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Filed on behalf of: AbbVie Biotechnology Ltd

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD,
Patent Owner.

Case IPR2017-02106
Patent No. 9,067,992

PATENT OWNER'S RESPONSE

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I. Introduction

U.S. Patent No. 9,067,992 (the "'992 patent") discloses the innovative work of AbbVie scientists to develop a novel method of reducing or inhibiting the symptoms of psoriatic arthritis ("PsA") (claim 2), including the progression of structural damage (claim 7), with the biologic drug HUMIRA® (adalimumab). The claimed dosing regimen includes a subcutaneous dose of 40 mg of adalimumab every-other-week.[1]

It is undisputed that the prior art did not disclose data from ***any*** study testing adalimumab in PsA, let alone at a specific dose. The Petition also does not cite a single example in which ***any*** agent (adalimumab or otherwise) was shown to reduce or inhibit the progression of structural damage in PsA. In the absence of such evidence, Petitioner's obviousness grounds rely on experience with ***other drugs*** (etanercept and/or infliximab) and in ***another disease*** (rheumatoid arthritis ("RA")) to fill in the gaps in the art. Petitioner's hindsight-driven arguments are insufficient to satisfy its burden to show that a person of ordinary skill in the art ("POSA") would

[1] Patent Owner has separately disclaimed claims 1, 5, and 6 of the '992 patent. (*See* Ex. 2051.) Accordingly, it does not address those claims or Petitioner's Ground 1 directed to those claims in this response.

have been motivated to arrive at the claimed invention with a reasonable expectation of success. Accordingly, the Petition should be rejected.

Petitioner's cited art related to RA ignores the multiple material differences between RA and PsA, including the types of tissues affected by the diseases and how TNFα is distributed in those respective tissues. Whereas RA is a monolithic disease of the joints, PsA also affects the skin, nails, spine, and entheses, and can be experienced in one of five different clinical subtypes that may change in a single patient over time. Petitioner fails to account for these differences in its analysis. Indeed, as of July 2003, it was known that multiple agents used to treat RA did not work to treat PsA.

Petitioner's cited art related to ***different drugs*** (etanercept and infliximab) fails to establish a reasonable expectation of success with respect to the claims at issue. Petitioner ignores the differences between those drugs and adalimumab and fails to address how the distribution and metabolism of those drugs when administered according to their respective dosing regimens compare to what a POSA would have expected for adalimumab. Moreover, Petitioner's cited art reveals the uncertainty and variability of dosing for other anti-TNFα inhibitors to treat PsA during the relevant time period. For example, the Petition identifies art showing infliximab was dosed to treat PsA at 5 mg/kg or higher, as opposed the 3 mg/kg dose used to treat RA. In view of this uncertainty and variability in the art, Petitioner has

not met its burden with respect to either of the challenged claims to show a reasonable expectation that adalimumab would reduce or inhibit the symptoms of PsA with the specific, claimed 40 mg every-other-week dose.

Petitioner's obviousness argument with respect to claim 7 fails for additional reasons. Claim 7 is directed to a PsA patient experiencing the symptom of structural damage and requires reduction or inhibition of the progression of structural damage after subcutaneous administration of 40 mg of adalimumab every-other-week. The Petition overlooks a simple, but important, fact relevant to claim 7: structural damage is different in PsA and RA. The ***only*** art relied upon by Sandoz that any agent could reduce or inhibit progression of structural damage relates to ***RA***. This is insufficient to show obviousness for multiple reasons.

First, the Petition fails to account for the considerable uncertainty in the art regarding structural damage in PsA. As of July 2003, the investigation of structural damage in PsA patients was in its early stages. Petitioner's cited references expressly state that the ability of an anti-TNFα agent to successfully reduce or inhibit progression of structural damage required further study. The cause of structural damage in PsA patients was unknown, and multiple cytokines that play no role in RA were understood to be implicated in PsA. Petitioner fails to address whether or how TNFα plays a role in structural damage in PsA versus RA (e.g., the distribution or dynamics of TNFα in affected tissue). The art recognized that "new therapies

above those developed for RA will be required to manage" unique clinical features of "radiographic progression [in PsA]." (Ex. 2009, 1519.) To meet its burden to show reasonable expectation of success, the Petition must do more than simply ignore those uncertainties.

Second, the Petition fails to establish that a POSA would have had a reasonable expectation that any agent (let alone adalimumab) could reduce or inhibit structural damage in PsA. Although there were multiple examples of agents (both small molecule and biologic) that reduced or inhibited structural damage in ***RA***, Sandoz does not rely on a ***single example*** of an agent that did so in ***PsA***. There were multiple instances where success in RA did not yield success in PsA. For example, although methotrexate was used to treat both RA and PsA and was known to reduce or inhibit structural damage in RA, a pre-2003 study showed it did not reduce or inhibit structural damage in PsA. This and other examples defeat Petitioner's hindsight-driven, conclusory premise that experience in RA can reasonable predict the same result in PsA.

Third, those in the art recognized that the clinical manifestations of PsA and RA were different and that PsA could damage tissues and cause deformities that RA does not. As a result, a ***different test*** was used to assess progression of structural damage in PsA. The fact that the results of these tests were not substitutable meant a POSA could not have had a reasonable expectation that what worked to address

structural damage in RA would successfully do so in PsA. The cursory analysis in the Petition glosses over these differences.

Fourth, the prior art relied upon by Petitioner does not support that the claimed 40 mg every-other-week ***dose*** of adalimumab would reasonably been expected to reduce or inhibit progression of structural damage in PsA. The Rau reference (Ex. 1021*) at most shows that ***higher*** intravenous, weight-based doses of adalimumab treated radiographic progression in ***RA***. And the Lorenz reference (Ex. 1028) is silent as to what dose was used in a study of combination therapy of infliximab and methotrexate in ***RA***. The Petition identifies ***no basis*** to support an expectation that a 40 mg every-other-week dose of adalimumab could reduce or inhibit structural damage in ***any disease***, let alone PsA. And it identifies ***no prior art evidence*** that the same dose (or even a similar dose) of any drug successfully inhibited progression of structural damage in both RA and PsA (i.e., that the same amount of drug would be sufficient to be distributed to and metabolized by the affected tissues). Absent identification of any such teaching or evidence in the art, the Petition has not shown a reasonable expectation of success with respect to claim 7.

Finally with respect to claim 7, Petitioner has not shown that reduction or inhibition of structural damage is an inherent outcome of an obvious method. Inherency requires that a result necessarily or inevitably flow from performance of

a claimed method and, when obviousness is the issue, that a POSA would have reasonably expected the allegedly inherent outcome when the patent was filed. By the admission of Petitioner's declarant, that is not the case: Dr. Helfgott agreed that "giving adalimumab at 40 milligrams every-other-week does not necessarily and inevitably lead to reducing or inhibiting structural damage in all psoriatic arthritis patients." (Ex. 2036, 88:13-19.) This ends the inquiry. "Inherency…***may not be established by probabilities or possibilities***." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014).[2] Petitioner has not shown that the claimed patients will necessarily or inevitably achieve the claimed result.

For these reasons, as set forth in more detail below, Petitioner has failed to meet its burden of showing the unpatentability of the challenged claims. The Board should therefore confirm the patentability of the claims and deny the Petition.

II. The Patented Invention

The '992 patent discloses and claims novel methods for reducing or inhibiting symptoms of PsA. These methods comprise subcutaneously administering to a patient 40 mg of adalimumab every-other-week. (Ex. 1001, col. 55-56.)

[2] All emphasis added unless otherwise noted.

Independent claim 2 of the ’992 patent recites as follows:

> 2. A method for reducing or inhibiting symptoms in a patient with psoriatic arthritis, comprising subcutaneously administering to said patient 40 mg of adalimumab every other week.

(Ex. 1001, 55:26-29; Ex. 2053, ¶¶20-21.) Dependent claim 7 depends from claim 2 and recites:

> 7. The method of claim 2, wherein said symptoms are progression of structural damage assessed by radiograph.

(Ex. 1001, 56:25-26; Ex. 2053, ¶¶22.)

The ’992 patent recites the results of a study of adalimumab administered according to the claimed method to PsA patients at a dose of 40 mg every-other-week. In that study, adalimumab was shown to be “more effective compared with placebo in inhibiting radiographic disease progression over a 24-week period.” (Ex. 1001, 40:23-25.) Table 3 recites the changes in modified Total Sharp Score at 24 weeks for patients administered adalimumab 40 mg every-other-week and patients administered placebo:

TABLE 3

Change* in Modified Total Sharp Score at Week 24

	Placebo N = 152 n (%)	Adalimumab N = 144 n (%)
Decrease in Sharp Score	8 (5.3%)	27 (18.8%)
No change in Sharp Score	100 (65.8%)	104 (72.2%)
Increase in Sharp Score	44 (28.9%)	13 (9.0%)

$p \leq 0.001$ placebo vs. adalimumab using CMH test
*Change defined as >0.5 units in mTSS Score

18.8% and 72.2% of patients experienced a decrease or no change in their modified Total Sharp Score over 24 weeks, respectively. Not all patients treated experienced a decrease or no change in mTSS: 9% experienced an increase in modified Total Sharp Score at week 24. (Ex. 2053, ¶¶23-24.)

III. Background

A. PsA

PsA is a complex disease that was and is poorly understood. It affects a wide range of tissues and has a variety of clinical presentations. (Ex. 2009, 1519). PsA is an autoimmune inflammatory disorder that affects the ligaments, tendons, entheses (the tissue that connects tendons to joints), and spinal or peripheral joints. (Ex. 2007,

42; Ex. 2009, 1511-12.)[3] Although PsA is a separate condition from psoriasis, most patients who suffer from PsA also develop some type of psoriasis. (Ex. 2009, 1511; Ex. 2008, 2449.) It is currently estimated that 3.2% of Americans have psoriasis and that, of those, 10% to 30% have PsA. (Ex. 2042, 512; Ex. 2005, 30.) PsA's etiology and pathogenesis are unknown. (Ex. 2009, 1512; Ex. 2053, ¶¶25-26, 28.)

