include additional clinical trials" with new TNFα biologics, such as adalimumab. (*Id*. at S18.) Petitioner's reliance on Lorenz's speculation that adalimumab *may* be tested and *might* have encouraging results in rheumatoid arthritis or other unspecified diseases is insufficient to establish a reasonable expectation of success in treating the specific claimed disease—

moderate-to-severe chronic plaque psoriasis—because "knowledge of [a] goal does not render its achievement obvious." *Abbott Labs. v. Sandoz, Inc*., 544 F.3d 1341, 1352 (Fed. Cir. 2008).

Contrary to Petitioner's contention, a POSA also would not have given any predictive weight to Lorenz's speculation regarding adalimumab. (*See* Pet. at 21-22.) Lorenz does not disclose how adalimumab is distributed to the affected tissue (skin) of a patient with moderate-to-severe chronic plaque psoriasis or that its distribution to the skin would be comparable to infliximab or etanercept. Petitioner also fails to address any pharmacokinetic differences between the drugs (e.g., differences in half-lives, distribution, and extent of absorption). Furthermore, Petitioner omits Lorenz's express teaching that "long-term observations" were "*required* concerning side effects and efficacy of these agents." (Ex. 1028 at S18 (emphasis added).)

Moreover, Dr. Helfgott incorrectly asserts that Lorenz "accurately predicted" etanercept's approval for Crohn's disease—in fact, Sandborn reported in 2001 that etanercept was *ineffective* in treating Crohn's disease. (Ex. 1002 at ¶ 37; Ex. 2013 at 6.) Petitioner omits this prior art failure. A POSA therefore would have understood Lorenz's speculation regarding both etanercept and adalimumab to be unreliable and not supportive of any reasonable expectation that adalimumab would successfully treat moderate-to-severe chronic plaque psoriasis. Thus the

prior art of Ground 1, a combination of Keystone, Lorenz, and Chaudhari, fails to support any reasonable expectation of success in treating moderate-to-severe chronic plaque psoriasis with adalimumab.

Petitioner's substitution of Mease 2000 (Ex. 1017) in Ground 2 for Lorenz does nothing to cure the lack of a reasonable expectation of success that adalimumab would treat moderate-to-severe chronic plaque psoriasis. Mease 2000 discusses using etanercept in some PsA patients (38 out of 60) with "evaluable psoriasis" of unspecified severity. (Ex. 1017 at 2.) Mease 2000 therefore does not disclose or suggest the use of adalimumab, any dosing of adalimumab, or the use of any drug for the treatment of moderate-to-severe chronic plaque psoriasis. Moreover, Petitioner fails to establish any correlation between the distribution and activity of etanercept with the corresponding properties of adalimumab. The prior art of Ground 2, a combination of Keystone, Mease 2000, and Chaudhari, therefore also fails to support any reasonable expectation of success in treating moderate-to-severe chronic plaque psoriasis with adalimumab.

2. Lorenz and Mease 2000 Do Not Disclose Treating Moderate-to-Severe Chronic Plaque Psoriasis with Any Other Agent

In addition to failing to disclose use of adalimumab for psoriasis, Lorenz and Mease 2000 do not disclose treating moderate-to-severe chronic plaque psoriasis with any other agent. Instead, Lorenz and Mease 2000 disclose using etanercept or

infliximab to treat PsA patients with just "psoriasis," and neither Petitioner nor its declarants establish that this disclosure of "psoriasis" teaches or suggests the claimed moderate-to-severe chronic plaque psoriasis.[3] The expectation-of-success analysis, however, "must match the highly desired goal, not switch to a different goal that may be [a] less challenging but less worthwhile pursuit." *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1344-46 (Fed. Cir. 2013) (reversing the Board's obviousness determination when the prior art provided no reasonable expectation of success in cleaving chromosomes located *in* yeast cells, as claimed, because the prior art only cleaved chromosomes *extracted from* yeast cells). Accordingly, Petitioner cannot establish a reasonable expectation of success by focusing on references that are not directed to the "highly desired goal" of treating moderate-to-severe chronic plaque psoriasis. *See id.* at 1346; *see also Roxane Labs., Inc. v. Novartis AG*, IPR2016-01461, Paper 9 at 9-10 (P.T.A.B. Feb. 13, 2017) (denying institution because the prior art only disclosed treating pancreatic tumors in general

[3] Although Drs. Helfgott and Plott define "moderate-to-severe" psoriasis as meaning "marked plaque elevation, scaling, and/or erythema" (Ex. 1002 at ¶ 22; Ex. 1012 at ¶ 19), the Petition neither cites to nor relies on this definition, and thus the Board should decline to consider it. *See Conopco, Inc. v. The Procter & Gamble Co.*, IPR2013-00510, Paper 9, at 8-9 (P.T.A.B. Feb. 12, 2014).

and not the claimed advanced pancreatic tumors).