PsA has five different clinical phenotypes: (1) arthritis of the distal interphalangeal joints only; (2) oligoarthritis, often asymmetric and affecting less than 5 joints; (3) polyarthritis, often symmetrical, affecting more than 5 joints; (4) destructive (mutilans) arthritis; and (5) spondyloarthropathy (SpA) usually associated with peripheral arthritis. (Ex. 2033, 1022; Ex. 2031, 675.) Several studies have demonstrated that PsA may change clinical phenotypes in a patient over the course of her disease. (Ex. 2033, 1023-25; Ex. 2031, 678.) This progression from one pattern to another does not proceed in a predictable manner or at a progressive rate. (Ex. 2033, 1023-25; Ex. 2031, 678; Ex. 2053, ¶¶27.)

PsA is a complex disease because it affects many, often distinct, tissues. In addition to causing inflammation of the synovial fluid of the joints, PsA causes

[3] 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.

enthesitis, i.e., inflammation of the point where tendon attaches to bone. (Ex. 2008, 2450; Ex. 2003, 1544.) PsA patients may also experience dactylitis, (swelling of an entire digit). (Ex. 2046, 157; Ex. 2008, 2450.) PsA may also affect a patient's spine, pelvis, ligaments, tendons, nails, and skin. (Ex. 2007, 42, 45-47; Ex. 2009, 1513.) Each patient may experience the effect of PsA in a different subset of these tissues, and which tissues are affected by the disease may change over time. The "wide variability in disease between patients" makes it difficult to study drug efficacy in PsA, particularly in small populations. (Ex. 2009, 1519; Ex. 2053, ¶28.)

B. PsA and RA Are Different Diseases

PsA and RA are distinct diseases: they affect different tissues, have different pathologies, are caused by different cytokines, and result in different symptoms.

PsA and RA Affect Different Tissues. Whereas RA affects the synovium of the joints, PsA not only affects a patient's joints, but can also affect his or her entheses (the tissue that connects tendons to joints), spine, nails, and skin. (Ex. 2008, 2450; Ex. 2003, 1544; Ex. 1023, 2.) For example, PsA patients frequently have spinal or pelvic involvement, whereas RA patients typically do not. (Ex. 2008, 2450.) RA patients also do not typically exhibit enthesitis or skin or nail issues as a result of RA. (Ex. 2008, 2450; Ex. 2003, 1544; Ex. 1023, 2.) And, unlike RA, PsA is defined not just by its effect on a patient's joints, but also by its association with psoriasis. (Ex. 2009, 1512.) It was and is unclear why and how PsA and RA affect

different tissues (e.g., why TNFα affects skin in PsA and not RA), and whether and how the two diseases affect the same tissue in different ways. (Ex. 2053, ¶29.)

The Pathology of PsA Is Different than RA. The pathology of PsA was and is still poorly understood. Nonetheless, due to their different clinical manifestations, it was understood that PsA and RA were different diseases that involved different pathologies. (Ex. 2009, 1512-14.) For example, in a 2004 publication, a study found that PsA synovial fluid more closely resembled synovial fluid from spondyloarthropathy patients ("SpA," a group of diseases including PsA, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, and others) than RA patients and found multiple differences between RA and PsA synovial fluid. (Ex. 2004, R569, R576-78.) A study has also found that PsA synovial fluid is more vascular than RA fluid and has significantly less synovial lining cell hyperplasia and fewer macrophages than RA fluid. (Ex. 2003, 1545; Ex. 2053, ¶30.)

PsA Has a Different Cytokine Profile than RA. As of July 2003, some scientists had found that the presence of TNFα in synovial fluid was higher in PsA patients than in RA patients. (Ex. 2003, 1544.) It was also known that more CD8+ T cells are present in PsA synovial fluid, whereas RA has more CD4+ T cells. (Ex. 2008, 2451.) Since July 2003, scientists have discovered still further differences in cytokine profiles between RA and PsA. For example, several IL-17 inhibitors, such as brodalumab and secukinumab have been shown to be effective in treating PsA.

(Ex. 2041; Ex. 2038, 2295.) However, these same biologics have been shown to be ineffective for use in RA patients, and IL-17 is thought to have a different role in RA patients than PsA patients. (Ex. 2029; Ex. 2028; Ex. 2052, 1152; Ex. 2038, 2303; Ex. 2053, ¶¶31-32.)

PsA and RA Patients Experience Different Clinical Symptoms. It was known as of July 2003 that PsA patients frequently have involvement of distal interphalangeal joints (certain joints of the hands and feet) and asymmetric joint involvement, whereas RA patients typically do not. (Ex. 2008, 2449; Ex. 2009, 1511.) Unlike in RA, dactylitis—the swelling of an entire digit—and "ray" joint distribution—disease effect in all joints in a single digit—are common in PsA patients. (Ex. 2008, 2449.) These different symptoms further indicated that PsA and RA have different pathologies and contributed to uncertainty regarding the biological pathways of the diseases relative to one another. (Ex. 2053, ¶33.)

C. The Progression of Structural Damage in PsA Is Different Than in RA

PsA was initially thought of as a relatively benign disease compared to RA, but studies published in the 1980s-1990s changed that understanding. (Ex. 2048, 127; Ex. 2030, 809; Ex. 2031, 675.) These studies recognized that the number of PsA patients who had structural joint damage increased over time, and that this increase in damaged joints occurred even where joint inflammation was reduced. (Ex. 2030, 811; Ex. 2033, 1025.) The recognition of the severity of structural damage

in PsA patients amid uncertainty as to its cause led those in the field to begin to examine and evaluate structural damage in PsA patients. (Ex. 2053, ¶34.)

Structural damage can be assessed by radiograph, *i.e.*, by x-ray. Such radiographic images taken over time can show the extent of damage to a patient's tissues. Assessing structural damage by radiographs involves assessing the changes to a patient's bones, such as bone loss, bone formation, and bone deformities. (Ex. 2046, 158; Ex. 2001, ii61; Ex. 2053, ¶35.) The presence of structural damage may depend on the length of time that a patient has experienced symptoms of PsA and may not be detectable by radiograph until it has progressed significantly. (Ex. 2053, ¶34.)

Radiographs of PsA patients reveal different structural damage than that experienced by RA patients. (Ex. 2008, 2450.) RA may display certain deformities in joints in the hands (referred to as "swan necking" or "boutonniere" deformities); PsA patients, in contrast, display rigid stiffening (ankylosis) of joints and shortening (telescoping) or floppy (flailing) digits. (*Id*.) Moreover, radiographs of PsA patients show erosive disease of the DIP joints, new bone formation (periostitis), spurs of the entheses (connections of tendon to bone), or a deformity in which digits appear to fit together like a pencil in a cup. (*Id*.) These radiographic features are not present in RA patients. (*Id*.) Indeed, "ankylosis, bone lysis [destruction of bone cells] and new bone formation are very particular to PsA and not commonly seen in RA," and "are

responsible for a large degree of the long-term loss of function and disability in [PsA] patients." (Ex. 2009, 1519; Ex. 2053, ¶36.)

These differences further demonstrate that RA and PsA likely have different pathologies. The structural damage experienced by RA patients typically involves joint erosions and narrowing of the space between the joints (*i.e.*, joint space narrowing or JSN). (Ex. 2046, 164.) PsA patients experience several additional types of structural damage. (Ex. 2046, 157-58; Ex. 2001, ii61.) For example, due to the different tissues involved in PsA, PsA patients can experience structural damage in their spine and pelvis, neither of which is typically affected by RA. (Ex. 2008, 2450, Table 2; Ex. 2001, ii61.) PsA can also cause structural damage in distal interphalangeal joints (*i.e.* the joints of the fingers), whereas RA usually does not. (Ex. 2008, 2450, Table 2; Ex. 2001, ii61; Ex. 2053, ¶37.)

Whereas structural damage in RA patients is typically shown by JSN and erosions, structural damage in PsA patients can be caused by:

- Osteolysis – destruction of the joint;
- Syndesmophytes – bony growth inside a ligament, typically a spinal ligament;
- Ossification – the growth of bone tissue;
- Ankylosis – fusion of the bones of a joint;
- Subluxation – partial dislocation of a joint; or

- Pencil in cup phenomena – a radiographic deformity observed in PsA patients caused by periarticular erosions and bone resorption.

(Ex. 2001, ii61-ii63; Ex. 2008, 2450; Ex. 2045, 2645; Ex. 2046, 158-59; Ex. 2053, ¶38.)

RA is a monolithic disease that progresses at a relatively constant rate. (Ex. 2047, 1571.) Methods of assessing radiographic damage in RA patients have been known for several decades. (Ex. 2044.) As of 2003, the art of assessing and evaluating the progression of structural damage in RA was well known and those of ordinary skill could assess a treatment's effect and compare that effect across a population of patients. By comparison, because of the nascent state of the art regarding assessment of structural damage in PsA patients and the heterogeneous nature of the disease, it was difficult to make that same assessment of progression of structural damage in PsA. (Ex. 2053, ¶39.)

Prior to the early 2000s, a "scoring" method—the Total Sharp Score—was developed to assess the extent of structural damage in RA patients. (Ex. 2044, 706-07.) The Total Sharp Score includes a score for defects and erosions and another score for joint space narrowing and ankylosis and allows quantification of the extent of structural damage in a patient. (*Id.*; Ex. 2053, ¶40.)

The Total Sharp Score used for RA patients does not fully account for all the affected tissues and types of structural damage in a PsA patient. It was understood

as of 2003 that PsA-specific methods were necessary to evaluate the clinical effect on the different structural damage manifestations in PsA. (Ex. 2046, 158; Ex. 2053, ¶41.)

PsA-specific scoring methods were not well-developed as of 2003, but several were under development. (Ex. 2001, ii61; Ex. 2046, 158.) For example, in 2001, Dr. Siegfried Wassenberg was developing a PsA scoring method with a separate proliferation score to account for bone formations typical for PsA and not RA. (Ex. 2046, 159.) Separately, Dr. Désirée van der Heijde modified the RA Sharp-van der Heijde method for PsA, accounting for not only erosions and joint space narrowing, but also (sub)luxation, ankylosis, gross osteolysis, and pencil in cup phenomena. (Ex. 2001, ii63 (2005).) This modified score assessed more joints than were assessed in RA patients by including the DIPs of the hands. (*Id.*; Ex. 2053, ¶42.)