Lorenz, for example, discusses studies using either etanercept or infliximab on patients with PsA who also had "psoriasis." (Ex. 1028 at S18-19). Lorenz does not disclose the treatment of moderate-to-severe chronic plaque psoriasis. (Ex. 1028.) Petitioner speculates that Lorenz's reference to "psoriasis" actually means moderate-to-severe chronic plaque psoriasis simply because Lorenz cites Chaudhari in one section and Chaudhari refers to moderate-to-severe chronic plaque psoriasis. (*See* Pet. at 22.) This amounts to no more than unsupported attorney argument. Petitioner's declarants do not support this assertion, and Petitioner fails to address that, consistent with Lorenz's use of only the word "psoriasis," the other studies cited by Lorenz, such as Van den Bosch, were *not* directed to moderate-to-severe chronic plaque psoriasis and reported very low PASI scores indicative of mild psoriasis. (Ex. 1037 at 431-32 (reporting a median PASI score of only 0.72); *see* Ex. 2005 at ii66 (Table 1); Ex. 2026 at 6.) This argument also ignores that PsA patients, like those in the studies referenced by Lorenz, often have very mild (*i.e.*, not moderate-to-severe) skin disease. (Ex. 2008 at 2455; Ex. 2009 at 1515.) Attorney arguments and conclusory statements unsupported by (and inconsistent with) factual evidence are entitled to little probative value. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). The

Board should therefore disregard Petitioner's conclusory and unsupported assertion that Lorenz discloses moderate-to-severe chronic plaque psoriasis.

Petitioner's reliance on Lorenz's statement that the "current therapeutic approaches for PsA are similar to those for RA" is also misplaced (Pet. at 36), because Petitioner fails to connect this statement to any expectation of success in treating moderate-to-severe chronic plaque psoriasis. (*Id*.) PsA is a distinct condition affecting different anatomy than psoriasis. (Ex. 2008 at 2448-50; Ex. 2009 at 1511-12; Ex. 2009 at 1513.) Moreover, PsA patients with psoriasis often have "very mild skin disease." (Ex. 2008 at 2455; Ex. 2009 at 1515.) At least two biologics (alefacept and efalizumab) were approved for use in moderate-to-severe chronic plaque psoriasis but *were not approved* (and are not approved) for either rheumatoid arthritis or PsA. (Ex. 2022 at 5; Ex. 2023 at 8; Ex. 2010 at 1; Ex 2011 at 7.) Notably, efalizumab was found *not effective* in treating PsA. (Ex. 2025 at 57.)

Mease 2000, part of Petitioner's second ground, suffers from similar deficiencies. It discusses treatment with etanercept in 60 patients with active PsA. (Ex. 1017 at 3.) A portion of the PsA patients (38 out of 60) had what Mease 2000 describes only as "evaluable psoriasis." (Ex. 1017 at 4.) The skin disease in PsA patients can often be very mild. (*See supra* Section III.B; Ex. 2008 at 2455; Ex. 2009 at 1515.) Indeed, Mease does not disclose that any of the PsA subjects had

moderate-to-severe chronic plaque psoriasis and neither Petitioner nor its declarants assert that one would understand Mease's subjects to have had moderate-to-severe chronic plaque psoriasis. (Ex. 1017; *see* Pet. at 24-25; *see also* Ex. 1002 at ¶¶ 44, 54-55; Ex. 1012 at ¶ 57.)

3. Petitioner's Background References Also Fail to Disclose or Suggest That Adalimumab Would Treat Moderate-to-Severe Chronic Plaque Psoriasis

In addition to the asserted prior art, Petitioner cites other references purportedly providing context for what a POSA would have understood regarding the state of the art. (*See* Pet. at 9, 34.)[4] Many of these references fail to disclose or suggest use of adalimumab. (Pet. at 23-25, 31-39; Ex. 1004; Ex. 1006; Ex. 1024; Ex. 1027; Ex. 1033; Ex. 1035; Ex. 1037; Ex. 1039; Ex. 1040; Ex. 1050.) For those that do discuss adalimumab, Petitioner fails to meet its burden to show that these references qualify as prior art printed publications. (*See infra* Section VIII.E.) Further, these additional references do not disclose or suggest that adalimumab would treat moderate-to-severe chronic plaque psoriasis.

[4] Petitioner's reliance on these alternative references highlights the infirmity of its arguments and violates the requirement to precisely identify the prior art relied upon to support a challenge. 37 C.F.R. § 42.104(b)(5).

Petitioner asserts, for example, that Japan Chemical Week (Ex. 1034) "confirms" that Lorenz teaches the use of adalimumab to treat psoriasis. (Pet. at 42.) This mischaracterizes the reference. At most, Japan Chemical Week, which Petitioner has not established is prior art, discusses the *potential* that adalimumab will follow infliximab and etanercept into the TNFα inhibitor market, and the *potential* that this market may expand to psoriasis. (Ex. 1034.) It does not, however, discuss any adalimumab dosing regimen or discuss moderate-to-severe chronic plaque psoriasis. (*Id*.)

Petitioner's reliance on a Press Release (Ex. 1049), which Petitioner has not established is prior art, is similarly insufficient. (*See* Pet. at 31.) The Press Release describes work by Patent Owner's predecessor, Abbott Laboratories, regarding the initiation of a psoriasis clinical trial and a PsA clinical trial using HUMIRA®. (Ex. 1049.) It does not describe any dosing regimen for adalimumab or any results in psoriasis, much less in moderate-to-severe chronic plaque psoriasis. Instead it only states a "hope" that future clinical trials will lead to a psoriasis treatment. (*Id*.) This hope is not enough to establish a reasonable expectation of success. *Abbott Labs.*, 544 F.3d at 1352.