It was unknown why PsA and RA patients experience structural damage so differently, and whether the same or different cytokines caused structural damage in the two diseases, although some offered theories as to why prior to 2003. By way of example, one study theorized that enthesitis plays a role in structural damage of PsA patients, which it does not do in RA patients. (Ex. 2017, 1080; Ex. 2053, ¶43.)

D. Treatments for PsA and RA Are Different

Several treatments used for RA were known as of July 2003 to be ineffective in treating PsA. Among conventional, non-biologic treatments, gold and

sulphasalazine were common treatments for RA, but were shown by some to have few or no benefits in treating PsA. (Ex. 1017, 6; *see also* Ex. 2005, 32-33.) Corticosteroids were also used in RA (Pet., 40, Table 3; Ex. 1002, ¶ 112, Table 2), but are a controversial treatment for PsA patients. Although corticosteroids are occasionally used to treat PsA patients, several papers have noted that they are "contraindicated in patients with PsA" because of their potential to cause serious side effects in the skin. (Ex. 2009, 1515; *see also* Ex. 2023, 31; Ex. 2008, 2453 (noting that corticosteroids have "potential long-term adverse effects" on PsA patients.) Hydroxychloroquine is also considered suitable for treating RA, but can exacerbate skin lesions in PsA patients and has been associated with precipitating pustular psoriasis. (Ex. 1023, 3; Ex. 2053, ¶44.)

Likewise, it was understood after July 2003 that there are multiple biologics that are not effective in treating PsA, despite being effective for RA. For example, rituximab is effective in treating RA, but studies have failed to show it has efficacy in treating PsA. (*See* Ex. 2006, 4, 5.) And both anakinra and tocilizumab are approved for use in RA, but have shown limited improvement in patients with PsA and have shown some evidence of worsening the disease. (Ex. 2055; Ex. 2010, 1; Ex. 2011, 216; Ex. 2012, 255.) Conversely, IL-17 inhibitors (including brodalumab and secukinumab) have proven to be effective in treating PsA, but are not effective

at treating RA. (Ex. 2041; Ex. 2029; Ex. 2052, 1152; Ex. 2028; Ex. 2038, 2295, 2303; Ex. 2053, ¶45.)

With respect to the reduction or inhibition of structural damage in patients with RA or PsA, treatment options and effects were also distinct. Petitioner has cited no reference discussing that a treatment (small molecule or biologic) successfully reduced or inhibited structural damage in PsA patients. (Ex. 2053, ¶46.) There are multiple examples of RA treatments that did not achieve that endpoint in PsA. (Ex. 2053, ¶47.) By way of illustration, in a 2003 review, Jones et al. identified nine agents that improved radiological outcomes for RA patients. (Ex. 2032, 10.) As summarized below, as of 2003, none had been shown to reduce or inhibit progression of structural damage in PsA:

Agent for Reduction/Inhibition of Structural Damage in RA	**Role in PsA**
Infliximab	Unknown effect on structural damage
Methotrexate	Did not reduce/inhibit structural damage
Sulphasalazine	Did not reduce/inhibit structural damage
Gold	Did not reduce/inhibit structural damage
Cyclosporine	Not used due to toxicity concerns
Corticosteroids	Not typically used due to toxicity concerns

Auranofin	Did not treat PsA
Leflunomide	Not shown to treat PsA
IL-1 receptor	Not shown to treat PsA

In the specific example of methotrexate, which was routinely used to treat PsA, a study reported that "[n]o improvement in radiographic progression was evident after treatment with methotrexate for 2 years compared with placebo." (Ex. 1023, 5; *see also* Ex. 2008, 2451; Ex. 2027, 241; Ex. 2053, ¶¶48-49.)

IV. The Asserted References

A. Keystone (Ex. 1003)

The Keystone abstract discusses the use of 20, 40, or 80 mg of adalimumab every-other-week with methotrexate to treat RA. (*See* Ex. 1003, A481.) Keystone does not discuss PsA or adalimumab's effect on, or distribution to, the tissues affected by PsA, much less a dosing regimen for treating patients with that condition. Keystone also does not discuss whether adalimumab inhibits progression of structural damage in any disease. (Ex. 2053, ¶51.)

B. Lorenz (Ex. 1028)

Lorenz provides an overview of clinical trials using infliximab or etanercept to treat different TNFα-mediated conditions, including RA, 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 generally* Ex. 1028.) (Ex. 2053, ¶52.)

Lorenz never discusses adalimumab (also referred to as D2E7) in connection with PsA. (*See* Ex. 1028, S17-19.) It also does not discuss any clinical trials, dosage, or results for adalimumab in the treatment of PsA. Rather, Lorenz speculates that "encouraging results might arise" if TNFα-directed agents, such as etanercept, onercept, PEG-TNFRI ("pegsunercept"), and adalimumab, were used in trials for other non-specified TNFα-associated conditions. (*Id.*, S17-18.) Lorenz cautions, however, that further studies of the efficacy of these agents "are required," and that, both for etanercept and D2E7, such studies should "focus[] particularly on radiological progression…in patients with RA." (*Id.*, S18.) (Ex. 2053, ¶53.)

The need for this caution was illustrated by known failures of various anti-TNFα biologics to treat specific TNFα-mediated diseases. Sandborn, for example, reported in 2001 that 25 mg etanercept twice a week failed to treat Crohn's disease. (Ex. 2013, 6.) Further, Phase 3 trials of onercept in psoriasis were later discontinued and the drug was never approved for this indication. (Ex. 2014, 1.) Similarly, pegsunercept was never approved for psoriasis. (*See generally* Ex. 2016.) Petitioner's declarant, Dr. Helfgott, confirmed that these agents that Lorenz speculated "might" work to treat such diseases were, in fact, never FDA approved. (Ex. 2036, 70:7-24.) Lorenz also lists multiple potential "new indications" for TNFα

therapy (Ex. 1028, S18-21), but in practice anti-TNFα agents are not, in fact, used to treat many of those indications. For example, despite being listed in Lorenz, a study showed that etanercept was "not effective" in maintaining remission in Wegener's granulomatosis patients. (Ex. 2018, 351.) (Ex. 2053, ¶54.)

Lorenz discusses clinical trials using 5 mg/kg of infliximab or 25 mg twice a week of etanercept to treat PsA patients. (Ex. 1028, S18-19.) Lorenz does not discuss using 3 mg/kg of infliximab to treat PsA. (Ex. 2053, ¶55.)

Lorenz references an unnamed and uncited study in which "combination therapy" of infliximab and methotrexate administered to RA patients "showed for the first time in any RA trial that there was no median radiological progression" after 12 months in patients given drug. (Ex. 1028, S17.) Lorenz does not provide details on the amount of drug administered in the study, the percentage of patients that achieved the stated outcome, or the effect of methotrexate as compared to infliximab. (Ex. 2036, 71:14-72:1, 72:25-73:4; Ex. 2053, ¶56.)

Lorenz does not discuss nor suggest a dosing regimen for adalimumab, any connection between adalimumab and PsA, or whether adalimumab could inhibit the progression of structural damage in PsA patients. Lorenz also does not discuss or suggest adalimumab's effect on or distribution to all the tissues affected by PsA. (Ex. 2053, ¶57.)

C. Mease 2000 (Ex. 1017)

Mease 2000 discusses twice-weekly administration of 25 mg of etanercept to treat PsA patients. (*See* Ex. 1017, 2.) Mease 2000 does not discuss any clinical trials or results using adalimumab, any dosing regimen for adalimumab, or any connection between adalimumab and PsA. Mease 2000 also does not discuss or suggest adalimumab's effect on or distribution to all the tissues affected by PsA, or how they may compare to the effect or distribution of infliximab or etanercept. (Ex. 2053, ¶58.)

Mease 2000 explains that "[t]he few controlled trials assessing patients with psoriatic arthritis have not shown consistent efficacy," and that "response to therapy [for PsA derived from clinical experience in RA] is often unsatisfactory." (*Id.)* It describes "unique features" of PsA versus RA, "includ[ing] the potential for asymmetric, oligoarticular, axial and/or distal interphalangeal joint involvement, dactylitis, and enthesial inflammation." (*Id.)* Mease 2000 does not report whether etanercept would inhibit the progression of structural damage in PsA patients. (*See id.*, 6.) (Ex. 2053, ¶59.)

D. Dechant (Ex. 1029)

Dechant discusses the use of infliximab to treat a small sample of 10 patients with PsA. (Ex. 1029, 8.) Patients in the study received 5 mg/kg infliximab at weeks 0, 2, and 6. After week 10, one patient stopped treatment and each remaining

patient's dose was personalized to an unspecified dose in the range of 3-4 mg/kg at an infusion interval of ≥8 weeks. (*Id.)* One patient received an increased dose at a shorter interval of 4 weeks after experiencing a flare. (*Id.)* As Dr. Helfgott acknowledged, Dechant does not discuss the specific dose that any single patient received. (*See* Ex. 1029, 9; Ex. 2036, 52:12-53:3.) (Ex. 2053, ¶60.)

Dechant does not discuss or suggest a dosing regimen for adalimumab, any connection between adalimumab and PsA, or whether adalimumab could inhibit the progression of structural damage in PsA patients. Dechant also does not discuss or suggest adalimumab's effect on or distribution to all the tissues affected by PsA, or how they may compare to the effect or distribution of infliximab or etanercept. (Ex. 2053, ¶61.)

E. Rau (Ex. 1021)

Rau discusses studies of adalimumab to treat RA. Rau does not discuss using adalimumab for any purpose other than to treat RA. Rau also does not discuss a 40 mg subcutaneous every-other-week fixed dose. Rau also does not discuss PsA or adalimumab's effect on or distribution to all the tissues affected by PsA, much less a dosing regimen for treating patients with that condition. Rau includes reports of the effect of doses of adalimumab of 1.0 mg/kg and higher on the Sharp Scores of patients with RA at 6 and 12 months, but it does not address the modified Total

Sharp Score for PsA or any other measure of radiographic progression used for PsA patients. (Ex. 1021, 7.) (Ex. 2053, ¶62.)

V. The Person of Ordinary Skill in the Art

Petitioner proposes a person of ordinary skill having an "M.D. and at least 3 years' post-residency experience treating patients for PsA and RA." (Pet., 14.) In its Institution Decision, the Board found that the level of ordinary skill in the art "do[es] not exclude RA experience" and that "the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention." (Paper 13, 12.) Petitioner's unpatentability arguments fail regardless of whether this definition is adopted, and Patent Owners expert, Dr. Allan Gibofsky, meets Petitioner's proposed definition of a POSA. (Ex. 2053, ¶¶63-64.)

VI. Priority

With respect to its obviousness grounds (Grounds 2 and 3), Petitioner assumes the challenged claims are entitled to a priority date of July 18, 2003 (Ground 2) or July 19, 2002 (Ground 3). (Pet., 9.) The Board, likewise, instituted this proceeding based on Petitioner's asserted priority dates. (Paper 13, 10.) For purposes of this

proceeding, Patent Owner does not dispute Petitioner's asserted alternative effective filing dates for the challenged claims. [4]

Petitioner suggests that claim 7 is entitled to an effective filing date of May 16, 2005, the date of U.S. Provisional App. No. 60/681,645. (Pet., 7.) But Petitioner's arguments do not rely on that alleged priority date; rather, each obviousness ground assumes that claim 7 is entitled to an effective filing date of July 18, 2003 or earlier. (*Id.*, 9; *see also* Ex. 2036, 22:16-23:5 (confirming Dr. Helfgott did not offer opinions based on priority dates other than July 2002 or July 2003).) Moreover, Petitioner does not assert any reference post-dating July 18, 2003. (Pet., 9.) Because Petitioner's alleged priority date for claim 7 is not relevant to any of the asserted obviousness grounds, Patent Owner does not address it here. *In re Magnum Oil Tools Int'l, Ltd*., 829 F.3d 1364, 1381 (Fed. Cir. 2016) ("the Board must base its decision on arguments that were advanced by a party").

VII. Claim Construction

Patent Owner disputes Petitioner's contentions that the preamble of claim 2 and the "wherein" clause of claim 7 do not limit the claims. (*Id.*)

[4] For the purposes of this response, Patent Owner assumes, but does not concede, a priority date of July 2003 for both Grounds asserted against claim 2.

A. The Preamble of Claim 2 Is Limiting

In its Institution Decision, the Board found it did "not need to determine whether the preamble phrase[] [of claim 2 is] limiting at this stage of the proceeding to resolve the parties' dispute." (Paper 13, 14.) Patent Owner agrees that, to the extent Petitioner acknowledges it must show that "reducing signs or inhibiting symptoms in a patient with [PsA]" would have been obvious to succeed in its challenge (*see* Pet., 14-15), there is no dispute about the construction of claim 2 that requires resolution.

To the extent there is any dispute, Patent Owner maintains that the preamble of claim 2 is limiting. The preamble of independent claim 2 substantively limits and provides antecedent basis for the claims because it is the only part of claim 2 that recites "psoriatic arthritis." (Ex. 1001, 55:26-29.) Moreover, claim 2 refers to the patient recited in the preamble with the phrase "said patient," and dependent claim 7 further limits claim 2 with reference to "said symptoms." (*Id.* 56:24-25; Ex. 2053, ¶65.)

The case cited by Petitioner, *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003), confirms that a preamble is limiting where "the preamble provides antecedents for ensuing claim terms and limits the claim accordingly." Further, the "preamble language will limit the claim if it recites not merely a context in which the invention may be used, but

the essence of the invention without which performance of the recited steps is nothing but an academic exercise." *Id.* Here, the preamble of claim 2 provides antecedent basis and the essence of the invention ("reducing or inhibiting" symptoms of PsA).

B. The Outcome Limitation of Claim 7 Is Limiting

In its Institution Decision, the Board "agree[d] with Patent Owner that the outcome limitation[] of [claim 7 is] entitled to patentable weight." (Paper 13, 15.) That decision was correct.

Claim 7 recites a method of reducing or inhibiting symptoms in a PsA patient "wherein said symptoms are progression of structural damage assessed by radiograph." (Ex. 1001, 56:25-26.) This claim introduces an efficacy requirement not otherwise found in the claims that "the written description discloses as important to the invention." (Paper 13, 15.*)* For example, the '992 patent explains that assessing progression of structural damage by radiograph for a patient is a specific means of assessing the effectiveness of a TNFα inhibitor:

> In one embodiment, joint destruction is measured using radiography. Such assays may be used to examine the efficacy of the TNFα inhibitor by determining whether an improvement occurs in a subject or patient population treated with the TNFα inhibitor. Generally, improvements are determined by comparing a baseline score determined prior to treatment, and a score determined at a time following treatment with the TNFα inhibitor.

(Ex. 1001, 26:43-51; *see also id.*, 4:55-5:4 ("The invention also includes a method for testing the efficacy of a TNFα antibody…[by] determining the efficacy of the TNFα antibody…using a baseline modified Total Sharp Score (mTSS)…wherein no change or a decrease in the mTSS" is achieved).) The '992 patent also recites a study showing some PsA patients achieved reduction or inhibition of the progression of structural damage assessed by radiograph. (Ex. 1001, 38:53-40:33; Ex. 2053, ¶¶67-68.)

As the Board correctly found, the additional limitation of claim 7 thus provides "a means for assessing the efficacy of the treatment recited in the claims, which the written description discloses as important to the invention." (Paper 13, 15.) Claim 7 therefore further limits claim 2 to those individual patients with structural damage that achieve the specific, recited efficacy result. *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."). (Ex. 2053, ¶¶66-68.)

VIII. The Challenged Claims of the '992 Patent Would Not Have Been Obvious

A. Claim 2 Would Not Have Been Obvious

Petitioner has failed to carry its burden of proving that either of its two asserted combinations renders claim 2 obvious. Petitioner has not demonstrated that the combination of Keystone, Mease 2000, and Lorenz, nor the combination of Keystone, Mease 2000, and Dechant 2000, renders claim 2 obvious. (Ex. 2053, ¶69.)

In its Institution Decision, the Board found that disclosure of "the same or similar doses and dosing regimens to effectively treat both" RA and PsA was sufficient to show a POSA "would have had a reason to treat PsA with 40 mg adalimumab administered every other week with a reasonable expectation of success." (Paper 13, 33-35.) Patent Owner respectfully disagrees.[5] As explained below, the Petition does not identify prior art treatment of PsA with adalimumab, does not account for the significant differences between RA and PsA, and relies on different doses and from studies of different molecules in a failed attempt to establish a reasonable expectation of success for the claimed dosing regimen. (Ex. 2053, ¶17).

1. None of Petitioner's Cited References Discloses Reduction or Inhibition of Symptoms of PsA with Adalimumab

Petitioner's cited references do not disclose or suggest that adalimumab would reduce or inhibit symptoms of PsA at all, let alone that it would do so at a particular

[5] In Application No. 14/634,478, Patent Owner separately has pursued claims directed to treating joint inflammation associated with an inflammatory arthritis with adalimumab based, in part, on disclosure including examples relating to the treatment of RA with 40 mg every-other-week of adalimumab. Patent Owner's proposed claims stand rejected, with the Examiner finding that disclosure related to the treatment of RA with adalimumab was not sufficient to support the disclosure of a method of treating inflammatory arthritis with the same dose.

dose. With respect to Ground 3, Petitioner does not dispute that none of Keystone, Dechant, or Mease 2000 discusses treatment of PsA with adalimumab. (Pet., 19, 26, 27; Ex. 2053, ¶70.)

With respect to Ground 2, Petitioner argues that Lorenz "clearly taught that adalimumab would be useful in treating PsA." (Pet., 44.) This is not correct. Lorenz separately mentions the ***words*** "D2E7" and "psoriatic arthritis," but nowhere does it state that D2E7 is a candidate for treating PsA, make any connection between adalimumab and PsA, or discuss adalimumab's ability to inhibit progression of structural damage in PsA patients. Rather, Lorenz's PsA section only discusses anti-TNFα therapy with infliximab and etanercept—not adalimumab. (Ex. 1028, S18-19.) In fact, Lorenz discusses adalimumab ***only*** in its "Summary" and "Rheumatoid arthritis and Crohn's disease" sections and ***never*** in connection with PsA. (*See generally* Ex. 1028.) (Ex. 2053, ¶71.)

Petitioner cites two additional "background" references—Japan Chemical Week and a Press Release—that are not a part of its Grounds.[6] As a threshold matter,

[6] For purposes of this IPR only, Patent Owner does not challenge the printed publication status of the Humira label or Press Release. As these are background references cited only in passing in the Petition, their printed publication status is irrelevant to resolving the patentability of the challenged claims.

Petitioner's reliance on these background references highlights the weakness of the arguments in Petitioner's Grounds and runs afoul of the Board's requirement to precisely identify the art relied upon. *See* 37 C.F.R. § 42.104(b). Regardless, neither reference discloses or suggests that adalimumab would treat PsA. Japan Chemical Week, a summary article providing analysis of the TNFα inhibitor market, ***does not mention PsA*** in discussing adalimumab. (*See* Ex. 1034, 1.) Rather, the article discusses adalimumab only in relation to other diseases and generally mentions PsA as a TNFα mediated disease. It also does not mention a specific dose (i.e., 40 mg) of adalimumab. The Press Release, which describes work by Patent Owner's predecessor (Abbott Laboratories) regarding initiation of a PsA clinical trial using HUMIRA®, does not describe any dosing regimen for adalimumab or any results in PsA. (Ex. 1049, 1-2.) Instead it merely states the trial will attempt to "help…understand the effect of HUMIRA in [PsA]." (Ex. 1049, 1.) (Ex. 2053, ¶72.)

Accordingly, no cited reference discloses that adalimumab would reduce or inhibit symptoms of PsA at any particular dose.

2. Petitioner Fails to Account for the Differences Between RA and PsA

Because Petitioner relies on the disclosure of 40 mg every-other-week dosing for RA in Keystone, to succeed in its obviousness Grounds, it must demonstrate that a POSA would have had a reasonable expectation that the ***same*** 40 mg every-other-week dose would successfully reduce or inhibit symptoms of PsA. The Petition fails

to do so because it does not provide any meaningful evidence that RA dosing and treatment could simply be extrapolated to PsA. Petitioner's failure to discuss or acknowledge the multiple differences between RA and PsA and its omission of the multiple examples in which drugs that were known to treat RA were ***not*** effective in treating other diseases, such as PsA, are material flaws in the Petition. (Ex. 2053, ¶73.)