Petitioner also cites Marzo-Ortega (Ex. 1004) as purportedly demonstrating "the efficacy of infliximab in treating PsA and PsO at the same 3 mg/kg dose that had been approved to treat RA." (Pet. at 42.) Marzo-Ortega, however, like Mease

2000, discusses treatment of patients with PsA. (Ex. 1004 at 6.) Although these patients are reported to also have "skin psoriasis," Marzo-Ortega does not disclose that it is moderate-to-severe chronic plaque psoriasis. (*Id*.) Neither Petitioner nor Drs. Helfgott or Plott connect Marzo-Ortega's "skin psoriasis" patients with moderate-to-severe chronic plaque psoriasis nor establish any correlation between the distribution of infliximab with that of adalimumab. (Pet. at 23-24; Ex. 1002 at ¶¶ 50-51; Ex. 1012 at ¶ 45.)

Petitioner also asserts that the 2002 Enbrel Package Insert (Ex. 1006), which Petitioner has not established is prior art, "taught that etanercept could be administered using the same dose and dosing regimen to treat both RA and PsO." (Pet. at 39.) The Enbrel Package Insert reports clinical trial data for the treatment of PsA patients with 25 mg twice-weekly etanercept. (Ex. 1006 at 10.) The insert discloses that some of the PsA patients had plaque psoriasis, but does not disclose that they had moderate-to-severe chronic plaque psoriasis. (*Id.* at 10-12.) Once again, Petitioner fails to make any connection between the "plaque psoriasis" referenced in the Enbrel Insert and the claimed moderate-to-severe chronic plaque psoriasis or address that PsA patients often have very mild skin disease. (*Id.*; Pet. at 38-39; *see also* Ex. 1002 at ¶ 92; Ex. 1012 at ¶ 56; Ex. 2008 at 2455; Ex. 2009 at 1515.) Nor does Petitioner establish any correlation between the distribution of etanercept with that of adalimumab, or address that etanercept is a dimeric fusion

protein with affinity for TNFα and TNFβ (Ex. 1005 at 2-3), whereas adalimumab is a human IgG1 monoclonal antibody specific for TNFα (Ex. 1026 at 1).

Accordingly, *none* of Petitioner's asserted or cited references supports any reasonable expectation of success in treating moderate-to-severe chronic plaque psoriasis with adalimumab. As such, the Petition should be denied. *See, e.g.*, *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070-71 (Fed. Cir. 2012) (holding claims nonobvious where the challenger did not prove an expectation of success in making the invention).

B. Petitioner Fails to Establish Any Motivation or Reasonable Expectation of Success in Treating Moderate-to-Severe Chronic Plaque Psoriasis with a 40 mg Every-Other-Week Dose of Adalimumab

Petitioner also fails to support any motivation or reasonable expectation of success in using the approved rheumatoid arthritis dose of adalimumab (40 mg every-other-week) to treat moderate-to-severe chronic plaque psoriasis. To the contrary, Petitioner's own asserted and cited references taught using *higher* doses than approved for rheumatoid arthritis to treat moderate-to-severe chronic plaque psoriasis.

1. Chaudhari Used Higher Doses to Treat Moderate-to-Severe Chronic Plaque Psoriasis Than for Rheumatoid Arthritis

Petitioner argues that a POSA would have had a motivation and reasonable expectation of success in treating moderate-to-severe chronic plaque psoriasis with

the known rheumatoid arthritis dosing regimen for adalimumab because the prior art purportedly taught using the approved infliximab and etanercept rheumatoid arthritis dosing regimens to treat psoriasis and PsA. (Pet. at 22, 36-39, 42, 43; Ex. 1002 at ¶¶ 45, 50-52, 55, 70, 81, 92, 94; Ex. 1012 at ¶¶ 45, 56, 67, 77.) Petitioner, for example, states that:

> The prior art established the ability of TNFα inhibitors to treat PsO and RA, and showed that they could do so using the same dosage regimens. Therefore one would expect a POSA to review the FDA approved labels for known TNFα inhibitors, such as adalimumab, etanercept and infliximab, to treat RA and PsO.

(Pet. at 37.) Petitioner's argument, however, lacks evidentiary support in the cited references.

Chaudhari (Ex. 1036) is the *only* reference in the proposed grounds of unpatentability directed to moderate-to-severe chronic plaque psoriasis. (Pet. at 26, 40, 51, 52; Ex. 1002 at ¶¶ 47, 68, 84, 100, 107, 112, 117, 122 (relying exclusively on Chaudhari for moderate-to-severe limitation); Ex. 1012 at ¶¶ 52, 81, 85, 93, 99, 103 (same).) Contrary to Petitioner's primary argument, however, Chaudhari tested doses of 5 mg/kg and 10 mg/kg of infliximab, which are *66% to 233% higher* than the infliximab dose approved to treat rheumatoid arthritis (3 mg/kg). (Ex. 1036 at

4; Ex. 1027 at 4.)[5] Therefore, even if infliximab's dosing for rheumatoid arthritis and psoriasis would have been considered predictive of adalimumab's dosing, Chaudhari would have motivated a POSA to test a *higher* dose to treat moderate-to-severe chronic plaque psoriasis than rheumatoid arthritis, not the same dose as Petitioner contends. Indeed, Chaudhari expressly acknowledges the prior approval of infliximab for rheumatoid arthritis, but *still* used a higher dose for treating moderate-to-severe psoriasis. (Ex. 1036 at 4.) Chaudhari's use of a *higher* infliximab dose for moderate-to-severe chronic plaque psoriasis as compared to rheumatoid arthritis therefore does not support any reasonable expectation of success in using the *same* dose of adalimumab to treat both diseases.

Petitioner's reliance on the non-approved rheumatoid arthritis dosing reported in Feldman and Perkins (which is not part of Petitioner's grounds) does not support Petitioner's argument that the approved rheumatoid arthritis dosing regimen would have been expected to effectively treat moderate-to-severe chronic

[5] Petitioner fails to establish that the weight-based, intravenously administered infliximab dosing regimen of Chaudhari (which could involve, for example, administering 500 mg to 1,000 mg per dose depending on patient weight) was comparable to or predictive of subcutaneously administering much smaller doses of 40 mg of adalimumab. (Ex. 1036 at 4.)

plaque psoriasis. (Pet. at 34 (Table 2).) Feldman and Perkins administered infliximab at 5, 10, or 20 mg/kg for rheumatoid arthritis. (Ex. 1039 at 65:12-15; Ex. 1040 at 8.) Like Chaudhari, these are *higher* doses than the approved infliximab dosing regimen for treating rheumatoid arthritis—3 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter. (Ex. 1027 at 4.)

Petitioner's reliance on the Remicade Package Insert (which is not part of Petitioner's grounds) is similarly unavailing. Petitioner repeatedly contends that a POSA would have expected that *approved* rheumatoid arthritis dosing regimens would also effectively treat moderate-to-severe chronic plaque psoriasis. (Pet. at 20, 22, 36, 37.) While the Remicade Package Insert discusses a study in which 10 mg/kg of infliximab was administered to treat rheumatoid arthritis, that dose was 233% higher per administration than the approved dose of 3 mg/kg. (Ex. 1027 at 2, 4.) Disclosure of this higher dose would not have given a POSA any motivation or reasonable expectation that the lower *approved* rheumatoid arthritis dose would successfully treat moderate-to-severe chronic plaque psoriasis. Nor does Petitioner explain how administering 1,000 mg or more of infliximab (depending on patient weight) would have been predictive of treating moderate-to-severe chronic plaque psoriasis by administering 40 mg of adalimumab.

Petitioner attempts to avoid the higher dosing used for moderate-to-severe chronic plaque psoriasis by asserting that a POSA would have used the "same or

similar" dose as used for rheumatoid arthritis. (Pet. at 42, 44, 45.) But Petitioner cites no case law establishing motivation or a reasonable expectation of success based on doses purportedly "similar" to a claimed dosing regimen. Petitioner also provides no evidence that a dose that is 66% to 233% higher than the rheumatoid arthritis dose would be considered "similar."

In sum, the asserted and cited references taught using significantly higher doses to treat moderate-to-severe chronic plaque psoriasis than those approved to treat rheumatoid arthritis.

2. The Differences Between the Diseases Also Would Have Suggested Using Higher Doses to Treat Moderate-to-Severe Chronic Plaque Psoriasis

The prior art use of higher doses for moderate-to-severe chronic plaque psoriasis is consistent with the knowledge in the art of the higher TNFα burden in those patients compared to rheumatoid arthritis patients. Petitioner does not address the differences between rheumatoid arthritis and moderate-to-severe chronic plaque psoriasis, underscoring the hindsight nature of its argument. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354-56 (Fed. Cir. 2013) (reversing obviousness determination as improperly based on hindsight).

As of the filing date of the '689 patent, moderate-to-severe chronic plaque psoriasis was known to affect *more tissue* than rheumatoid arthritis. Psoriasis is a disorder of the skin, the largest organ of the body, and moderate-to-severe chronic

plaque psoriasis affects a significant percentage of body surface area. (*E.g.*, Ex. 1036 at 5.) On the other hand, as the patent explains, rheumatoid arthritis affects discrete and relatively small amounts of joint tissue in the body. (Ex. 1001 at 27:53-57.) Based solely on the sites affected, a POSA would expect a patient with moderate-to-severe chronic plaque psoriasis to have a higher TNFα burden than a patient with rheumatoid arthritis.

Moreover, psoriasis patients on average are overweight, thereby having greater body surface area (i.e., more skin) on average than rheumatoid arthritis patients, who are typically average size or underweight.[6] (Ex. 2017 at 350; Ex. 2018 at 1098; Ex. 2019 at 328.) A POSA would have understood the compounding effects of these factors: psoriasis patients are generally heavier, and heavier patients with more total skin are also likely to have a higher percentage of affected tissue, increasing TNFα burden.

Not only is more tissue affected in psoriasis patients, but those patients were also known to have *higher concentrations* of TNFα in affected tissue. By the filing

[6] Petitioner acknowledges that psoriasis patients were known to be heavier than rheumatoid arthritis patients, noting that the patients in the Wollina study (Ex. 1050) weighed 100 kg, while alleging the average adult weighed 70 kg. (*See* Pet. at 34 n.31.)

date of the ’689 patent, it was known that the affected skin tissue of psoriasis patients had, on average, concentrations of TNFα that were more than three times higher than in the synovial fluid of affected joints of rheumatoid arthritis patients. (*Compare* Ex. 1013 at 3 (approximately 496 pg/ml of TNFα in affected psoriasis skin lesions) *with* Ex. 2020 at 202 (157 pg/ml of TNFα in the synovial fluid of affected joints in rheumatoid arthritis).) On average, patients with psoriasis also have higher levels of TNFα in serum than patients with rheumatoid arthritis. Specifically, TNFα is detectable in serum of 81% of psoriasis patients versus just 6% of rheumatoid arthritis patients. (*Compare* Ex. 2021 at 116, 117 (Fig. 1) *with* Ex. 2020 at Table 1(A).)