As explained in Section III, there are several differences between PsA and RA. The two diseases were believed to have different pathologies and different cytokine profiles. They also affect different tissues and cause different structural damage. Based on these differences, it was understood by POSAs in July 2003 that treatment options needed to be separately studied in PsA patients, and that a treatment's efficacy in RA could not necessarily be extrapolated to PsA patients. (Ex. 2005, 29; *see also* Ex. 2008, 2451, 2456.) Petitioner has not acknowledged these differences, let alone how they impacted the dosing regimens for infliximab or etanercept. For example, Petitioner has not explained the specific TNFα burden of PsA as opposed to RA, the location or amount of TNFα in the affected tissues of PsA and whether and how drug is distributed to those locations, or how the adalimumab antibody and its route of administration and dose amount compare to those of other anti-TNFα inhibitors with respect to their ability to bind TNFα. (Ex. 2053, ¶¶73-74.)

Each of these differences between PsA and RA—which are unaddressed and unanswered by the Petition—would have been relevant to a POSA because of the history of failures in the art. Several treatments used for RA were known as of July 2003 to be ineffective in treating PsA. Among conventional and small molecule treatments, gold and sulphasalazine are common treatments for RA, but were known to have few or no benefits in treating PsA. (Ex. 1017, 6; *see also* Ex. 2005, 32-33.) Corticosteroids were also used in RA (Pet., 40, Table 3; Ex. 1002, ¶ 112, Table 2), but were "contraindicated in patients with PsA" because of their potential to cause serious side effects in the skin. (Ex. 2009, 1515; *see also* Ex. 2023, 31; Ex. 2008, 2453.) Similarly, hydroxychloroquine was considered suitable for treating RA, but was known to exacerbate skin lesions in PsA patients and to be associated with precipitating pustular psoriasis. (Ex. 1023, 3; Ex. 2053, ¶75.)

There are also multiple biologics that have been shown since July 2003 to be ineffective in treating PsA, despite being effective for RA. For example, rituximab is effective in treating RA, but studies have failed to show it has efficacy in treating PsA. (*See* Ex. 2006, 4, 5.) And both anakinra and tocilizumab are approved for use in RA, but have shown limited improvement in patients with PsA and have shown some evidence of worsening the disease. (Ex. 2055; Ex. 2010, 1; Ex. 2011, 216; Ex. 2012, 255.) Conversely, IL-17 inhibitors (including brodalumab and secukinumab)

have proven to be effective in treating PsA, but are not effective in treating RA. (Ex. 2038; Ex. 2041; Ex. 2029; Ex. 2028; Ex. 2052, 1152; Ex. 2053, ¶¶76-77.)

3. Petitioner's Cited References Involving Etanercept and Infliximab Do Not Establish a Reasonable Expectation of Success with Respect to the Claimed Dosing Regimen for Adalimumab

Petitioner argues that a POSA would have expected that the 40 mg every-other-week adalimumab dose disclosed for the treatment of RA in Keystone would also have successfully reduced or inhibited symptoms of PsA because other TNFα inhibitors had been shown to treat both diseases at the "same or similar dosing regimens." (*E.g.*, Pet., 45.)[7] This is not sufficient to demonstrate a reasonable expectation of success as to the claimed method. (Ex. 2053, ¶78.)

Petitioner has not shown that experience with etanercept and/or infliximab would have given a POSA a reasonable expectation of success regarding a method of treatment with adalimumab. Infliximab and etanercept are different than adalimumab in multiple ways. Infliximab is a chimeric antibody, not a fully human antibody like adalimumab, that is dosed on a patient-weight basis using intravenous infusion and with more frequent dosing early in the regimen. (Ex. 1027, 4.) This individualized, weight-based intravenous dosing for infliximab is materially

[7] Petitioner does not explain what it means by "similar" doses or how "similar" doses are relevant to its obviousness analysis.

different than the fixed, subcutaneous dose of adalimumab, and a POSA could not have predicted a specific adalimumab dosing regimen based on infliximab's regimen. For example, Petitioner does not address how the distribution and metabolism of infliximab administered according to its dosing regimen compare to what a POSA would have expected for adalimumab in tissues affected by RA or PsA. Further, PsA patients typically have a higher body mass index than RA patients. As a result, weight-based dosing of infliximab results in more drug being administered to PsA patients, even when administered according to the same regimen as RA. (Ex. 2053, ¶79.)

Etanercept is a fusion protein, not an antibody. Petitioner argued in IPR2017-01987 and IPR2017-01988 that, based on this difference, a POSA would have distinguished results with etanercept in RA from results that would have been expected with an antibody (such as adalimumab). (Ex. 2049; Ex. 2054.) In view of this argument, the Board should disregard Petitioner's argument here (Pet., 16) that a POSA would have had a reasonable expectation of success of adalimumab dosing based on experience with etanercept as contradictory and unreliable. Further, etanercept is administered subcutaneously multiple times per week. A POSA could not have predicted a specific adalimumab dosing regimen based on etanercept's dosing regimen. For example, Petitioner does not address how the distribution and metabolism of etanercept administered according to its dosing regimen compare to

what a POSA would have expected for adalimumab in tissues affected by RA or PsA. (Ex. 2053, ¶80.)

In its Institution Decision, the Board acknowledged that Petitioner failed to address the differences in structures, distribution, or pharmacokinetic parameters between adalimumab and either etanercept or infliximab. (Paper 13, 30.) In his deposition, Petitioner's declarant, Dr. Helfgott conceded that there are differences between TNFα inhibitors, including regarding their site of binding. (Ex. 2036, 43:3-21; 48:14-50:22.) Both Petitioner and Dr. Helfgott fail to address or explain why results from other TNFα inhibitors can be extrapolated to adalimumab notwithstanding those differences.[8] Instead, they summarily dismiss those differences as not "relevant to clinical practice." (*Id.*, 43:3-21)

Petitioner and Dr. Helfgott fail to explain whether or how 40 mg every-other-week of adalimumab administered subcutaneously would be distributed or metabolized to tissues affected by PsA in a manner that was similar to 3 mg/kg or 5

[8] The Board suggested that Patent Owner should "direct [it] to evidence in the current record to support" an argument that those differences would mean a POSA would not have a reasonable expectation of success with adalimumab based on etanercept or infliximab. (Paper 13, 30.) But, it is ***Petitioner's*** burden to show a reasonable expectation of success. 35 U.S.C. § 316(e).

mg/kg of infliximab or 25 mg multiple times a week of etanercept.[9] (Ex. 2053, ¶¶81, 83.) Rather, Petitioner argues that because adalimumab is a TNFα inhibitor, a POSA would have had a reasonable expectation of success based on other TNFα inhibitors even in the absence of clinical results. (Pet., 17.) But the uncertainty in the art with respect to the specific structures of TNFα inhibitors and how they bind, their distribution, and their pharmacokinetic parameters contributed to uncertainty and unpredictability with respect to the necessary dose of adalimumab to reduce or inhibit symptoms of PsA.

In fact, Dr. Helfgott himself reported in an article submitted in 2002 and March 2003 that there was ***no correlation*** between the clinical response to infliximab as compared to etanercept in patients with RA, even though both are anti-TNFα inhibitors. (Ex. 2034, 2315-2316 ("[O]ur findings suggest a lack of correlation

[9] The amount of drug administered to a patient under these different regimens is materially different. For example, by week 12, a 70 kg patient would receive 630 mg of infliximab (at 3 mg/kg) or 600 mg of etanercept (at 25 mg twice weekly). A patient administered 40 mg of adalimumab every-other-week only receives 240 mg of drug by week 12. Accordingly, the infliximab and etanercept dosing cited by Petitioner would not have been reasonably predictive of 40 mg every-other-week dosing of adalimumab for reducing or inhibiting symptoms of PsA.

between the clinical responses…when etanercept and infliximab were used in the same patients.").) Dr. Helfgott explained that a patient's joint count and acute-phase reactant responses to etanercept did not correlate with similar responses to infliximab, even though both drugs inhibited TNFα. (*Id.*) He suggested that the lack of correlation of responses "may be due to molecular differences between the 2 agents such as differences in induction of neutralizing antibodies, cell lysis with surface-bound TNF-α, lymphotoxin inhibition, or binding affinity to TNF-α." (*Id.* at 2316 (citations omitted).) In view of these acknowledged differences in anti-TNFα inhibitors, Petitioner's "clinical practice" argument cannot be sufficient to sustain Petitioner's burden to show a reasonable expectation of success in view of the lack of cited clinical results and the differences between adalimumab and the agents relied upon in the asserted prior art. (Ex. 2053, ¶82.)

Moreover, the doses of anti-TNFα inhibitors used to treat PsA identified by Petitioner (*see* Pet., 37-38 (Table 2)) and their relationship to corresponding doses used to treat RA vary from drug to drug and study to study. For example, infliximab dosing differed from study to study, with multiple studies using variable dosing or higher doses than those for RA. This inconsistency in the art illustrates its unpredictability: in view of the varied approaches that those in the art took to dosing ***other*** agents, a POSA could not have formed a reasonable expectation as to what

dose to use for adalimumab to treat PsA.[10] (Ex. 2053, ¶85.)[11] Accordingly, Petitioner has failed to meet its burden to show that a POSA would have had a reasonable

[10] Petitioner also cites dosing of certain small molecule drugs to support its arguments that the "same or similar" dosing was used in RA and PsA. (Pet., 39-40.) As the Board correctly found, such dosing "evidence is less relevant…because those drugs are not biologic TNFα inhibitors." (Paper 13, 32 n.32.) Moreover, Petitioner's Table 3, which lists certain small molecules, does not support its argument. The labels for Hydrocortone®, Cortone®, Decadron®, Prelone®, and Celestone® state that their dosages vary depending on the disease. (Ex. 1035, 27, 20, 24, 33, 42.) They do not state that the same dose was used for PsA and RA, and Petitioner has not shown that they were. (*See id*.) (Ex. 2053, ¶86.)