Based on these differences, a POSA would not have been motivated to use adalimumab’s rheumatoid arthritis dose to treat moderate-to-severe chronic plaque psoriasis and would not have reasonably expected that using adalimumab’s rheumatoid arthritis dose would adequately neutralize the much larger amounts of TNFα in moderate-to-severe chronic plaque psoriasis patients. Instead, a POSA would have expected that higher doses (such as those used for infliximab in Chaudhari) would be required to adjust for the greater TNFα burden.

3. Petitioner's Background References Also Used Higher Doses to Treat Moderate-to-Severe Chronic Plaque Psoriasis than for Rheumatoid Arthritis

Several of Petitioner's background references also disclose using higher doses to treat moderate-to-severe chronic plaque psoriasis than to treat rheumatoid arthritis. Ogilvie, for example, discusses the need for systemic treatments for "patients suffering from severe psoriasis with widespread skin lesions" and states that a *higher* dose of 5 mg/kg of infliximab was effective in treating psoriasis patients who were unresponsive to methotrexate therapy and had baseline PASI scores up to 31.7. (Ex. 1033 at 6, 7 (Fig. 1), 8.) This is consistent with the use of higher doses in Chaudhari and the eventual approval of infliximab at this higher 5 mg/kg dose. (Ex. 2012 at 1.)

Petitioner also relies on Wollina, which used a more aggressive regimen for patients with "widespread plaque-type psoriasis." (Ex. 1050 at 7; Pet. at 33, 34.) Specifically, Wollina disclosed administering infliximab more frequently (300 mg administered intravenously at weeks 0, 2, 4, and 8, along with weekly methotrexate) than the approved rheumatoid arthritis dose (3 mg/kg at weeks 0, 2, and 6, and then every 8 weeks thereafter). (*Compare* Ex. 1050 at 7, *with* Ex. 1027 at 4.)

Petitioner also cites Van den Bosch (Ex. 1037) as disclosing the effectiveness of 5 mg/kg of infliximab in treating "psoriatic skin disease." (Pet.

at 33.) Van den Bosch, however, discloses treatment of patients with very low PASI scores indicative of mild psoriasis. (*See supra* Section VIII.A.2.) It also reports a *higher dose* of infliximab than approved for rheumatoid arthritis (Ex. 1037 at 431-32; Ex. 1027 at 4), contradicting Petitioner's argument that a POSA would have selected the same dose (*See e.g.*, Pet. at 37, 42).

Administering higher doses to treat moderate-to-severe chronic plaque psoriasis was also reported for drugs other than infliximab. For example, Trexall (methotrexate) was approved at a higher initial dosing and higher recommended maximum dose per week for severe psoriasis as compared to rheumatoid arthritis. (Ex. 1024 at 8, 10.) Etanercept was approved after the '689 patent's priority date to treat moderate-to-severe chronic plaque psoriasis using a *higher* dose (50 mg *twice* weekly for the first three months) than approved for rheumatoid arthritis (50 mg *once* weekly). (Ex. 1048 at 3.)

4. Petitioner's Table 3 Confirms that a POSA Would Not Have Expected the Same Dosage to Work for Different Diseases

Petitioner's assertion that all of the small molecules in Table 3 were approved for rheumatoid arthritis and psoriasis at the "same" dose is incorrect. (*See* Pet. at 36-37 (Table 3).) The labels for Hydrocortone, Cortone, Decadron, Prelone, Solu-medrol, and Celestone, all state that the dosages vary *depending on the disease*. (Ex. 1035 at 27, 20, 24, 33, 38, 42.) Petitioner provides no evidence

establishing that the dose for rheumatoid arthritis was the same as for psoriasis or any other indication. (Pet. at 36-37.) Rather than supporting Petitioner's assertion that the *same* dose would be used for rheumatoid arthritis and moderate-to-severe chronic plaque psoriasis, Table 3 instead confirms that a POSA would not have expected the same dosage to work for different diseases.

Additionally, Petitioner fails to establish that a POSA would have viewed these small molecules as relevant to the dosing of a biologic drug such as adalimumab. These molecules are directed to different targets and display vastly different pharmacokinetics. (*See* Ex. 1024 at 8-9; *see also* Ex. 1035 at 2-3, 25-27, 19-20, 22- 24, 32-33, 37-38, 42.) Petitioner fails to establish, for example, that the dosing for Gengraf, a cyclosporine, would be relevant to the dosing of an anti-TNFα biologic like adalimumab for moderate-to-severe chronic plaque psoriasis. Moreover, dermatologists largely *discouraged* the use of systemic steroids, such as those listed in Table 3, for psoriasis due to the severe rebound flare, exacerbation, and pustular psoriasis that routinely occurred upon withdrawal. (Ex. 2026 at 31; Ex. 2009 at 1515; Ex. 1031 at 16-17.) Petitioner and its declarants ignore this entirely. Petitioner's cherry-picked analysis also obscures that small molecule drugs such as methotrexate were approved at a *higher* initial dose and *higher* recommended maximum dose per week for severe psoriasis as compared to "severe, active, classical or definite rheumatoid arthritis." (Ex. 1024 at 8, 10.)