[11] In its Institution Decision, the Board references a dose of 3 mg/kg of infliximab for PsA patients reported in Marzo-Ortega. (Paper 13, 34.) Marzo-Ortega is ***not*** part of Petitioner's grounds. Marzo-Ortega reports results from only 5 patients without identifying which of the various subtypes of PsA each of those patients had. Given the small size of the study and the lack of reported subtype information for the patients involved, Marzo-Ortega fails to establish any reasonable expectation of success regarding infliximab, much less adalimumab, dosing. (Ex. 2053, ¶84.)

expectation that 40 mg every-other-week of adalimumab would successfully reduce or inhibit symptoms of a PsA patient.

B. Claim 7 Would Not Have Been Obvious

Claim 7 recites a method of reducing or inhibiting the progression of structural damage assessed by radiograph in a PsA patient with structural damage by administering 40 mg of adalimumab every-other-week. (Ex. 1001, 56:25-26.) Petitioner fails to establish that claim 7 would have been obvious based on the teaching of the combination of Keystone, Lorenz, and Mease 2000, or of Keystone, Dechant, Mease 2000, and Rau. (Ex. 2053, ¶¶87-88.)

1. The Petition Fails to Establish a Reasonable Expectation of Success

With respect to the efficacy limitation of claim 7, Petitioner relies on Lorenz in Ground 2 and Rau in Ground 3. For the reasons discussed above, the references in each ground do not render obvious a method of reducing or inhibiting symptoms of PsA with a subcutaneous 40 mg every-other-week dose of adalimumab. Petitioner's arguments with respect to claim 7 and its additional limitation fail for at least four additional reasons: (1) Petitioner cites no evidence that any agent reduced or inhibited progression of structural damage in PsA; (2) the references cited in each Ground are explicit that the art was uncertain and further study was required; (3) differences in structural damage in RA and PsA defeat a reasonable expectation of

success in PsA based solely on experience in RA; and (4) Petitioner does not address the claimed dose. (Ex. 2053, ¶18.)

a) Petitioner's Failure to Cite Evidence That Any Agent Reduced or Inhibited Progression of Structural Damage in PsA Defeats Any Reasonable Expectation of Success

The Petition is devoid of evidence that ***any*** agent successfully reduced or inhibited the progression of structural damage as assessed by radiograph in PsA patients as of July 2003. This is fatal to Petitioner's obviousness challenges to claim 7.

The sole evidence in the Petition regarding reduction or inhibition of structural damage relates to the treatment of rheumatoid arthritis. (Pet., 18.) Petitioner cites Rau (Ground 3), which reports on a study of ***RA*** patients treated with adalimumab, and Lorenz (Ground 2), which generally discusses a study of ***RA*** patients treated with infliximab and methotrexate. Neither suggests, let alone discusses, that an anti-TNFα inhibitor would successfully reduce or inhibit progression of structural damage in ***PsA*** patients. The Petition is devoid of any link between any agent (TNFα or otherwise) and successful reduction or inhibition of the progression of structural damage in PsA. (Ex. 2053, ¶¶89-91.)

Petitioner offers no testimony or prior art evidence to bridge this gap. For example, the Petition does not discuss the cause of structural damage in PsA, whether or what role TNFα (or other cytokines) plays in structural damage in PsA,

the effect of a TNFα inhibitor on structural damage in PsA, or the distribution and metabolization of a TNFα inhibitor to or by tissues affected by structural damage in PsA. Nor does Petitioner compare any of these considerations for PsA to those in RA. Absent any link between structural damage in RA and PsA or their clinical treatments, a POSA would not have a reasonable expectation of success. (*See* Ex. 2036 at 20:23-21:13 ("[I]f I were to use a drug that had no link to the pathogenesis of a certain disease, I wouldn't expect a reasonable expectation of success with that drug…").) (Ex. 2053, ¶92.)

Petitioner's obviousness theory is pure hindsight reconstruction. In the absence of any contemporaneous documentary evidence, Petitioner's claim 7 Grounds rely on the conclusory statements that "because of the similarities between RA and PsA, a POSA would have expected similar inhibition of progression of structural damage when adalimumab was used to treat PsA." (Ex. 1002, ¶156; *see also id.*, ¶140), and "[a] POSA would expect based on [Lorenz] that blockade of TNF-α by use of TNF-α-inhibitor therapy would similarly inhibit progression of structural damage in PsA…." (*Id.*, ¶49.) This conclusory testimony is not enough to show a reasonable expectation of success. *See, e.g.*, *Genzyme Corp. v. Dr. Reddy's Labs, Ltd.*, 716 F App'x 1006, 1010 (Fed. Cir. 2017) (affirming finding of no reasonable expectation of success where, *inter alia*, challenger pointed to no evidence of achieving claimed result with any agent in class, let alone the claimed

agent); *K/S Himpp v. Hear-Wear Techs. LLC*, 751 F.3d 1362, 1365-66 (Fed. Cir. 2014) (affirming Board decision rejecting conclusory assertion that prior art element was known when documentary evidence in record did not support it); *Lupin Ltd. v. Pozen Inc.*, IPR2015-01775, Paper 37, 33 (P.T.A.B. Feb. 28, 2017) (denying petition where Petitioner provided only conclusory argument regarding reasonable expectation of success and failed to explain specific import of prior art disclosure). As discussed further below, each statement is also contradicted by the evidence.

b) Petitioner's Asserted References Confirm the Uncertainty in the Art of Reducing or Inhibiting Progression of Structural Damage in PsA

Significantly, ***Petitioner's asserted art*** explicitly acknowledges that the ability of an anti-TNFα agent to inhibit progression of structural damage could not be reasonably expected by one of ordinary skill. Lorenz states that in RA "[f]urther long-term observations are required…focusing particularly on radiological progression under therapy with anti-TNF agents in combination with methotrexate…[and] specifically for the combinations of etanercept plus methotrexate and D2E7 plus methotrexate in patients with RA." (Ex. 1028, S18.) Lorenz thus expressly declines to make even part of the logical leap urged by Petitioner—that because one anti-TNFα agent (infliximab) could inhibit progression of structural damage in a particular disease (RA), that another (adalimumab) could as well. Petitioner does not address this passage, let alone explain how a POSA could

have reasonably expected adalimumab to inhibit progression of structural damage in patients in a ***different disease*** (PsA) based on Lorenz. (Ex. 2053, ¶¶94-95.)

Mease 2000 similarly urges additional study of radiographic progression, stating that, "[f]urther study in this population would be useful" and "[w]hether etanercept would improve articular damage measured radiographically should be examined." (Ex. 1017, 6; Ex. 2053, ¶93.) Thus, contrary to Petitioner's hindsight-driven theory, Mease and Lorenz explain that, with respect to inhibition of structural damage, a POSA could not simply reasonably expect success based on results in RA, results in another agent, or, indeed, results in PsA with the same agent. This defeats Petitioner's obviousness theory with respect to claim 7. (Ex. 2053, ¶¶93, 95.)

c) Experience in RA Is Insufficient to Show a Reasonable Expectation of Success that Adalimumab Would Reduce or Inhibit Progression of Structural Damage in PsA

With respect to Ground 3, Petitioner cites Rau and argues that because Rau "reported that adalimumab treatment inhibited progression of structural damage…in ***RA*** patients," a "POSA would have expected similar inhibition of the progression of structural damage in PsA patients treated with adalimumab." (Pet., 56-57.) For Ground 2, Petitioner similarly relies on Lorenz's discussion of "inhibition of progression of structural damage, as measured by radiograph, in ***RA***" using infliximab and methotrexate to argue a POSA "would have expected that a similar

inhibition in progression of structural damage would result from TNF-α inhibitor treatment of patients with PsA." (Ex. 1002, ¶ 140; Pet., 52-53.)

Petitioner is incorrect that a POSA would have had a reasonable expectation that adalimumab would have successfully reduced or inhibited the progression of structural damage in PsA patients merely "because of the similarities between RA and PsA." (Ex. 1002, ¶156.) As an initial matter, Petitioner and Dr. Helfgott do not identify ***what*** similarities between RA and PsA would lead a POSA to expect reduction or inhibition in the progression of ***structural damage specifically***. This omission, alone, is fatal to Petitioner's claim 7 Grounds. (Ex. 2053, ¶¶96-98.)

In fact, there are multiple material differences in the progression of structural damage in patients with PsA, as compared to RA. (*See* Section III.C, *supra*.) As a result, a POSA could not have simply assumed—with no evidence that ***any*** agent was successful in PsA—that an agent that reduced or inhibited structural damage in RA would do so for PsA. In particular, those in the art recognized that:

> Radiographic progression [in PsA], when it occurs in the mutilating forms, can proceed rapidly and is poorly understood. The ankylosis, bone lysis and new bone formation ***are very particular to PsA and not commonly seen in RA***. They are responsible for a large degree of the long-term loss of function and disability in these patients and it may well be that specific new therapies above those developed for RA will be required to manage these problems.

(Ex. 2009, 1519.) (Ex. 2053, ¶99.)

Structural Damage Progresses Differently in PsA and RA. It was known as of July 2003 that disease progressed differently in the bodies of PsA patients than RA patients. In a 1998 study, Wolfe, et al showed that structural damage in RA patients progresses at a relatively constant rate. (Ex. 2047, 1571.) This recognition allowed physicians to compare changes in radiograph scores in RA patients to known linear progression to assess whether progression of structural damage had been reduced or inhibited. (Ex. 2053, ¶100.)

In contrast, as of July 2003, available evidence confirmed that PsA does not progress at a constant rate in a significant number of patients. Several studies showed that PsA patients may switch over time between different clinical phenotypes, each of which could correlate to patterns of structural damage. (Ex. 2033, 1023-25; Ex. 2031, 678; Ex. 2009, 1519.) For example, in a study of 35 PsA patients, over two thirds of patients (27) changed clinical phenotypes over time. (Ex. 2033, 1024.) As a result, a POSA would have understood that the linear progression model that applied to RA would not apply to her PsA patients. As Dr. Gibofsky explains, as of 2003, the understanding of the progression of structural damage in PsA and the development of mechanisms to measure it in PsA was still developing, which contributed to considerable uncertainty about treatment in the art. (Ex. 2053, ¶101.)

RA and PsA Structural Damage Clinical Results Differed. As of 2002, there were "no prospective, controlled studies looking at radiological progression" in PsA patients. (Ex. 2008, 2451.) What clinical outcomes were observed as of July 2003, however, revealed different clinical results for treating structural damage in RA and PsA. As detailed in Section III.D, several treatments failed to reduce or inhibit structural damage in PsA patients ***despite achieving that outcome in RA patients***. Thus, although it was known in 2002 that the following nine agents improved radiological outcomes for RA patients—infliximab, cyclosporine, sulphasalazine, leflunomide, methotrexate, parenteral gold, corticosteroids, auranofin and IL-1 receptor antagonist (Ex. 2032, 10)—Petitioner and Dr. Helfgott have cited no evidence that any of those nine had been shown as of 2003 to reduce or inhibit progression of structural damage in PsA patients. (Ex. 2053, ¶¶104, 106.)

To the contrary, it was known that parenteral gold, sulphasalazine, and methotrexate did not reduce or inhibit the progression of structural damage in PsA patients (Ex. 2008, 2451-2452; Ex. 2027, 241; Ex. 2043, 1957; Ex. 2039, 139); corticosteroids and cyclosporine were understood to potentially be harmful in PsA patients (Ex. 2005, 33; Ex. 2008, 2452-53); leflunomide and IL-1 receptor antagonist had not shown efficacy in treating PsA in July 2003 (Ex. 2005, 33; Ex. 2008, 2452-53; Ex. 2009, 1517); and auranofin, i.e., oral gold, was shown to be ineffective in treating PsA. (Ex. 2005, 33; Ex. 2008, 2453.) A POSA would have understood based

on these examples that a drug's ability to inhibit or reduce the progression of structural damage in RA patients would not be predictive of the drug's performance in PsA patients. Petitioner and Dr. Helfgott have not cited a single instance of any agent, let alone a TNFα inhibitor, that was known as of July 2003 to reduce or inhibit the progression of structural damage in both RA and PsA. (Ex. 2053, ¶¶103, 105.)

Reduction or inhibition of the progression of structural damage assessed by radiograph is a significant efficacy outcome that is far from routine or expected. The FDA has a separate indication for reducing or inhibiting the progression of structural damage in patients with PsA. (*See, e.g.*, Ex. 2022, 1 (FDA letter separately approving "new indication[] for inhibiting the progression of structural damage" in PsA patients for HUMIRA®).) Not all drugs used to treat PsA are used for this separate indication. For example, although methotrexate is used to treat PsA (at a different dose than approved for RA), studies showed that it does not successfully inhibit the progression of structural damage. (Ex. 1023, 371; Ex. 2053, ¶¶102-103.)

The Cause of Structural Damage in PsA Was Uncertain. A POSA would have been uncertain as to the cause of structural damage in PsA and, accordingly, its treatment. PsA affects a diverse set of tissues and can affect tissues in diverse ways. (*See* Section III.A-III.C) Before 2003, the mechanism and cytokines implicated in PsA, including for structural damage in PsA, were unknown and still the subject of study by those of skill in the art. (Ex. 2053, ¶107.)

As of 2003, a POSA would not have known whether there was a precise cytokine pattern that caused structural damage in PsA or, if so, what it was. Dr. Helfgott has cited no evidence that any particular type of inhibitor (TNFα inhibitor or otherwise) successfully had an effect on the progression of structural damage in PsA. Therefore, a POSA could not have reasonably predicted which cytokine (or cytokines) would need to be inhibited in order to reduce or inhibit such progression (or, for example, whether inhibition of one would be sufficient in view of the presence of another). A POSA also could not have compared the cytokine profile of structural damage in PsA to that of RA, let alone the manner in which any particular agent (e.g., an anti-TNFα inhibitor) would work in view of the particular cytokines involved. Contrary to Dr. Helfgott's suggestion, (Ex. 1002, ¶156) this gap in the art could not have been filled by mere supposition that any agent that worked to reduce or inhibit structural damage in RA would do the same in PsA, because it was understood that there were cytokines present in PsA that were not present in RA and vice versa. (Ex. 2009, 1513; Ex. 2008, 2451.)[12] Petitioner has not shown that a POSA

[12] As explained by Dr. Gibofsky, at least two sets of researchers identified different theories that explained the clinical manifestations of PsA, including that structural damage in PsA is caused by different proteoglycans than RA (Ex. 2040, 30), and that structural damage in PsA may be caused primarily by enthesitis, which is not a

could or would have reasonably expected that TNFα was sufficiently responsible for structural damage in PsA such that inhibition of TNFα without inhibition of other cytokines would be sufficient to reduce or inhibit progression of structural damage. (Ex. 2053, ¶108.)

Structural Damage is Measured Differently in PsA and RA. Based on the different ways that structural damage manifests itself in RA and PsA patients (*see* Section III.C, *supra*), it was known that different methods than those used in RA needed to be developed for evaluating whether the progression of structural damage was inhibited or reduced in PsA patients. Thus, as of 2003 and even after, several groups of scientists were developing and validating different techniques for assessing a PsA patient's radiographs. (Ex. 2046; Ex. 2001.) It was recognized that these different scoring techniques needed to be repeatable and reliable across all PsA

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common symptom of RA (Ex. 2017, 1080). These theories, which were in development in July 2003, contributed to the significant uncertainty in the art and would have defeated any reasonable expectation that a TNFα inhibitor that had worked to reduce or inhibit structural damage in RA would, absent any evidence of the role of TNFα in structural damage in PsA, also successfully treat that symptom in PsA patients. (Ex. 2053, ¶¶109-110.)

patients' radiographs and had to account for the specific tissues affected by PsA. (Ex. 2046, 158, 161-65; Ex. 2053, ¶112.)

As a result, different scoring techniques than those used in RA were developed to assess PsA-specific features that appear on radiographs. (Ex. 2046, 157-58; Ex. 2001, ii61.) These developments beyond what was measured in RA were necessary because without assessing structural damage specific to PsA (for example, pencil-in-cup phenomena), a POSA could not fully understand whether a drug in fact was reducing or inhibiting a PsA patient's structural damage. Whereas the Sharp score was used to measure radiographic progression in RA, a modified Sharp score ("mTSS") was ultimately used to evaluate radiographic progression in PsA. (*See* Ex. 2001, ii62-63.) The mTSS score used in PsA measured ***additional*** parameters than those measured for RA, meaning that the scores could not simply be substituted for one another. (*See id*.) (Ex. 2053, ¶¶113-114.)

Petitioner bears the burden show why a POSA would have had a basis for reasonably expecting adalimumab would successfully reduce or inhibit structural damage in ***PsA***. Petitioner's reliance ***solely*** on data related to structural damage in ***RA***, without any further link to PsA, is not sufficient in view of the bare conclusory statements in the Petition. Petitioner fails to cite any reference disclosing that any agent successfully inhibited the progression of structural damage in PsA patients, omits discussion of uncertainty and requests for further analysis called for by its

cited references, fails to address the difficulty of achieving the claimed outcome, and ignores the differences and potential differences between diseases reflected in, among other metrics, different scoring methods. Petitioner also ignores the multiple examples of agents that successfully reduced or inhibited structural damage in RA but had not been shown to do the same for PsA as of July 2003. (Ex. 2053, ¶¶104-105.)

d) Petitioner Fails to Address the Claimed Dose

Petitioner's second conclusory argument that the additional limitation of claim 7 would have been obvious is that "[a] POSA would expect based on [Lorenz] that blockade of TNF-α by use of TNF-α inhibitor therapy would similarly inhibit progression of structural damage in PsA…." (Ex. 1002, ¶49.) As discussed in Section VIII.B.1(c) *supra*, the experience with structural damage in RA in Rau and Lorenz would not lead to a reasonable expectation of success in structural damage with PsA. (Ex. 2053, ¶111.) But even if it did, Petitioner fails to address the claimed *dose*. Claim 7 requires reduction or inhibition of the progression of structural damage in a PsA patient after subcutaneous administration of *40 mg every-other-week* of adalimumab, and Petitioner must show that a POSA would have reasonably expected *that dose* would be adequate to reach the affected tissues to yield that result. Petitioner has failed to do so.

Petitioner's Ground 3 relies on the Rau reference. Rau reports results from a study of adalimumab to treat RA at multiple intravenous weight-based doses, ***not*** the claimed fixed subcutaneous 40 mg every-other-week dose. (*See* Ex. 1021, 5; Ex. 2036, 74:19-22.) Petitioner nowhere argues that any particular weight-based dose in Rau would be instructive as to the outcome to be expected for any particular fixed dose, let alone 40 mg every-other-week. (Ex. 2053, ¶¶115-118.)

In fact, Rau at most shows that adalimumab inhibited radiographic progression in RA patients at ***higher*** doses than the claimed 40 mg every-other-week. Table 3 of Rau, for example, reports Sharp Erosion Score data at 6 months and 12 months for patients in study DE003. (Ex. 1021, 7.) Figures 4 and 5, however, demonstrate that at ***12 weeks***, *i.e.*, well before the 6-month data in Table 3 relied upon by Petitioner was collected, no patient in the 0.5 mg/kg arm of the DE003 study remained in the study. (Ex. 1021, 5-6, Figs. 4, 5 (showing 0.5 mg/kg arm of study ended at 12 weeks); *see* Ex. 2036, 81:20-83:6 (acknowledging end of line in Figures 4, 5 indicated no patients remained in study arm as of 12 weeks).) (Ex. 2053, ¶119.)

Thus, Rau cannot and does not establish that adalimumab had any effect on structural damage in RA patients receiving 0.5 mg/kg (or, hypothetically, an

intravenous dose of 40 mg for an 80 kg patient).[13] At the very most, the data collected in Rau and cited by Petitioner would support that an intravenous dose of 1.0 mg/kg or higher was needed to inhibit structural damage in RA patients. By way of example, an 80 kg patient receiving 1.0 mg/kg, would have received 80 mg intravenously. Moreover, because drug was re-administered only upon disease flare, the DE003 study in Rau did not disclose a standard every-other-week dosing interval. (*See id.*, 5, Table 1.) Such data do not support Petitioner's claim that a POSA would expect that a fixed, 40 mg every-other-week subcutaneous dose would successfully inhibit progression of structural damage in RA patients—let alone in PsA patients. (Ex. 2053, ¶119.)

Petitioner's Ground 2 suffers from a similar deficiency. There, Petitioner cites Lorenz's summary disclosure that a study of infliximab plus methotrexate showed no median radiological progression over 12 months in treating RA. (Pet., 51.) Neither Petitioner nor Lorenz, however, discusses at what ***dose*** such results were achieved. Nor does Lorenz provide details on the number of patients observed, the

[13] Patent Owner does not concede that any particular weight-based dose can be assumed to equal a particular fixed subcutaneous dose. Nor does Patent Owner concede that the amount of an intravenous dose is equivalent to the amount of a subcutaneous dose.

percentage of patients that achieved the result, the weight of the patients (which would affect the amount of drug administered in infliximab's weight-based regimen), or any other clinical detail. These are fatal omissions. Claim 7 requires not only that adalimumab inhibit progression of structural damage in PsA patients, but that it do so at a fixed subcutaneous dose of 40 mg every-other-week. (Ex. 2053, ¶¶120-121.)

Moreover, Petitioner fails to address the fact that the study summarily discussed in Lorenz involved co-administration of infliximab and methotrexate. (*See* Ex. 1028, S17.) As of July 2003, it was known that methotrexate could, ***on its own***, reduce or inhibit the progression of structural damage in ***RA***, but studies had shown that it ***did not do so*** in ***PsA***. (Ex. 2032, 7, 10; Ex. 2027, 241.) Absent further information than that discussed by Lorenz, a POSA would not have known whether the effects demonstrated in the study were attributable to infliximab or to methotrexate, whether infliximab demonstrated an additional benefit beyond methotrexate monotherapy, or, if it did, at what dose infliximab was administered to achieve such a benefit. Dr. Helfgott acknowledged that he did not account for the potential differences between monotherapy and combination therapy in forming his opinion. (Ex. 2036, 65:24-66:17.) Accordingly, the disclosure in Lorenz is not sufficient to demonstrate that an anti-TNFα inhibitor, infliximab, reduced or inhibited progression of structural damage in RA, let alone at any particular dose. In

the absence of any discussion about the dose at which the alleged prior art achieved the cited result, Petitioner's grounds regarding claim 7 should be denied. (Ex. 2053, ¶122.)

Furthermore, as discussed, structural damage is different in RA and PsA, and the cause of structural damage in PsA was uncertain. Petitioner has not addressed how a POSA would have had a reasonable expectation that 40 mg every-other-week would be sufficient in view of the uncertainty regarding the cytokine(s) responsible for PsA (versus RA) structural damage and distribution and metabolization of TNFα inhibitors to tissues affected by structural damage in PsA versus RA. (Ex. 2053, ¶¶108-110, 115.)

2. Petitioner Has Failed to Demonstrate that Reducing or Inhibiting Progression of Structural Damage Is Inherent

As a part of its obviousness grounds, Petitioner makes the bare assertion that the recited "reduction/inhibition of 'progression of structural damage' is a natural consequence of an obvious method of treatment." (Pet., 50.) The Federal Circuit has explained, however, where the issue is obviousness, there is a "high standard" for inherency that requires that the doctrine be "carefully circumscribed in the context of obviousness." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014); (Ex. 2053, ¶19.)

The heightened standard for demonstrating inherency in the obviousness context includes showing (unlike anticipation) that the allegedly inherent result

would have been recognized by a skilled artisan at the time of invention. As the Federal Circuit has held, "'[t]hat which may be inherent is not necessarily known' and that which is unknown cannot be obvious," such that the Board would "err[] as a matter of law" if it "dismiss[ed] properties of [a] claimed invention as merely inherent, without further consideration as to unpredictability and unexpectedness." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354–55 (Fed. Cir. 2017) (quoting *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993); *see also, e.g.*, *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (no inherent obviousness where "[n]o expert testified that they foresaw, or expected, or would have intended, the reaction between bortezomib and mannitol, or that the resulting ester would have the long-sought properties and advantages"); *PAR*, 773 F.3d at 1195-96. Further, to show that a claim limitation is inherent, a Petitioner must demonstrate that "the limitation at issue ***necessarily must be present***, or the ***natural result*** of the combination of elements explicitly disclosed by the prior art." *PAR*, 773 F.3d at 1196. Under this standard, "'[i]nherency…***may not be established by probabilities or possibilities***. The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient.'" *Id.*; *see also, e.g.*, *Southwire Co. v. Cerro Wire LLC*, 870 F.3d 1306, 1311 (Fed. Cir. 2017) ("The Board cited no evidence that a reduction of 30% in the pulling force would

necessarily result from the claimed process, which contains no steps that ensure such reduction" (quotation marks omitted)).

The only basis for Petitioner's claim that patients administered adalimumab according to the claimed method would inherently achieve the claimed reduction or inhibition of structural damage is the '992 patent's statement that "'[a]dalimumab was more effective compared with placebo in inhibiting radiographic disease progression over a 24-week period.'" (Pet. 65-66 (quoting Ex. 1001, 40:23-25).) This "evidence" is completely inadequate to show inherency.

First, Petitioner cites no prior art at all in support of its inherency argument, and its declarant, Dr. Helfgott, has not opined on the issue.

Second, there is no evidence to establish that one of ordinary skill would have expected the claimed result, as required in the obviousness context. Rather, as further discussed in Section VIII.B.1, *supra*, and as Dr. Gibofsky has testified, there is no evidence in the record that any agent successfully reduced or inhibited the progression of structural damage ***in PsA*** or that reduction or inhibition of structural damage in RA could be extrapolated to structural damage in PsA. In view of these omissions, a skilled artisan would not have reasonably expected 40 mg every-other-week of adalimumab would successfully reduce or inhibit the progression of structural damage in PsA patients generally, let alone necessarily or naturally result in such an outcome for ***all PsA patients***. (Ex. 2053, ¶124.)

Third, as explained by Dr. Gibofsky, not all PsA patients with structural damage that are administered adalimumab according to the claimed regimen achieve reduction or inhibition of structural damage. (Ex. 2053, ¶124.)[14] Dr. Helfgott agrees. (*See* Ex. 2036 at 87:6-89:7 ("[G]iving adalimumab at 40 milligrams every-other-week does not necessarily and inevitably lead to reducing or inhibiting structural damage in all psoriatic arthritis patients.")); *see, e.g., Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378-79 (Fed. Cir. 2005) (finding claim directed to treatment of patients with sunburned skin not inherently anticipated by disclosure of application of claimed compound to skin generally).

In its Institution Decision, the Board found that the efficacy result of claim 7 would have been the necessary result of the claimed method, which the Board viewed as obvious. (Paper 13, 36.) Respectfully, the Board's reliance solely on the alleged obviousness of the method evidences the incorrect application of a *per se* rule that efficacy limitations in a method of treatment claim are always irrelevant to patentability. The Federal Circuit, however, has repeatedly held that no such *per se*

[14] The data in the '992 patent confirms that 9% of patients experienced an ***increase*** in modified Total Sharp Score (compared to 28.9% for placebo). (Ex. 1001, 39:1-10 (Table 3).) Petitioner has not demonstrated that any of those patients experienced a reduction or inhibition of structural damage, let alone all of them.

rule exists. *E.g., Allergan Sales, LLC v. Sandoz, Inc.*, 717 F. App'x 991, 994 (Fed. Cir. 2017) ("without loss of efficacy" recited in method of reducing number of daily administrations was not inherent); *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1294 n.1 (Fed. Cir. 2013) (similar analysis of same limitation in same claim); *PAR*, 773 F.3d at 1196 ("no substantial difference in C_{max}" recited in method of increasing body mass in a patient suffering from loss-of-body-mass conditions not inherent).

Following this precedent, the Board has rejected inherency arguments in similar contexts. For example, in *Celltrion Inc. v. Genentech, Inc.*, IPR2016-01667, Paper 15 (P.T.A.B. Mar. 2, 2017), the Board rejected an inherency challenge where the Petitioner showed only a probability that patients met a claim limitation. In *Celltrion*, the claim at issue required "a human patient who experiences an inadequate response to a TNFα-inhibitor." *Id.* at 10. Petitioner relied on expert testimony that, "'it is virtually certain, based on my clinical and epidemiological understanding of the RA patient population, that at least one patient who received th[e] [relevant] dose [from the potential population in the prior-art study] belongs to the population that innately experiences an inadequate response to TNFα-inhibitor treatment.'" *Id.* at 9. The Board found that this was not enough to establish inherency, as Petitioner established only "probabilities," not that the claimed limitation would necessarily or inevitably be met. *Id.* at 9; *see also Luye Pharma Grp. Ltd. v. Alkermes Pharma Ireland Ltd.*, IPR2016-01096, Paper 74 at 17-20, 22-

28 (P.T.A.B. Nov. 28, 2017). And in *Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00712, Paper 9 (P.T.A.B. Sept. 22, 2016), the Board found that, in an obviousness challenge to claims reciting a method of treating prostate cancer, an expert's "conclusions" that an outcome would be inherent—which were "drawn from a description of PK analysis in the [challenged] patent"—"[were] not sufficiently explained to satisfy the high standard required for inherency in an obviousness context." *Id.* at 17. The Board reached this conclusion because Patent Owner put on evidence that certain variables "impact the recited PK distribution ranges," but Petitioner and its expert failed to address how these variables "may affect PK distribution profiles." *Id.* at 17-18.

In short, the doctrine of inherency has no application here. To show inherency, Petitioner was required to demonstrate with facts and testimony that the claimed outcome will necessarily or naturally result from the performance of the claimed method for ***each patient*** covered by the claim and that a person of ordinary skill would have expected such a result. Petitioner has not even attempted, much less made, such a showing.

IX. Conclusion

Petitioner has not met its burden of showing, by a preponderance of the evidence, that claims 2 and 7 of the '992 patent would have been obvious. The Board

should therefore enter a final written decision that claims 2 and 7 have not been shown to be unpatentable.

Respectfully submitted,

Date: July 6, 2018 By: / *William B. Raich* /

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Response** contains 13,969 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: July 6, 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 Response** and Exhibits 2027-2055 were served electronically via email on July 6, 2018, in their entirety on the following:

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Petitioner has consented to service by email.

Dated: July 6, 2018

By: / *William Esper* /
William Esper
Legal Assistant

Finnegan, Henderson, Farabow,
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