C. Petitioner Fails to Establish that the Efficacy Limitations of Claims 16 and 19 Were Disclosed or Inherent

Claim 16 recites that the patient "achieves at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score at week 12 of the treatment." (Ex. 1001 at 58:24-27.) Claim 19 recites that the patient "achieves at least a Physician Global Assessment (PGA) score of clear or almost clear at week 12 of the treatment." (*Id*. at 58:32-35.) Petitioner fails to establish the unpatentability of claims 16 and 19 under either of its theories: (1) that the claims would have been obvious based on the disclosure of Chaudhari or (2) that the efficacy requirements were inherent from the teachings of the prior art.

1. Petitioner Does Not Establish Any Reasonable Expectation of Success in Achieving PASI 75 or a PGA Score of Clear or Almost Clear

Petitioner argues that the efficacy requirements of claims 16 and 19 "are the obvious result of anti-TNFα therapy," relying on Chaudhari's disclosure of PASI and PGA results. (Pet. at 48.) Yet Chaudhari, which disclosed infliximab administration, only achieved the disclosed PASI and PGA results in patients with moderate-to-severe chronic plaque psoriasis by using *higher* doses of infliximab as compared to the approved dose for rheumatoid arthritis. (Ex. 1036 at 4; *see supra* Section VIII.B.1.) Chaudhari therefore cannot form a basis for any reasonable expectation that using the *lower* approved rheumatoid arthritis dose of adalimumab would successfully achieve the claimed efficacy requirements. *Gillette Co. v. S.C.*

Johnson & Son, Inc., 919 F.2d 720, 724 (Fed. Cir. 1990) ("Focusing on the obviousness of substitution and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.").

Drs. Helfgott and Plott nevertheless assert that the efficacy requirements are "the obvious results of successful TNFα blockade" and therefore treatment with a regimen known to inhibit TNFα would result in at least some patients meeting the claimed efficacy requirements. (Ex. 1002 at ¶¶ 112-13, 133-34; Ex. 1012 at ¶¶ 85-87; 103-105.) Yet Drs. Helfgott and Plott also rely exclusively on Chaudhari, which used *higher* doses of infliximab as compared to the approved dose for rheumatoid arthritis. (*Id*.; Ex. 1036 at 4; *see supra* Section VIII.B.1.) Neither declarant cites any other objective evidence to support their opinions, which the Board should therefore disregard. *See Upjohn Co. v. MOVA Pharm. Corp*., 225 F.3d 1306, 1311 (Fed. Cir. 2000) (requiring factual support for an expert's conclusory opinion).

Notably, PASI 75 is a difficult target to achieve, with some practitioners proposing that the FDA should use a lower PASI 50 score as a clinical endpoint. (*See* Ex. 2006 at 860.) This difficulty is reflected in the Enbrel label, which states that only 23% of PsA patients with skin lesions (not specific to moderate-to-severe chronic plaque psoriasis) achieved a PASI 75 score after *six months of treatment*

with the rheumatoid arthritis dose of etanercept (25 mg twice weekly). (Ex. 1006 at 11-12.)

2. Petitioner Fails to Establish That the Efficacy Requirements Would Have Been Inherent

Petitioner alternatively argues that the efficacy requirements are inherent results of practicing the claimed method. Petitioner fails to establish, however, that the efficacy limitations are *necessarily present* at week 12, and thus fails to prove inherency. To the contrary, Petitioner and Drs. Helfgott and Plott assert that this result is only achieved by "*some* portion of treated patients." (Pet. at 61, n. 34 (emphasis added); Ex. 1002 at ¶¶ 113, 134 ("[T]reatment with the claimed dosing regimen of adalimumab . . . would result in at least some patients with moderate to severe chronic plaque psoriasis achieving the claimed PASI and PGA endpoints"); Ex. 1012, ¶¶ 86, 104 (same).) This is legally insufficient to establish inherency. "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient" to establish inherency. *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (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)).

Petitioner's inherency argument therefore fails to cite any prior art disclosing—or expert testimony addressing—a treatment lasting at least 12 weeks in which the patient being treated achieves PASI 75 at week 12. (Pet. at 48-49.)

Indeed, Petitioner cites only the '689 patent itself to support its conclusion that achieving PASI 75 efficacy at week 12 would be the result achieved by administering 40 mg adalimumab every-other-week. (*Id*.; *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.")).

Petitioner thus fails to establish—or even assert—that the efficacy requirements of claims 16 and 19 are necessarily present, as required for inherency.

D. Petitioner Fails to Establish That the Prior Art Would Inherently Treat the Patient Populations Recited in Claims 16 and 19

Claims 16 and 19 recite methods in which the patient has *both* moderate-to-severe chronic plaque psoriasis *and* psoriatic arthritis. Petitioner asserts that "[t]reating PsO patients with the claimed method, which is obvious for the reasons explained above, would inherently treat the percentage of PsO patients which also have PsA." (Pet. at 47.) This unsupported blanket assertion of inherency on top of alleged obviousness is legally improper, and far from the "carefully circumscribed" application of inherency required by the Federal Circuit. *Par Pharm.* 773 F.3d at 1195. Here, Petitioner's assertion of obviousness stands *only if* a POSA would have found it obvious to use 40 mg of adalimumab to treat moderate-to-severe chronic plaque psoriasis in the first place, and further, *only if* that patient

necessarily also had PsA. This is simply too many "ifs," as inherency "may not be established by probabilities or possibilities." (*Id.*)

Petitioner fails to establish that treating patients with moderate-to-severe chronic plaque psoriasis would *necessarily* result in treating PsA. Rather, the prior art demonstrates that only a small percentage of psoriasis patients have PsA. Lorenz, for example, discloses that only 6-20% of psoriasis patients have PsA. (Ex. 1028 at S18.) Mease 2000 discloses even lower numbers, indicating that only 5-7% of psoriasis patients also have PsA. (Ex. 1017 at 2.) Thus, the "necessary consequence" of treating psoriasis is not treating patients with PsA. *Glaxo Group Ltd. v. Teva Pharms. USA, Inc.*, C.A. No. 02-219, 2004 WL 1875017, *18-20 (D. Del. Aug. 20, 2004) (reference disclosing treatment of migraine pain did not inherently anticipate claims directed to using the same drug to treat nausea and vomiting because only 90% of migraine patients suffered from nausea and only 50% suffered from vomiting).

Petitioner's evidence also is not specific to the claimed patient population. Neither Lorenz nor Mease expressly discloses that patients in those studies have both *moderate-to-severe chronic plaque psoriasis* and PsA. (Ex. 1028 at S18-S19; Ex. 1017 at 2-3.) A disclosure of treating a general patient population does not inherently disclose treating a subset of that population or other patient populations. For example, in *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368 (Fed. Cir.

2005), the Federal Circuit held that a claim directed to treating sunburn with a compound was not inherently anticipated by a reference disclosing use of the compound on skin in general, because the reference did not necessarily disclose application to sunburned skin. *Id.* at 1378-79. Although *Perricone* is an inherent anticipation case, the Federal Circuit has warned that the use of inherency in obviousness must be even more restricted. *See Par Pharm*, 773 F.3d at 1195.

Consistent with this principle, the Board has denied institution when the prior art did not *necessarily* disclose treatment of the claimed patient population. *See Roxane Labs., Inc.*, IPR2016-01461, Paper 9 at 9-10 (denying institution because claims were directed to treating patients with advanced pancreatic neuroendocrine tumors (PNETs) who had failed to respond to cytotoxic chemotherapy, while the prior art taught using the drug to treat advanced solid tumors in patients as well as treating PNETs in animal models but contained no disclosure of treating advanced PNETs after failure of cytotoxic chemotherapy); *see also Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01094, Paper 12 at 7-8, 15-16 (P.T.A.B. Oct. 2, 2017) (denying institution because claims were directed to treating patients over 60 with a type of intermediate-grade non-Hodgkin's lymphoma (NHL) and bulky disease, but the prior art taught treatment of only intermediate-grade NHL without indicating which patients, if any, had bulky disease, and only 30% of patients have concomitant bulky disease).

Petitioner's catch-all argument that a "POSA would reasonably expect the claimed dosing regimen to treat patients with PsO, including in patients that have PsA" (Pet. at 47), is also unpersuasive. No evidence establishes that a POSA would have had any reasonable expectation of success in using the rheumatoid arthritis dose of adalimumab for a patient with *both* moderate-to-severe chronic plaque psoriasis and PsA. As discussed above, Petitioner has cited no prior art using the approved rheumatoid arthritis dose of any drug to treat moderate-to-severe chronic plaque psoriasis. (*See supra* Section VIII.B.) Moreover, Chaudhari discloses use of a *higher* dose of infliximab than approved for rheumatoid arthritis to treat moderate-to-severe chronic plaque psoriasis. (Ex. 1036 at 4; Ex. 1027 at 4; *see supra* Section VIII.B.1.)

E. Petitioner Fails to Show that Certain Background References Qualify as Prior Art Printed Publications

Petitioner asserts that Japan Chemical Week (Ex. 1034), the Press Release (Ex. 1049), the Enbrel Package Insert (Ex. 1006), and the Humira Insert (Ex. 1026) qualify as prior art either under 35 U.S.C. § 102(a) or (b), but provides no evidence that they were publicly available. (Pet. at viii, x, xi, xiii, 23, 31.) Even for these alleged "background references," Petitioner still must meet its burden of making a threshold showing that each alleged prior art reference was available as a printed publication. *See Coal. for Affordable Drugs IV LLC v. Pharmacyclics, Inc.*, IPR2015-01076, Paper 33 at 5-6 (P.T.A.B. Oct. 19, 2015). Here, Petitioner has

failed to do so. 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).

Petitioner asserts a publication date of September 13, 2001, for Japan Chemical Week (Ex. 1034), but cites only the exhibit itself with no evidence as to its source (Dow Jones, Japan Chemical Week, or Factiva) and provides no evidence as to its publication, dissemination, or public availability. (Pet. at 23.) The September 13, 2001 date printed on the exhibit, alone, is insufficient to establish public availability. *See LG Elecs., Inc. v. Advanced Micro Devices, Inc.*, IPR2015-00329, Paper 13 at 13 (P.T.A.B. July 10, 2015). Indeed, Petitioner fails to reconcile this date with the other dates listed on the exhibit—May 28, 2014 and a 2014 copyright date. (Ex. 1034.) Petitioner thus has not shown that Exhibit 1034 qualifies as a printed publication as of September 13, 2001.

Similarly, Petitioner characterizes Exhibit 1049 as an "AbbVie Press Release" published on March 3, 2003, but cites only the exhibit itself with no evidence as to its source, publication, dissemination, or public availability. (Pet. at xiii, 31.) Compounding Petitioner's failure, Exhibit 1049 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. 1049.) Petitioner does not address whether the webpage was available on March 3, 2003, and, moreover, mere availability on a website is not enough to establish public accessibility. *Celltrion, LLC v. Biogen, Inc.*, IPR2017-01230, Paper 10 at 13-15 (P.T.A.B. Oct. 12, 2017). Petitioner also provides no evidence establishing: whether the webpage was indexed; whether an interested person would have been aware of the web address; how the Wayback Machine archives webpages; or how archiving through this site relates to public availability. *See Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349-50 (Fed. Cir. 2016) (reference was not publicly accessible because no evidence showed that an interested person would be aware of the web address or that an Internet search would have located the reference). Petitioner thus has not shown that Exhibit 1049 was published on March 3, 2003.

Petitioner also fails to show that the Enbrel Package Insert (Ex. 1006) and Humira Package Insert (Ex. 1026) were available as prior art. Petitioner asserts that Enbrel was approved in 2002 to treat PsA, citing the Enbrel Package Insert (Ex. 1006). (Pet. at 38.) Petitioner also describes Exhibit 1006 as being from "Immunex Corp. Jan 2002." (Pet. at viii.) Similarly, Petitioner refers to Humira's approval in December 2002, citing the Humira Package Insert (Ex. 1026). (Pet. at 19, n.27.) But nothing in the Petition establishes either of these exhibits as printed publications. First, the dates printed on these package inserts do not prove public

availability. *See LG Elecs.*, IPR2015-00329, Paper 13 at 13 (P.T.A.B. July 10, 2015). Petitioner offers no evidence showing what "Issued: December 2002" on Ex. 1026 or "Issue Date 01/2002" on Ex. 1006 means, or equating "Issued" with public accessibility. *See Coal. for Affordable Drugs IV*, IPR2015-01076, Paper 33 at 7-8 ("[u]pdated" date on document did not prove publication without evidence of what "[u]pdated" meant). Petitioner also cites no evidence tying the FDA approval of Enbrel or Humira to public dissemination of these package inserts.

The Board has repeatedly held that dates on a drug's package insert do not establish the insert as a printed publication. *See*, *e.g.*, *Frontier Therapeutics, LLC v. Medac Gesellschaft Für Klinische Spezialpräparate MBH*, IPR2016-00649, Paper 10 at 22 (P.T.A.B. Sept. 1, 2016); *see also Mylan Pharm., Inc. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01565, Paper 17 at 19-20 (P.T.A.B. Feb. 9, 2017). Petitioner also provides no evidence of the source of the Enbrel Package Insert (Ex. 1006) or the Humira Package Insert (Ex. 1026), how one could have obtained copies of them, or whether they were reasonably accessible to the interested public. *See Mylan Pharm., Inc. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01563, Paper 16 at 14 (P.T.A.B. Feb. 3, 2017). Petitioner's failure to include any of this information compels a finding that it did not establish either Exhibit 1006 or Exhibit 1036 as a printed publication.

IX. Conclusion

Petitioner fails to establish that a POSA would have been motivated to treat or have had a reasonable expectation of success in treating patients with moderate-to-severe chronic plaque psoriasis using the same dosing regimen of adalimumab approved for rheumatoid arthritis. Accordingly, Petitioner has not shown a reasonable likelihood of establishing that any challenged claim is unpatentable. The Board therefore should deny institution of the Petition.

Respectfully submitted,

Date: January 5, 2018 By: / *William B. Raich* /

William B. Raich, Reg. No. 54,386
Michael J. Flibbert, Reg. No. 33,234
Maureen D. Queler, Reg. No. 61,879
Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP

Counsel for Patent Owner
AbbVie Biotechnology Ltd

CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** contains 10,299 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.

Dated: January 5, 2018

By: / William B. Raich /

William B. Raich, Reg. No. 54,386

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response and Exhibits 2001-03, 2005-23, 2025-26** were served electronically via email on January 5, 2018, in their entirety on the following:

Deborah E. Fishman
Arnold & Porter Kaye Scholer LLP
5 Palo Alto Square, Suite 500
3000 El Camino Real
Palo Alto, CA 94306
deborah.fishman@apks.com

David R. Marsh
Arnold & Porter Kaye Scholer LLP
601 Massachusetts Ave., NW
Washington, DC 20001-3743
david.marsh@apks.com

David K. Barr
Arnold & Porter Kaye Scholer LLP
250 W. 55th Street
New York, NY 10019
David.Barr-PTAB@apks.com

Daniel L. Reisner
Arnold & Porter Kaye Scholer LLP
250 W. 55th Street
New York, NY 10019
Daniel.Reisner@apks.com

Petitioner has consented to service by email.

Date: January 5, 2018

By: / William Esper /
William Esper,
Legal Assistant
Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP