UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Sandoz Inc.,
Petitioner,

v.

AbbVie Biotechnology Ltd,
Patent Owner.

Case IPR2018-00156
U.S. Patent No. 9,187,559

PATENT OWNER'S PRELIMINARY RESPONSE

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I. Introduction

AbbVie's U.S. Patent No. 9,187,559 ("the '559 patent") is directed to a multiple-variable dose method for treating idiopathic inflammatory bowel disease ("IBD") with the biologic drug Humira® (adalimumab). In contrast to the only approved method for using adalimumab at the time (administering 40 mg of adalimumab every-other-week to treat a different disease, rheumatoid arthritis), all of the claims require an induction dosing regimen involving subcutaneously administering to an IBD patient a dose of *160 mg* of adalimumab and, two weeks later, a dose of *80 mg* of adalimumab.

Petitioner presents a single proposed ground challenging claims 1-30 of the '559 patent as obvious based on a combination of the Humira® Label and WO '330 in view of Goodman, the Remicade® Label, and Hanauer. (Pet. at 12.)

The Board should deny institution for several reasons. Most fundamentally, none of the asserted references describes or suggests an induction dosing regimen for adalimumab. Further, no asserted reference suggests the administration of a fixed dose of 160 mg, much less a multiple-variable dosing regimen involving a 160 mg dose followed two weeks later by an 80 mg dose. The Humira® Label, for example, describes subcutaneously administering 40 mg of adalimumab every-other-week to treat rheumatoid arthritis. It does not address IBD or disclose a 160 mg dose, let alone suggest a specific combination of 160 mg and 80 mg doses to

treat IBD. WO ’330 describes the potential treatment of various disorders, including IBD, by subcutaneously administering (weekly or biweekly) a most preferred dose of about 40 mg of adalimumab. But it also does not disclose administering an initial dose of 160 mg, let alone a specific combination of 160 mg and 80 mg doses. The remaining asserted references do not discuss adalimumab or any dosing regimen for treating IBD with adalimumab, nor do they disclose a 160 mg/80 mg dosing regimen for any drug. Thus, none of the asserted references suggests using an induction dose for adalimumab.

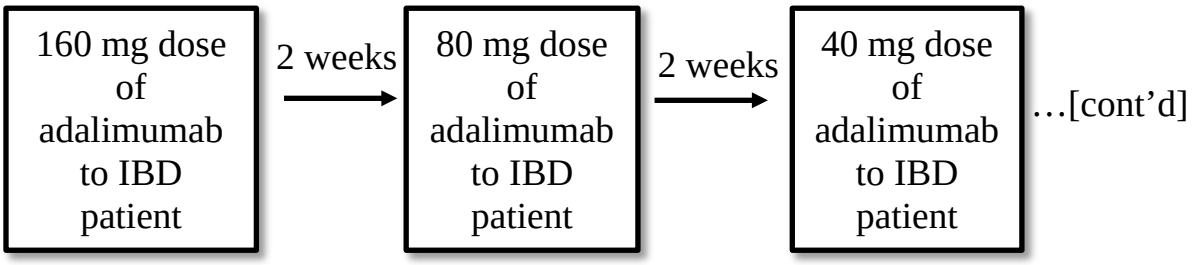
Even if one would have been motivated to design an induction dosing regimen for adalimumab, Petitioner fails to show that one of ordinary skill would have combined and substantively modified the disclosures of the asserted references to create the claimed 160 mg/80 mg dosing regimen. Petitioner, for example, asserts that WO ’330’s clinical data in treating *rheumatoid arthritis* suggest that 80 mg adalimumab every-other-week “should be considered as a basis for an IBD induction dosing regimen.” (Pet. at 22.) But WO ’330 itself does not suggest that the disclosed rheumatoid arthritis clinical results could be extended to IBD, nor does it disclose or suggest *any* “basis” dose or “induction” dosing regimen. Further, WO ’330 describes the 40 mg (weekly or biweekly) results as *better* than the 80 mg results, contradicting Petitioner’s position that one would have sought to use higher doses to achieve stronger responses in patients.

Petitioner also fails to establish a reasonable expectation of success. As of the April 2004 priority date, no reference described the clinical evaluation of adalimumab in IBD patients, and there was no known pharmacokinetic/ pharmacodynamic (PK/PD) relationship for adalimumab in IBD. In an effort to overcome these deficiencies, Petitioner proposes an internally inconsistent dosing theory using an unsupported intermediate "basis" dose. But, as explained below, Petitioner's theory is expressly undermined by the asserted references. Further, the etiology of IBD was poorly understood, and the art was replete with failed attempts to develop new therapies. Before the priority date, for example, the anti-TNFα drugs oxpentifylline, etanercept (Enbrel®), CDP571, and onercept all failed to treat IBD. Petitioner disregards these failures, which establish a high level of unpredictability in the art and contradict Petitioner's speculative and unsupported obviousness theory. Petitioner's obviousness contentions are therefore based entirely on an improper hindsight reconstruction of the claims, not any disclosures of the prior art.

The claimed invention's unexpected results strongly support nonobviousness. Clinical studies revealed that IBD patients treated with the claimed 160 mg/80 mg regimen of adalimumab (followed by 40 mg doses every-other-week) were significantly more likely to achieve remission *one year* after initial treatment compared to patients treated with an 80 mg/40 mg regimen of

adalimumab (followed by 40 mg doses every-other-week). This remarkable long-term efficacy was entirely unexpected. Petitioner was aware of this compelling evidence of unexpected results and submitted it in this proceeding, yet chose not to address it. (Pet. at 51-54.) The claimed invention's unexpected results are therefore undisputed.

Additional reasons support the patentability of the dependent claims. Claim 2, for example, further requires administering a subcutaneous injection of 40 mg of adalimumab two weeks after the 80 mg dose of claim 1, and claim 3 requires administering subsequent 40 mg subcutaneous injections two weeks apart. Similar three-tiered regimens are recited in claims 5, 6, 8, 15-20, and 22-30. The asserted references fail to disclose or suggest this claimed combination of *three* different doses of adalimumab to treat IBD.



Indeed, this claimed *three-tiered* dosing regimen is unlike anything described in Petitioner's asserted references and is inconsistent with Petitioner's argument that following the "general rule," one would have selected an induction dose by doubling the maintenance dose.

Dependent claims 13, 14, 16, 19, 25, and 28 further require that the patient achieves a Crohn's Disease Activity Index (CDAI) score of <150. Petitioner's argument that this limitation is inherent because "*some* percentage of patients" achieves this clinical endpoint is insufficient as a matter of law to prove inherency. (Pet. at 47 (emphasis added).) Inherency cannot be established by probabilities or possibilities, and nothing in the asserted references expressly or inherently taught that such outcomes could be attained with adalimumab, much less by using adalimumab according to the claimed regimen.

Finally, Petitioner fails to establish that the Humira® Label was publicly accessible before the critical date and thus qualifies as prior art. This alone defeats the Petition.

As further detailed below, Petitioner has not shown a reasonable likelihood that it will prevail in establishing that any challenged claim is unpatentable. The Board should therefore deny institution of the Petition.

II. Background

A. The Invention of the '559 Patent

IBD includes two related chronic inflammatory disorders of the intestinal tract, Crohn's disease and ulcerative colitis. (Ex. 1001 at 28:60-64; Ex. 2001 at 47; Ex. 1016 at 3.)[1] The '559 patent discloses and claims novel methods of treating

[1] Citations refer to the original page numbering of each exhibit except for

IBD using the biologic drug adalimumab, the active ingredient in Humira®. (*See, e.g.*, Ex. 1001 at 28:51-29:33, 93:55-96:36.) Many thousands of IBD patients have benefited from this treatment.

The ’559 patent describes methods of administering adalimumab to induce remission of IBD using a multiple-variable dose regimen, including a 160 mg dose followed two weeks later by an 80 mg dose. (*Id.* at 63:53-58.) The patent further describes administering 40 mg of adalimumab every-other-week as a treatment phase after the initial 160 mg and 80 mg doses. (*Id.* at 64:5-18.)

The ’559 patent discloses the first published results of trials evaluating the clinical use of adalimumab in IBD patients. (*Id*. at 73:40-76:20.) Specifically, it reports that IBD patients treated with a 160 mg/80 mg dosing regimen achieved a statistically significant remission rate of 36% versus a placebo rate of 12%. (*Id*. at 74:34-36.) Remission was measured by the CDAI, which is a standard measure of the severity of Crohn’s disease. (*Id.* at 4:37-40, 29:20-24, 74:38-48.) The CDAI is a composite index that accounts for disease features including abdominal pain, general well-being, number of liquid or soft stools, and other factors. (Ex. 1016 at 18, 20 (Table 103-4).)

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references that have been stamped with page numbers. Citations to such references refer to the stamped-on page numbers.

Later clinical studies evaluated the efficacy of multiple-variable adalimumab dosing regimens in treating IBD over periods of a year or more. (Ex. 1024 at 140.) Colombel compared the results from two dosing regimens: (1) 160 mg at week 0; 80 mg at week 2; and 40 mg at week 4 and every-other-week thereafter until week 52; and (2) a dosing regimen of 80 mg at week 0; 40 mg at week 2; and 40 mg at week 4 and every-other-week thereafter until week 56. (*Id*.) Thus, in both studies, patients received the same 40 mg dose every-other-week beginning at week 4 and continuing through week 52 or 56. (*Id*. at 140-41.)

Remarkably, Colombel reported that patients treated with the 160 mg/80 mg induction regimen were *3.7 or 4.8 times more likely* (depending on the analysis) to achieve *one-year remission* than patients treated with the 80 mg/40 mg regimen, even after adjusting for age, sex, baseline CDAI, weight, prior anti-TNF exposure, disease duration, and baseline medications. (*Id.* at 143.) Further, the 160 mg/80 mg induction regimen was associated with more time in remission and fewer hospitalizations during the every-other-week maintenance therapy. (*Id*. at 140.)

During prosecution of the grandparent application to the ’559 patent, the Examiner rejected the claims in a non-final office action, citing an alleged “general rule” from Aulton that a loading dose should be twice the size of a maintenance dose if the selected dosage time interval corresponds to the biological half-life of the drug. (Ex. 1024 at 5-6.) In response, Patent Owner submitted, *inter alia*, a

declaration by Dr. Diane Mould, an expert in pharmacokinetics, in which she explained that the remarkable long-term efficacy results reported by Colombel with the 160 mg/80 mg dosing regimen over the 80 mg/40 mg dosing regimen were surprising and unexpected, given that both groups received the *same 40 mg dose* from week 4 through the end of the trials. (*Id*. at 13-14.) The Examiner of the grandparent application found this evidence of unexpected results convincing. (Ex. 2006 at 3 (citing Ex. 1024 at 13-14).)

The ’559 patent claims reflect this ground-breaking invention:

- Independent claims 1 and 4 recite a multiple-variable dose method for treating idiopathic IBD comprising subcutaneously administering a first dose of 160 mg of adalimumab within a day, and subcutaneously administering a second dose of 80 mg adalimumab within a day, two weeks following administration of the first dose.
- Claims 2 and 5 depend from claims 1 and 4, respectively, and recite subcutaneously administering 40 mg of adalimumab within a day, two weeks following administration of the second dose. Claims 3, 6, 8, 15-20, and 22-30 require similar three-tiered regimens.
- Claims 9, 11, 15, 18, 24, and 27 recite that the human subject has Crohn’s disease. Claims 13, 14, 16, 19, 25, and 28 depend from these claims and require achieving a CDAI score of < 150.

- Claims 10, 12, 17, 20, 26, and 29 recite that the human subject has ulcerative colitis.
- Claims 7 and 21 depend from claims 4 and 1, respectively, and recite administering each subcutaneous injection using a prefilled syringe.

(Ex. 1001 at 93:55-96:36.)

The claims cover the approved method of using Humira® (adalimumab) to treat patients with Crohn's disease and ulcerative colitis. (*See* Ex. 1056 at 4-5.)

B. IBD Was a Chronic Inflammatory Condition of Poorly Understood Etiology

IBD is a lifelong illness that typically first appears in young adulthood, but onset can occur at any age. (Ex. 2003 at 3.)

Crohn's disease primarily affects the intestinal tract, presenting with mucosal inflammation of the intestinal walls. (*Id.* at 7-8; Ex. 2009 at I114-15.) Typical symptoms include diarrhea, abdominal pain, weight loss, and malnutrition. (Ex. 2003 at 7-8.)

Ulcerative colitis primarily affects the colon and rectum, which constitute the large intestine. (Ex. 2007 at 361.) It presents with mild to severe mucosal inflammation of the bowel walls. (*Id.*) Typical symptoms include diarrhea, rectal bleeding, and abdominal pain. (Ex. 2003 at 6.) Symptoms of these IBD disorders range from mild to severe, on a patient-by-patient basis. (*Id.*)

The precise etiology of IBD was unknown in 2004. (Ex. 2002 at 7; Ex. 2034 at 1.) Manifestations of IBD vary widely based on the area of the intestinal tract affected (in Crohn's disease) or the amount of the colon and/or rectum affected (in ulcerative colitis). (Ex. 2003 at 5-7; Ex. 2007 at 361.) IBD has a relapsing-remitting course, alternating between active periods of inflammation known as flares and short periods of reduced symptoms. (Ex. 2002 at 6.)

As of 2004, several interrelated factors were believed to contribute to IBD, including genetics, the local enteric environment (e.g., gut bacteria and microflora), and mucosal immunity. (Ex. 2001 at 34-35; Ex. 2034 at 1-2; *see also* Ex. 2004 at 182 (noting the "complex and enigmatic" nature of IBD), 196-98.) Researchers described a multiplicity of paths leading to IBD, with these genetic, environmental, and immunological defects each being capable of causing or contributing to the disease. (Ex. 2001 at 34, 40-41, 44, 47; Ex. 2005 at 296.) Because no single agent or mechanism could explain IBD's etiology (Ex. 2001 at 34), researchers found it "naïve" to conclude that IBD resulted from a single inflammatory cause or cytokine. (Ex. 2027 at 4; Ex. 2002 at 7; Ex. 2005 at 296.)

The relapsing/remitting course of IBD complicated treatments and drug development efforts, because patients with active inflammation could experience periods of reduced symptoms without any therapeutic treatment. (Ex. 2010 at 68 ("high and unpredictable placebo response rates present a major impediment to the

success of clinical trials in inflammatory bowel disease").) Thus, physicians prescribing drugs for their patients and researchers investigating new treatments could not be certain whether reduced symptoms were due to drug effects or the disease's natural course. As a result, it was essential to use controlled clinical trials to compare efficacy results against placebo. (*See id.* at 68-69; *see*, *e.g.*, Ex. 2008 at 107 (Table 1 describing placebo rates as high as 35% and 50% in Crohn's disease clinical trials of anti-TNFα drugs).)

C. Anti-TNF Drugs for Treating IBD Have Been Difficult to Develop and Have Frequently Failed

Before the April 2004 priority date, IBD was known to be difficult to treat. (Ex. 2001 at 33.) The most common treatments were general immunosuppressant therapies that had existed for over fifty years. (*Id.* at 65-73.) These drugs did not target any particular inflammatory mediator, much less TNFα. And while some of these therapies might maintain remission,[2] others had little or no ability to induce remission of IBD. (*Id*.) Instead, physicians used steroids for short-term treatment of acute flares. (*Id.* at 67-68.) Prednisolone and hydrocortisone remained the preferred steroid treatments, but had limited efficacy, severe side effects, and a propensity to lead to steroid dependence. (*Id.*) Azathioprine and 6-mercaptopurine

[2] In clinical trials, remission for Crohn's disease has been defined by a patient's CDAI score falling below a particular threshold (e.g., 150 points). (Ex. 1017 at 12.)

were options for steroid-resistant patients, but they had a slow onset of action and were often discontinued due to side effects. (*Id.* at 70-71; Ex. 2018 at S72.)

Anti-TNFα research and related attempts at drug development for IBD treatment were unpredictable and often unsuccessful. (Ex. 2011 at 54; Ex. 2008 at 109.) Anti-TNFα agents were the "first representatives of new biological therapies" for IBD but posed "a challenge for drug development." (Ex. 2008 at 109.)

Researchers struggled to understand the role of TNFα in IBD. Attempts to correlate disease activity with TNFα levels were disappointing. For example, one study analyzing both ulcerative colitis and Crohn's disease found that "tissue levels of TNF-α transcripts were *not increased* in IBD specimens." (Ex. 2013 at 823-24 (emphasis added).) Another study evaluated whether heightened serum TNFα levels correlated to Crohn's disease activity, but found *no relationship* between disease activity and TNFα levels. (Ex. 2012 at 235.) Attempts to develop cytokine-based correlations with IBD were viewed as "conceptually flawed." (Ex. 2005 at 296 (using only a single inflammatory marker to "describe what are dynamic and clinically heterogeneous disease processes is probably naïve"); Ex. 2002 at 7.)

As of 2004, infliximab was the only biologic drug approved to treat Crohn's disease. It had also been approved for treating rheumatoid arthritis. But unlike adalimumab, it was administered intravenously using a weight-based dose. (Ex.

1068 at 6.) And for *both* indications, the approved infliximab dosing regimen required using the *same* weight-based dose throughout the regimen (3 mg/kg for rheumatoid arthritis and 5 mg/kg for Crohn's disease) at 0, 2, and 6 weeks and every 8 weeks thereafter. (*Id.*) It did not use a higher initial dose or doses. Infliximab's mechanism of action in Crohn's disease, including its precise mechanism of TNFα inhibition, was unknown. (Ex. 2009 at I118.)

After initial infliximab clinical trials reported positive results in treating Crohn's disease, researchers evaluated whether other anti-TNFα drugs would have similar efficacy in IBD. As detailed below, until Patent Owner's success with Humira®, all of those efforts failed, underscoring the difficulty in treating IBD and the unpredictability in developing drugs to treat IBD. (*E.g.*, Ex. 2014 at 470; Ex. 2015 at 6; Ex. 2016 at 1092-93.)

1. Oxpentifylline Failed to Treat IBD

Based on infliximab's results in Crohn's disease patients, researchers hypothesized that "other drugs that also reduce TNFα should have similar effects." (Ex. 2014 at 470.) To test this hypothesis, they treated Crohn's disease patients with oxpentifylline, a strong suppressor of TNFα. (*Id.*) But they found *no improvement* of any intestinal inflammation or clinical symptoms of Crohn's disease. (*Id.* at 470-71.) Neither Petitioner nor its declarants address oxpentifylline's clinical failure in IBD.

2. Etanercept Failed to Treat IBD

In 2001, Sandborn et al. reported the failure of the biologic anti-TNFα drug etanercept in Crohn's disease, with the investigators concluding that etanercept was "not an effective therapy." (Ex. 2015 at 6.)

A follow-up publication in 2001 explained that the investigators had hoped to find an "anti-TNF-α class effect" for treating Crohn's disease with etanercept in view of its efficacy for rheumatoid arthritis, since infliximab had obtained FDA approval for both diseases. (Ex. 2016 at 1092-93.) But etanercept's failure contradicted any anti-TNFα class effect. Moreover, the investigators could not explain why etanercept failed. (*Id.*) Etanercept has never been shown to treat Crohn's disease or ulcerative colitis. (*See, e.g.*, Ex. 2017 at S33 (investigation of etanercept to treat Crohn's disease was "discontinued by the manufacturer").) Neither Petitioner nor its declarants address etanercept's clinical failure in IBD.

3. CDP571 Failed to Treat IBD

Dr. Posner notes that, as of 2001, the humanized anti-TNFα monoclonal antibody CDP571 had initially shown potential benefit in IBD patients. (Ex. 1025 at ¶ 59 (citing Ex. 1065).) In 2003, however, after unsuccessful testing in larger Phase III clinical trials, CDP571's developer abandoned the drug because "it was shown to have no discernible benefits" for patients. (Ex. 2019.)

The report (which is prior art) indicated that CDP571's failure was not unique, as it followed "a string of disappointing late stage trial results for Crohn's disease therapies." (*Id.*) Neither Petitioner nor its declarants acknowledge CDP571's clinical failure in treating IBD.

4. Onercept Failed to Treat IBD

Between late 2001 and early 2003, researchers conducted a clinical trial of another biologic anti-TNFα drug, onercept, for Crohn's disease. (Ex. 2028 at 889-90.) This drug also failed. (*Id.* at 888 (onercept was "not effective").) And, like etanercept, the investigators *could not explain* the failure. (*Id.* at 892 ("The reason why onercept was not efficacious in the present study is unclear.").) To date, onercept has not been shown to treat IBD at any dose. Neither Petitioner nor its declarants address the failure of onercept in treating IBD.

These failures of anti-TNFα drugs (oxpentifylline, etanercept, CDP571, and onercept) in IBD clinical trials demonstrate the high level of unpredictability of the art. Indeed, Petitioner's own expert, Dr. Bjarnason, stated in 2005 that drug therapy to treat IBD was still "*empirical* rather than based on sound understanding of the disease mechanism." (Ex. 2021 at 179 (emphasis added).) Thus, as of 2004, it was known that one could not "simply extrapolate[]" the results from one anti-TNFα drug to another because the factors leading to clinical efficacy of anti-TNFα

treatments were "only partly known" and needed "to be studied in more detail." (Ex. 2009 at I116.)

D. The Prior Art Use of Adalimumab to Treat Rheumatoid Arthritis

As of the April 2004 priority date, adalimumab was approved only to treat rheumatoid arthritis, and published clinical evaluations of adalimumab were limited to studies conducted in rheumatoid arthritis patients. (Ex. 2024 at 3, 4.) The applications leading to the '559 patent were the first disclosures of the clinical evaluation of adalimumab for the treatment of IBD. (Ex. 1001 at 73:40-76:20.)

The FDA-approved dose of adalimumab for treating rheumatoid arthritis was 40 mg every-other-week. (Ex. 2024 at 5.) No other adalimumab dosing regimen was FDA-approved in 2004. Moreover, none of the asserted references disclose using an initial dose of adalimumab that was higher than subsequent doses of adalimumab—for IBD or any other disease.

This 40 mg dose of adalimumab had a "rapid" onset of action in treating patients with rheumatoid arthritis. (Ex. 2020 at 35.) Moreover, raising the fixed dose of adalimumab to levels above 40 mg did not generate any improved therapeutic effect in rheumatoid arthritis patients and was associated with serious safety concerns. (Ex. 1020 at 35:21-26, Figs. 1B and 2-4; Ex. 2024 at 4.)

E. The Asserted References

1. WO 02/100330 (Ex. 1020)

WO 02/100330 (WO ’330) discloses adalimumab, a human antibody that binds to TNFα. (Ex. 1020 at 2.) It identifies multiple disorders for which adalimumab could be used, including IBD, rheumatoid arthritis, sepsis, autoimmune diseases, infectious diseases, transplantation, malignancy, pulmonary disorders, cardiac disorders, and others. (*Id*. at 29:24-33:12.) WO ’330 discloses an exemplary, non-limiting range for a therapeutically or prophylactically effective amount of adalimumab of 10-100 mg and states that the amount is most preferably 40 mg. (*Id*. at 27:37-39.) WO ’330 does not disclose using multiple-variable doses of adalimumab to treat any disease.

WO ’330 contains three examples reporting the results of clinical trials of adalimumab in rheumatoid arthritis patients. (*Id*. at 33:17-35:26.) In Example 1, weekly, subcutaneous, weight-based doses of adalimumab achieved a quick onset of action, with 78% of patients achieving a therapeutic response “during the first weeks of treatment.” (*Id.* at 33:20-30.) Example 2, which discloses the weekly subcutaneous administration of 20, 40, and 80 mg of adalimumab in patients with rheumatoid arthritis, concludes that 40 mg/week, rather than the higher 80 mg/week dose, had the strongest effects. (*Id.* at 34:18-27.) Example 3 reports the results of every-other-week subcutaneous administration of 20, 40, and 80 mg

adalimumab in rheumatoid arthritis patients. (*Id*. at 34:28-35:26, Figs. 1B and 2-4.) All three doses were statistically significantly better than placebo, with the 40 and 80 mg doses achieving greater efficacy than the 20 mg dose. (*Id*.) Figures 1B and 2 also show that raising the dose from 40 mg to 80 mg did not improve ACR response (diagnostic criteria for measuring the effectiveness of rheumatoid arthritis treatments). (*Id.* at Figs. 1B and 2-4.)

WO ’330 does not disclose any clinical evaluations of adalimumab (or any other antibody) in IBD patients or any pharmacodynamic data for adalimumab in IBD. It also does not disclose an adalimumab dose as high as 160 mg for any disease or the use of any multiple-variable dosing regimen using different doses of adalimumab, much less the claimed 160 mg/80 mg or 160 mg/80 mg/40 mg dosing regimen. (*See generally* Ex. 1020.)

2. Humira® Label (Ex. 1026)

The Humira® Label, which Petitioner has not established as prior art, concerns Humira®, AbbVie’s adalimumab product. The Humira® Label states that adalimumab is a fully human monoclonal antibody that binds specifically to TNFα and blocks its interaction with the p55 and p75 cell surface TNF receptors. (Ex. 1026 at 1.) As the label reflects, Humira® was approved at the time only for treating rheumatoid arthritis. (*Id.* at 4.) Rheumatoid arthritis was understood to be

an "aggressive disorder [that] demands the early institution of an equally aggressive therapeutic approach." (Ex. 2033 at 4.)

The Humira® Label states that the approved dose for adults with rheumatoid arthritis is 40 mg administered every-other-week as a subcutaneous injection. (Ex. 1026 at 9.) The label states that some patients with rheumatoid arthritis may derive additional benefit from increasing the dose *frequency*, not the dose *amount*. (*Id*.) Although the label states that up to 10 mg/kg had been administered to patients in clinical trials without evidence of dose-limiting toxicities, it also states that the maximum tolerated dose had not been established. (*Id.*) Moreover, the label contains a "black box" warning about the risk of tuberculosis infection, explaining that the incidence of tuberculosis reactivations was "particularly increased at doses of Humira that were higher than the recommended dose" of 40 mg. (*Id.* at 1, 5.)

The label does not disclose or suggest using adalimumab to treat IBD (Crohn's disease or ulcerative colitis). It contains no information about adalimumab's distribution from the bloodstream to the intestinal tract after subcutaneous administration, the drug's pharmacokinetics in the intestinal tract, or how the drug's concentration in blood serum correlates to its concentration in the intestinal tract. (*See generally* Ex. 1026.) It also does not disclose or suggest using any higher initial dose, much less an initial dose of 160 mg (*quadruple* the

approved 40 mg dose for rheumatoid arthritis) or any multiple-variable dosing regimen, much less a 160 mg/80 mg or 160 mg/80 mg/40 mg dosing regimen.

3. Remicade® Label (Ex. 1023)

The Remicade® Label describes the FDA-approved dosing regimen of infliximab, a chimeric monoclonal antibody, for the treatment of Crohn's disease and rheumatoid arthritis. (Ex. 1023 at 1, 4.) The label states that the approved dose of infliximab for treating Crohn's disease is 5 mg/kg given as an "induction regimen" at weeks 0, 2, and 6, followed by a "maintenance regimen" of the *same* 5 mg/kg every 8 weeks thereafter. (*Id*. at 4.)

For patients who initially respond to infliximab treatment but eventually lose their response, the label states that "consideration may be given to treatment with 10 mg/kg." (*Id.*) Thus, the label discloses either using the *same 5 mg/kg dose* for the induction and maintenance regimens for treating Crohn's disease, or using a higher *treatment* dose (10 mg/kg) compared to the initial induction dosing (5 mg/kg). (*Id*.) The Remicade® Label recommends the *same* dosing schedule for treating rheumatoid arthritis as Crohn's disease (weeks 0, 2, and 6, and then every 8 weeks thereafter), only at a fixed dose of 3 mg/kg or up to 10 mg/kg in patients who lose their response. (*Id*.)

Infliximab's induction regimen extends over a 14-week period, and the induction doses are unevenly spaced over that period. (*Id*.) The label does not

describe any achievement of steady-state plasma concentrations of infliximab in IBD patients. To the contrary, the label states that "[n]o systemic accumulation of infliximab occurred upon continued repeated administration." (*Id.* at 1.) Indeed, while the label describes infliximab dosing at weeks 0, 2, and 6 weeks, and then every 8 weeks thereafter, it states that the half-life of infliximab is only 8-10 days. (*Id.*)

The Remicade® Label does not disclose adalimumab, compare infliximab to adalimumab, or disclose using any higher initial doses of infliximab compared to later doses. (*See generally* Ex. 1023.)

4. Hanauer (Ex. 1027)

Hanauer, a 2001 review article, summarizes a variety of known or potential treatments for IBD. (Ex. 1027 at 6.) It states that conventional approaches to treating IBD were "directed at *either* induction *or* maintenance of remission." (*Id.* (emphasis added).) Hanauer states, for example, that corticosteroids were the "current mainstay of inductive therapy," but were "ineffective as maintenance therapies." (*Id.* at 10.) It similarly reports that azathioprine and 6-mercaptopurine were effective maintenance therapies, but not ideal for induction therapy. (*Id.* at 11 (reporting a lengthy, 3-4 month period for onset of action).) Hanauer concludes that it is "unlikely that a single agent will be effective in treating all phases of

[IBD] without inducing profound and unacceptable immune suppression." (*Id*. at 18.)

Hanauer discusses the use of infliximab to treat Crohn's disease. It states that a series of clinical trials had only "begun to define a role for infliximab as both an inductive and maintenance agent for [Crohn's disease]." (*Id*. at 13.) It reports on clinical trials of infliximab that administered single intravenous infusions of 5, 10, or 20 mg/kg, in which the lowest dose, 5 mg/kg, showed the best results. (*Id*. at 13-14.)

In addition to infliximab, Hanauer discusses other drugs under investigation at the time for treatment of IBD, including etanercept and CDP-571. (*Id*. at 15.) Petitioner relies on Hanauer, published in 2001, without acknowledging the prior art publications reporting on the eventual failures of these anti-TNFα biologics to treat IBD. (*See supra* § II.C.)

Hanauer does not disclose any investigations involving adalimumab, or the use of adalimumab to treat IBD. (*See generally* Ex. 1027.)

5. Goodman (Ex. 1030)

A textbook chapter by Grant R. Wilkinson in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* ("Goodman") discusses "General Principles" of pharmacokinetics. (Ex. 1030 at 12.) It describes the general concepts of "loading doses" and "maintenance doses" and defines a loading dose as "one or

a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly."[3] (*Id*. at 35-36.) Goodman states that a loading dose may be desirable if the temporal demands of the condition (e.g., a life-threatening myocardial infarction) are more immediate than the time required to attain steady state with the drug (e.g., lidocaine, which takes 4-8 hours to achieve a therapeutic concentration). (*Id*. at 36.)

Goodman cautions, however, that loading doses have "significant disadvantages." (*Id*.) It explains, for example, that a "particularly sensitive individual may be exposed abruptly to a toxic concentration of drug"; and that, "if the drug involved has a long half-life, it will take a long time for the concentration to fall if the level achieved was excessive." (*Id*.) It also explains that loading doses tend to be large and are often given parenterally and rapidly, which can be "particularly dangerous" if toxic effects occur. (*Id*.) Accordingly, Goodman recommends more frequent doses over a large initial dose, i.e., that it is "usually advisable to divide the loading dose into a number of smaller fractional doses that are administered over a period of time." (*Id*.) This recommended strategy of more

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

frequent dosing is consistent with the approved induction regimen of infliximab, which administers the same 5 mg/kg dose at weeks 0, 2, and 6 rather than administering higher initial doses. (Ex. 1023 at 4.)

Similarly, Goodman points out that increasing a drug's dose increases the risk of adverse effects. (Ex. 1030 at 34.) Therefore, unless a drug is nontoxic, "increasing the dose is not a useful strategy for extending a drug's duration of action." (*Id*.)

Goodman does not discuss the treatment of IBD or the use of adalimumab to treat any disease. Indeed, its examples of loading doses are limited to coronary care (myocardial infarction and congestive heart failure) using non-biologic drugs. (*Id.* at 36.)

III. Claim Construction

The preambles of independent claims 1 and 4 recite a multiple-variable dose method for treating idiopathic IBD in a human subject. (Ex. 1001 at 93:55-95:5.) Petitioner asserts, in conclusory fashion, that these preambles are non-limiting statements of intended use. (Pet. at 18.) As an initial matter, the fundamental deficiencies of Petitioner's proposed obviousness ground do not depend on any construction of the preamble language. The asserted references, for example, fail to disclose or suggest the claimed 160 mg/80 mg dosing regimen irrespective of whether the preambles are limiting. Thus, the Board need not construe the

preambles in denying institution. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (claim terms need only be construed to the extent necessary to resolve the controversy).

To the extent the Board reaches this issue, Patent Owner disagrees with Petitioner's assertion that the preambles are non-limiting. The only portion of the preambles that Petitioner addresses is the term "treating." (Pet. at 18-19.) And to support its position that "treating" is non-limiting, Petitioner cites *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339 (Fed. Cir. 2003). (Pet. at 18.) But this decision *rejected* an argument that a claim preamble was non-limiting. *Boehringer*, 320 F.3d at 1345. The claim at issue there concerned a method of "growing" and "isolating" a virus. *Id.* at 1344. The Court held that these preamble terms *were* limiting because, in the context of the claim as a whole, they were "not merely circumstances in which the method may be useful," but instead were "the *raison d'être* of the claimed method itself." *Id.* at 1345. Similarly, the claimed method here is fundamentally directed to a method of treating IBD, as the claim language as a whole shows. The specification is also replete with references to a multiple-variable dose regimen for treating IBD. (Ex. 1001 at title, abstract, 2:17-24, 2:40-59, 7:1-30, 28:50-29:33, 73:44-76:20.) This confirms that treating IBD is an important characteristic of the claimed invention and thus the "treating" claim term is limiting. *Poly-Am., L.P. v. GSE Lining Tech.*,

Inc., 383 F.3d 1303, 1309-10 (Fed. Cir. 2004) (holding that repeated references to preamble term "blown-film" in specification supported interpretation of the term as limiting).

The preamble of each claim also provides antecedent basis for the phrase "the human subject" appearing in the body of the claims. For this additional reason, the preamble claim language is limiting. *E.g.*, *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1338-1340 (Fed. Cir. 2003) (holding preamble limiting where it provided antecedent basis for limitation in the body of a claim); *Bicon, Inc. v. Straumann Co*., 441 F.3d 945, 952-53 (Fed. Cir. 2006) (same).

Petitioner argues, alternatively, that the term "treating" should be interpreted to mean reducing the signs and/or symptoms of IBD by inducing remission and/or maintaining symptom remission, but that no specific level of therapeutic effect is required. (Pet. at 18.) For purposes of this preliminary response, Patent Owner will not dispute that "treating" IBD means reducing the signs and/or symptoms of IBD by inducing remission and/or maintaining symptom remission. Inducing or maintaining remission in an IBD patient, however, *does* refer to a specific level of therapeutic effect. (*See, e.g.*, Ex. 1017 at 12, 15.) Therefore, the Board should not accept Petitioner's "no specific level of therapeutic effect" qualifier, which is unsupported, illogical, and internally inconsistent.

IV. Petitioner Fails to Establish a Reasonable Likelihood of Prevailing as to Any Challenged Claim

A. Petitioner Fails to Establish Any Motivation to Combine and Modify the Asserted References to Achieve the Claimed Method of Treating IBD

According to Petitioner, IBD therapy requires both induction-of-remission and maintenance-of-remission dosing regimens, with the former achieved by using higher doses or more frequent dosing. (*E.g.*, Pet. at 2, 20, 35-37, 39.) Petitioner concedes that the asserted references do not disclose administering 160 mg of adalimumab followed by 80 mg of adalimumab, but contends that one of ordinary skill would have been "motivated to design" the specific claimed multi-tiered dosing regimen for treating IBD with adalimumab to more rapidly reach steady-state blood levels and provide more rapid relief of IBD symptoms. (*Id.* at 20-22, 35-36.) As detailed below, however, the asserted references refute Petitioner's hindsight-based theory.

1. The Adalimumab References Do Not Suggest Any Induction Dose, Much Less the Claimed 160 mg/80 mg Regimen

Petitioner's proposed obviousness ground includes two primary references, which discuss adalimumab: the Humira® Label and WO '330. Both of these references exclusively disclose the use of fixed doses. (Ex. 1020; Ex. 1026.) Neither reference discloses using an initial dose that is higher than subsequent doses or suggests any need to use a higher initial dose or doses, let alone the claimed 160 mg/80 mg regimen.

Petitioner repeatedly characterizes the Humira® Label and WO '330 as disclosing "maintenance" adalimumab dosing regimens, but in fact neither reference refers to separate maintenance or induction dosing or suggests using an induction dose for adalimumab. (Pet. at 3, 20, 21, 24, 26, 36-37.) Rather, the Humira® Label only discloses a dosing regimen for rheumatoid arthritis using the *same single fixed dose* throughout treatment: 40 mg of adalimumab administered subcutaneously once every-other-week. (Ex. 1026 at 9.) WO '330 likewise does not refer to any separate maintenance or induction dosing; instead, it discloses using the *same single fixed dose* throughout treatment, most preferably about 40 mg. (Ex. 1020 at 27:37-39, 33:16-35:26.) Indeed, each of its three examples describes dosing regimens only using the same single fixed dose throughout treatment at the same interval. (*Id.* at 33:16-35:26.)

Petitioner argues that WO '330 describes 40 mg every-other-week as a maintenance dose because it states that it is a "prophylactically effective amount." (Pet. at 26.) But Petitioner's omits that WO '330 discloses the dose ranges as "*therapeutically or* prophylactically effective" amounts without characterizing them as maintenance or induction doses. (Ex. 1020 at 27:37-39 (emphasis added).) Thus, neither adalimumab reference suggests using a higher initial dose or doses to induce remission of IBD.

Petitioner emphasizes that IBD was known to cause severe symptoms requiring a "rapid therapeutic response," but does not assert that IBD requires a more rapid therapeutic response than rheumatoid arthritis. (Pet. at 32-33.) In fact, the prior art indicated that rheumatoid arthritis is an "aggressive disorder" that "demands the early institution of an equally aggressive therapeutic approach" to avoid irreversible bone and joint damage. (Ex. 2033 at 4.) It was also known that, in contrast to rheumatoid arthritis, many symptoms of IBD were reversible, and the disease could go into remission without treatment. (*See* Ex. 2002 at 6 (IBD has a relapsing-remitting course, alternating between active periods of inflammation known as flares and periods of reduced symptoms).) Thus, Petitioner's stated rationale for needing higher adalimumab doses to treat IBD compared to the 40 mg dose used for rheumatoid arthritis is unsupported and based on hindsight.

Both the Humira® Label and WO '330 disclose clinical data for rheumatoid arthritis, not IBD. But to the extent these data are deemed relevant, they contradict Petitioner's suggestion that, absent a higher initial dose, adalimumab would not obtain a sufficiently "rapid" effect. (*E.g.*, Pet. at 4, 38-39.) The Humira® Label indicated that adalimumab provided a rapid therapeutic effect in treating rheumatoid arthritis without using higher initial doses. (Ex. 1026 at 2 (treatment with adalimumab generated "a rapid decrease in . . . reactants of inflammation").) Indeed, the recommended 40 mg every-other-week dose was reported in the prior

art to achieve "significant, rapid, and sustained" responses, with the greatest proportion of patients achieving therapeutic response within one week of treatment. (Ex. 2020 at 43.) WO '330 further showed that, following weekly dosing of 0.5 mg/kg of adalimumab, up to 78% of patients reached a therapeutic response during the first weeks of treatment. (Ex. 1020 at 33:20-30.)

The only asserted references that are specific to adalimumab therefore fail to disclose or suggest using different doses of adalimumab for the treatment of IBD, the use of adalimumab doses as high as 160 mg, or the need for induction and maintenance regimens with adalimumab. Indeed, these references contradict any need in the art to modify the known use of a *single* dose level (i.e., 40 mg) for adalimumab. The asserted references do not suggest using *any* induction dose for adalimumab, much less the specific claimed dosing regimen of 160 mg followed by 80 mg.

2. Petitioner's Pharmacokinetic Arguments Are Unsupported and Reflect Hindsight Bias

Lacking prior art support for the claimed regimen, Petitioner attempts to "design" (reconstruct) the claimed 160 mg/80 mg dosing regimen. (Pet. at 35-44.) Petitioner's arguments, however, are factually unsupported, internally inconsistent, and based on improper hindsight reasoning.

a) Applying Petitioner's Purported "General Rule" of Doubling a Maintenance Dose Would Not Have Led to the Claimed Regimen

Relying on Goodman and the non-asserted Aulton and Ritschel references, Petitioner identifies a purported "general rule" for calculating an induction dose by doubling a maintenance dose. (Pet. at 34-35 (citing Ex. 1029 at 284-85; Ex. 1003 at 353; Ex. 1030 at 25-27).) As an initial matter, these references discuss basic pharmacology concepts and do not mention adalimumab or IBD. (Ex. 1003; Ex. 1029; Ex. 1030.) Thus, at best they provide only "general guidance" and are insufficient to show unpatentability of the claimed invention. *Monosol RX, LLC v. ICOS Corp.*, IPR2017-00412, Paper 11 at 8-10 (P.T.A.B. July 3, 2017) (denying institution where petitioner relied on general principles in the pharmaceutical field to support obviousness because "a claimed invention is not shown to be unpatentable where 'the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it'") (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

But even following these references' general teachings would not have led one to the claimed adalimumab regimen. Goodman provides an equation for calculating a loading dose using certain pharmacokinetic properties of a drug. (Ex. 1030 at 36.) Based on this equation and certain assumed characteristics (such as linear pharmacokinetics and a dosing frequency of about one half-life), Petitioner

asserts that an initial loading dose of about 160 mg could be used to achieve adalimumab blood levels comparable to those resulting from every-other-week administration of 80 mg. (Pet. at 40-41.) Aulton states that as a "general rule" the loading dose is twice the size of the maintenance dose, if the dosing time interval corresponds to the drug's biological half-life. (Ex. 1029 at 13.) Ritschel provides a similar "rule of thumb" for calculating loading doses, stating that when the dosing interval is equal or somewhat shorter than the elimination half-life, then the loading dose to maintenance dose ratio should be 2:1. (Ex. 1003 at 3.) Ritschel likewise states that if a known dose of a drug yields satisfactory therapeutic effectiveness, then the maintenance dose should be one-half of the loading dose. (*Id.*)

But Petitioner repeatedly asserts that, in April 2004, one would have recognized *40 mg every-other-week* as the "preferred maintenance regimen" of adalimumab to treat IBD. (*E.g.*, Pet. at 3, 20, 21, 23, 25-27, 36-37, 45.) Indeed, although not described as a "maintenance" dose, 40 mg every-other-week was the approved dose described in the Humira® Label, and the most preferred dose identified in WO '330. (Ex. 1026 at 9; Ex. 1020 at 27:37-39.) Thus, even applying this purported "general rule" of doubling the alleged 40 mg maintenance dose would *not* have resulted in a *quadruple*-sized initial 160 mg dose, let alone the claimed 160 mg/80 mg dosing regimen. (*See* Ex. 1001 at claims 1-30.) As the

Office recognized during prosecution of the grand-parent application to the '559 patent, "it is unclear what would have motivated the ordinarily skilled artisan to not just double, but double and *also quadruple*, the 40 mg, every other week dose. . . ." (Ex. 2006 at 3.)

b) No Reference Suggests Using a "Basis" Dose to Calculate a Higher Initial Dose

Confronted with this gaping hole in its logic, Petitioner cuts from whole cloth a new theory: that one allegedly would have identified an intermediate dose—a dose higher than the alleged maintenance dose of 40 mg yet lower than the induction dose—to serve as the "basis" for calculating an induction dose. (Pet. at 3-4, 22-23, 35.) In a textbook case of improper hindsight, Petitioner selects 80 mg as the purported intermediate "basis" dose and, applying an equation from Goodman, doubles it to reach an "induction" dose of 160 mg. (*Id*. at 40-42.)

But *none* of Petitioner's asserted references disclose or suggest using an intermediate "basis" dose to calculate a loading or induction dose. (*E.g.*, Ex. 1029; Ex. 1003; *see also* Ex. 1030.) Petitioner's pharmacokinetics declarant, Dr. Posner, likewise fails to identify *any* support for the concept of an intermediate "basis" dose. Instead, he states that an induction dose is determined by doubling the treatment dose and simply relies, without analysis, on Dr. Bjarnason's unsupported statement that 80 mg would be the appropriate dose for calculating the induction dose. (Ex. 1025 at ¶¶ 39, 62, 72-73; Ex. 1002 at ¶ 95.)

Petitioner's wholly conclusory allegation that one would have doubled a nonexistent "basis" dose of 80 mg to arrive at the claimed 160 mg dose reflects improper hindsight reasoning and should be disregarded. 37 C.F.R. § 42.65(a); *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (hindsight-based attempts to retrace an inventor's path are "always inappropriate" under § 103). The internal inconsistency of Petitioner's theory is glaring: Petitioner identifies *40 mg* every-other-week as the ultimate treatment dose, but nevertheless calculates the initial dose by targeting blood levels obtained from *80 mg* every-other-week dosing. (Pet. at 35-38.) Petitioner then tacks on, with no citation support, the claimed second dose (80 mg two weeks after the 160 mg dose) because it would purportedly result in more rapid relief. (*Id.* at 42.) But Petitioner fails to address how this would influence blood levels or the selection of the initial 160 mg dose. As discussed in Section IV.D below, Petitioner's hindsight-driven construct becomes even more nonsensical when applied in the context of the dependent claims requiring three-tiered dosing of 160 mg at week 0, 80 mg at week 2, and 40 mg thereafter.

c) The Adalimumab References Point to 40 mg as the Most Preferred Dose and Show That Higher Doses Did Not Improve Efficacy

Petitioner's "basis" dose argument incorrectly assumes that one of ordinary skill would have sought a higher initial dose or doses of adalimumab to achieve a

greater therapeutic response. (*E.g.*, Pet. at 35-38.) But, even if one assumes (as Petitioner has done) that rheumatoid arthritis studies are relevant, the asserted adalimumab references refute this argument. They show that increasing the adalimumab dose did *not* improve therapeutic response in rheumatoid arthritis patients. Example 3 of WO '330, for instance, studied every-other-week subcutaneous administration of 20, 40, and 80 mg adalimumab. (Ex. 1020 at 34:28-35:5.) The results show that the 80 mg dose did *not* provide greater efficacy than the 40 mg dose. (*Id.* at 35:21-26, Figs. 1B and 2-4.) Similarly, Example 2, which examined weekly subcutaneous administration of 20, 40, and 80 mg adalimumab, shows that the 80 mg dose did not provide greater efficacy than the 40 mg dose. (*Id.* at 34:14-27.)

Likewise, the Humira® Label does not suggest using higher doses to achieve greater therapeutic effect in rheumatoid arthritis patients. Instead, the label notes that some individual rheumatoid arthritis patients not on methotrexate "*may* derive additional benefit from *increasing the dosing frequency* of Humira to 40 mg every week." (Ex. 1026 at 9 (emphasis added).)

d) The Asserted References Criticize the Use of Large Initial Doses and Doses Greater than 40 mg

Goodman discusses "significant disadvantages" of high initial doses and specifically *criticizes* their use. (Ex. 1030 at 36.) It states that "if the drug involved has a long half-life, it will take a long time for the concentration to fall if the level

achieved was excessive." (*Id.*) For this reason, Goodman recommends that, if one were to use a loading dose, it is "usually advisable to divide the loading dose into a number of smaller fractional doses that are administered over a period of time" instead of using a single large dose, which can be "particularly dangerous." (*Id.*)

Goodman's warning against using a high loading dose would have been particularly applicable to adalimumab, which, according to Petitioner, has a "long" half-life. (Pet. at 33; Ex. 1030 at 36.) Further, as noted above, the Humira® Label expressly *warns* against administering doses higher than the recommended 40 mg dose because of the increased risk of tuberculosis reactivation. (Ex. 1026 at 1, 5; *see also* Ex. 1024 at 11-13, 61-62.) Moreover, the label includes a "black box" warning specifically about the risk of tuberculosis infection. (Ex. 1026 at 1.) The FDA reserves such "black box" warnings for special problems that "may lead to death or serious injury." *See* 21 C.F.R. § 201.57(c)(1) (2015). Thus, the Humira® Label cautions *against* any doses higher than 40 mg.

Accordingly, Petitioner's argument that one of ordinary skill would have selected 80 mg and then doubled it to 160 mg (*quadruple* the most preferred 40 mg dose) is contradicted by Goodman and the Humira® Label.

e) Petitioner's Reliance on the Use of Induction Doses for Other Drugs Does Not Support Obviousness

Petitioner also relies on the general use of induction doses for drugs other than adalimumab to treat diseases other than IBD, including: (1) an erythropoietin

(red blood cell) stimulating drug used to treat anemia, (2) copper binding agents used to treat certain fibrotic and inflammatory conditions, (3) antiviral agents used to treat viral infections, and (4) tizaofurin and ribavirin used to treat cancers. (Pet. at 30-31.) But Petitioner fails to establish that any of these diseases relate to autoimmune disorders, let alone IBD, or that any of the drugs relate to monoclonal antibodies, let alone adalimumab, such that one of ordinary skill would have found them relevant.

The Board should therefore reject Petitioner's hindsight-driven pharmacokinetic calculation arguments and hold that Petitioner has failed to establish any reason or motivation for combining and modifying the asserted references to achieve the claimed 160 mg/80 mg adalimumab dosing regimen for treating IBD.

3. The Infliximab References Used More Frequent Dosing for Induction Rather than Higher Initial Doses

Petitioner includes two infliximab references in its proposed obviousness ground: the Remicade® Label and Hanauer. (Pet. at 10.) These references do not mention adalimumab, much less describe any adalimumab dosing regimen to treat IBD. (Ex. 1023; Ex. 1027.) They further undermine Petitioner's "basis" dose theory by confirming the use of more frequent dosing instead of the use of a higher initial dose or doses. (Ex. 1023 at 4; Ex. 1027 at 13-14.) Alone or in combination,

these references would not have motivated a skilled person to pursue the claimed 160 mg/80 mg dosing regimen.

a) The Remicade® Label Concerns Infliximab, Not Adalimumab

Citing the Remicade® Label, Petitioner asserts that one of ordinary skill would have been motivated to administer higher doses of adalimumab based on the dosing regimen of infliximab. (*See e.g.*, Pet. at 28-30.) Infliximab, however, is a different biologic drug than adalimumab, dosed on a patient-weight basis (not as a fixed dose) using intravenous infusion (not subcutaneous administration) and with more frequent dosing early in the regimen (not higher doses). (Ex. 1023 at 4.) Unlike adalimumab, infliximab was also dosed more frequently early in the regimen for treating rheumatoid arthritis. (*Compare* Ex. 1023 at 4 *with* Ex. 1026 at 9.)

Petitioner disregards these fundamental differences between the drugs and thus fails to show that one of ordinary skill would have looked to infliximab when designing an *adalimumab* dosing regimen.

b) The Remicade® Label Recommends the Same Dose for Inducing and Maintaining Treatment

Even if one were to consider the Remicade® Label, Petitioner fails to show that one would have been motivated to use higher initial doses of adalimumab in light of infliximab's administration of the *same 5 mg/kg dose throughout the*

treatment period. (Ex. 1023 at 4 (disclosing dosing 5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter).) Thus, while Petitioner relies heavily on infliximab's use of an induction regimen, Petitioner disregards that infliximab's dosing regimen does *not* follow Petitioner's purported "general rule" of calculating an induction dose by doubling a maintenance dose. (Pet. at 28-30, 34.) Rather, as Petitioner admits, infliximab uses "more frequent dosing" earlier in the regimen, not a doubled dose (or any higher dose). (Pet. at 2, 29.)

Infliximab's more frequent early dosing is consistent with the teaching in Goodman to avoid the use of large, early doses. (*See supra* § IV.A.2.d.) As stated in Goodman, "[i]t is . . . usually advisable to divide the loading dose into a number of smaller factional doses that are administered over a period of time." (Ex. 1030 at 36.)

In addition to ignoring the use of consistent 5 mg/kg doses throughout treatment, Petitioner disregards infliximab's *14-week* (unevenly spaced) induction regimen, which differs from the claimed *4-week* (evenly spaced) 160 mg/80 mg dosing regimen. Petitioner's picking and choosing from only certain parts of the infliximab regimen, while ignoring others, belies its reliance on hindsight. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the

exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." (citations omitted)).

The Remicade® Label also contradicts Petitioner's theory that one would have sought to use a 160 mg dose of adalimumab to rapidly achieve steady-state plasma concentrations, which Petitioner alleges were needed to rapidly treat IBD. (*See* Pet. at 4, 22-23, 38-39.) Although infliximab was dosed more frequently early in the regimen, this was not done to achieve steady-state concentrations earlier in the regimen. (*See* Ex. 1023 at 4.) The Remicade® Label states that patients achieved and maintained remission even though *no systemic accumulation* of infliximab occurred upon continued repeated administration at 4 or 8 weeks. (*Id.* at 1.) Indeed, infliximab has a half-life of roughly 8-10 days, illustrating that drug blood levels reset to near zero between each dose administered at 4- or 8- week intervals, rather than achieving higher, steady-state concentrations. (*See id*.)

c) Hanauer Suggests Using Different Drugs for Inducing and Maintaining Remission in IBD

Hanauer contains a general discussion of IBD therapies, including infliximab, that were known or prospective in 2001. (Ex. 1027.) Hanauer does not mention adalimumab. (*See id*.)

Petitioner cites Hanauer for the general concept that IBD therapies require both inducing and maintaining remission, but this does not establish motivation to design the specific claimed adalimumab IBD dosing regimen using a higher initial

dose of 160 mg followed by a lower dose of 80 mg. (Pet. at 27-28, 36.) Hanauer states that approaches to IBD therapy were "directed at *either* induction *or* maintenance of remission." (Ex. 1027 at 6 (emphasis added).) Thus, Hanauer suggests using *different* therapies to induce or maintain remission. For example, Hanauer describes corticosteroids as a mainstay of inductive treatment but ineffective as maintenance therapies. (*Id.* at 10.) Azathioprine and 6-mercaptopurine, on the other hand, were effective maintenance therapies but not useful for induction therapy. (*Id.* at 11.) Hanauer describes mesalamine as useful to both induce and maintain remission, but it was approved for a *single* fixed dosing regimen throughout treatment. (*Id.* at 7; Ex. 2026 at 5.)

The infliximab references therefore fail to cure the deficiencies of WO '330, the Humira® Label, and Goodman. Thus, even if combined, the five asserted references do not suggest the claimed 160 mg/80 mg dosing regimen.

B. Petitioner Fails to Establish Any Reasonable Expectation of Success in Achieving the Claimed Method of Treating IBD

Petitioner ignores the unpredictability in the art as of April 2004. The absence of any clinical data for adalimumab in IBD, the failures of other anti-TNFα inhibitors to treat IBD, and the lack of any known PK/PD relationship for adalimumab in IBD defeat Petitioner's allegation that would one have reasonably expected success in treating IBD using the claimed dosing regimen.

1. The Failures of Anti-TNFα Drugs to Treat IBD Demonstrate the Unpredictability in Developing an Adalimumab Dosing Regimen for Treating IBD

As of the April 2004 priority date, no published clinical data for adalimumab in IBD patients were available. The asserted references discussing adalimumab—the Humira® Label and WO '330—only include clinical data for treating rheumatoid arthritis, not IBD. (Ex. 1026; Ex. 1020.) Moreover, IBD was notoriously difficult to treat using *any* therapy. (*See, e.g.*, Ex. 2001 at 33.) Further complicating matters, a hoped-for anti-TNFα "class effect" for IBD had been disproven. (Ex. 2016 at 1092-93.) After infliximab exhibited positive results, researchers hypothesized that other drugs that reduce TNFα should have similar effects. (Ex. 2014 at 470-71 (identifying infliximab as cA2 antibody).) They tested the small-molecule drug oxpentifylline, a "strong suppressor of TNFα." (*Id.* at 470.) But they found no improvement in Crohn's patients, which cast doubt on the relevance of TNFα for IBD. (*Id.* at 470-71, 473.) Oxpentifylline's failure suggested that infliximab's positive results could be due to its ability to inhibit inflammation mediators apart from TNFα. (*Id.* at 473.)

Subsequently, investigators tested etanercept in Crohn's disease, again hoping to find an "anti-TNF-α class effect"—i.e., to demonstrate that an anti-TNFα biologic that worked for rheumatoid arthritis would also treat IBD. (Ex. 2016 at

1092-93.) Their efforts also failed, and they could not explain why. (*Id.*) Etanercept has never been shown to treat IBD. (*See* Ex. 2017 at S33.)

In 2003, CDP571, a humanized monoclonal anti-TNFα antibody, was abandoned after it was shown to have "no discernible benefits" for IBD patients. (Ex. 2019.) CDP571's developer then dismissed proposals for additional clinical trials. (*Id.*) CDP571's failure followed "a string of disappointing late stage trial results for Crohn's disease therapies." (*Id.*)

Between 2001 and 2003, yet another anti-TNFα biologic drug, onercept, failed an IBD clinical trial. (Ex. 2028 at 888, 892.) When the results were published in 2006,[4] the investigators still could not explain why it failed. (*Id.* at 892 (it was "unclear" why onercept was ineffective).) Onercept has never been shown to treat IBD.

Other biologic drugs, including anakinra and abatacept, have been approved to treat rheumatoid arthritis while failing to treat IBD. (Ex. 2029 at 3; Ex. 2030 at 4; Ex. 2031 at 3; Ex. 2032 at 62.) Although these biologic drugs are not TNFα

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[4] *See Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd*, IPR2017-01009, Paper 11 at 18 (P.T.A.B. Sept. 7, 2017) (later publications may demonstrate unpredictability in the art as of a patent's priority date (citing *In re Hogan*, 559 F.2d 595, 605 (C.C.P.A. 1977))).

inhibitors, their failures to treat IBD despite FDA approval for rheumatoid arthritis show the difficulty and unpredictability of developing IBD treatments. Consistent with this unpredictability in the art, Petitioner's declarant, Dr. Bjarnason, reported in 2005 that drug therapy for IBD was still "empirical rather than based on sound understanding of the disease mechanism." (Ex. 2021 at 179 (emphasis added).)

Neither Petitioner nor its declarants acknowledge or address the lack of *any* prior art clinical evaluation of adalimumab for IBD or the failures of the anti-TNFα drugs oxpentifylline, etanercept, CDP571, and onercept to treat IBD. Nor do they address the failures of other biologic drugs approved for rheumatoid arthritis, such as anakinra and abatacept, to treat IBD. These failures preclude any reasonable expectation of success. *E.g.*, *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1081 (Fed. Cir. 2012) ("[T]here can be little better evidence negating an expectation of success than actual reports of failure." (citation omitted)).

2. Petitioner's Dose Selections in the Absence of Any Known Dose-Response Curve Are Based on the Improper Use of Hindsight

Petitioner refers to the pharmacokinetics of adalimumab reported in the Humira® Label, but omits that the pharmacodynamics of adalimumab in IBD was unknown in April 2004. (Pet. at 4, 22, 38, 40, 42, 51.) In the absence of a known PK/PD relationship, Petitioner's allegation that a 160 mg/80 mg regimen would

have been obvious to "provide more rapid relief of IBD symptoms" (Pet. at 39) amounts to "merely throw[ing] metaphorical darts at a board." *Cyclobenzaprine*, 676 F.3d at 1070-71 (emphasizing "the importance of the lack of a known PK/PD relationship" in reversing a court's holding of obviousness); *see also Avanir Pharms., Inc. v. Actavis S. Atl., LLC*, 36 F. Supp. 3d 475, 487, 506 (D. Del. 2014) (holding non-obvious patent claims that recited two ranges of drug components and stating that efficacy cannot be predicted "based on in vivo or in vitro pharmacokinetic studies when the dose-effect relationship was unknown"), *aff'd, Avanir Pharms. Inc. v. Par Pharm., Inc.*, 612 F. App'x 613 (Fed. Cir. 2015) (Rule 36 affirmance).

Moreover, Petitioner's bare assertion that higher doses of adalimumab would result in greater therapeutic effect ignores the fact that (1) adalimumab doses higher than 40 mg did *not* improve efficacy in rheumatoid arthritis patients (*see supra* § IV.A.2.c); (2) Goodman recommends avoiding higher initial doses because they are "particularly dangerous" and carry increased risk of toxicity, especially for drugs with "a long half-life" (*see supra* § IV.A.2.d); and (3) the Humira® Label expressly cautions against administering doses higher than the recommended 40 mg dose because of the increased risk in tuberculosis reactivation (*see supra* § IV.A.2.d).

In summary, no asserted reference disclosed any clinical evaluation of adalimumab in IBD, and no PK/PD relationship was known. The state of the art of treating IBD in April 2004 was highly unpredictable and challenging, as illustrated by the many failures of anti-TNFα therapies to treat IBD. Petitioner and its declarants simply ignore these failures. Further, Petitioner's assertion that one would have used adalimumab doses higher than 40 mg to achieve greater therapeutic effect is unsupported, as doses greater than 40 mg did not improve efficacy in rheumatoid arthritis. Because Petitioner has failed to establish that one would have had any reason or motivation to combine the asserted references with a reasonable expectation of success, it has not met its burden of proving unpatentability for any challenged claim, and institution should be denied.

C. Petitioner Fails to Challenge the Unexpected Results of Record for the Claimed Method

Petitioner submitted Patent Owner's evidence of unexpected results in this proceeding but failed to challenge it. (Pet. at 50; Ex. 1024.) For this additional reason, institution should be denied based on the undisputed and compelling evidence of unexpected results.

During prosecution of the priority '136 patent, Patent Owner submitted a declaration from Dr. Mould and a poster by Colombel et al. (Ex. 1024 at 1, 140-43.) Colombel reports the results of clinical trials evaluating two different induction regimens: 160 mg/80 mg or 80 mg/40 mg. (*Id.* at 140-41.) After the

induction regimen (i.e., the first two doses), patients from *both* groups were administered the *same* dose of 40 mg every-other-week for the rest of the year-long treatment period. (*Id.*)

The 160 mg/80 mg multiple-variable induction regimen of adalimumab yielded a surprisingly and unexpectedly high degree of long-term efficacy in IBD patients. (*Id.* at 143.) Depending on methodology used to analyze the data, patients treated with the 160 mg/80 mg regimen were 4.8 or 3.7 times more likely to achieve one-year remission than patients treated with the 80 mg/40 mg regimen. (*Id.*) Dr. Mould discusses these remarkable results in her declaration, explaining that a skilled artisan in 2004 "would not have been able to predict, *a priori*, that an adalimumab dosing regimen of 160/80 mg would result in patients being 3.7-4.8 times more likely to be in remission after 1-year when compared to an adalimumab dosing regimen of 80/40 mg." (*Id.* at 14.) The Examiner found these unexpected results "convincing" during prosecution of the '559 patent's priority application. (Ex. 2006 at 3.)

Petitioner placed Dr. Mould's declaration and the Colombel publication into evidence yet does not challenge this undisputed evidence of unexpected results. (Pet. at 50-54.) Accordingly, the Board should deny institution for this additional reason. *See Praxair Distrib., Inc. v. Ino Therapeutics, Inc.*, IPR2015-00522, Paper 12 at 16-17 (P.T.A.B. July 29, 2015) (denying institution when petitioner failed to

address the unexpected results arguments raised during prosecution, despite petitioner including the file history as an exhibit).

D. Petitioner Has Not Established a Reasonable Likelihood of Prevailing as to the Dependent Claims

1. Administering 40 mg Doses of Adalimumab Every-Other-Week After a 160 mg/80 mg Dosing Regimen Would Not Have Been Obvious

Claims 2, 5, 8, 15-17, 22, and 24-26 require multiple-variable dose methods of treating IBD, comprising administering a dose of 160 mg, followed two weeks later by a dose of 80 mg, followed two weeks later by a dose of 40 mg. (Ex. 1001 at 93:66-96:26.) Claims 3, 6, 18-20, 23, and 27-30, which depend from claims 2 or 5, further require administering subsequent adalimumab doses of 40 mg two weeks apart. (*Id.* at 94:56-96:36.)

Petitioner identifies no reference teaching or suggesting the claimed *three-tiered* 160 mg/80 mg/40 mg dosing regimen for treating IBD, as these claims require. (*See, e.g.*, Pet. at 45.) As discussed above, Petitioner has not identified *any* example of an IBD dosing regimen for a biologic using a higher initial dose, let alone an example of an IBD dosing regimen for a biologic using a three-tiered dosing regimen.

Petitioner also points to no reference disclosing or suggesting an adalimumab induction regimen *lasting only four weeks*, as claimed. The induction regimen of infliximab, which Petitioner relies on, lasted *14 weeks*. (Ex. 1023 at 4.)

Petitioner's assertion that some patients on infliximab achieved remission of symptoms in as little as four weeks (Pet. at 22, 42) does not indicate that those patients stopped infliximab at four weeks or support limiting adalimumab's induction regimen to four weeks. Other IBD drugs used to induce a response were given for much longer than four weeks. (*See, e.g.*, Ex. 1027 at 11 (noting that fixed doses of 2.5 mg/kg azathioprine and 1.5 mg/kg 6-mercaptopurine can be used to treat active Crohn's disease but "require at least 3 to 4 months before their benefit can be assessed"); Ex. 2001 at 70 (same).)

Petitioner also fails to identify any reason or motivation in the prior art that would have led one of ordinary skill to achieve the claimed 160 mg/80 mg/40 mg regimen with a reasonable expectation of success. Even if, as Petitioner contends, one would have selected 40 mg of adalimumab every-other-week as the "maintenance regimen" for IBD, the asserted references would *not* have led one to a multiple-variable dosing regimen featuring a dose of 160 mg followed two weeks later by a dose of 80 mg, followed two weeks later by a dose of 40 mg.

Specifically, Petitioner relies on Goodman and the non-asserted Aulton and Ritschel references for "how to determine an appropriate induction dose." (Pet. at 33-35.) As explained above, these references do not mention adalimumab or IBD and would not have led to the claimed regimens. (*See supra* § IV.A.2.) Aulton describes a loading dose as "a large *single* dose" given to achieve peak plasma

concentration and describes maintenance doses as "smaller, *equal* doses" given after the loading dose. (Ex. 1029 at 12-13 (emphasis added).) Ritschel discloses that a plateau is reached after about 5-10 doses and that "to obtain this plateau *with the first dose*, a larger dose has to be given as a loading dose." (Ex. 1003 at 3 (emphasis added).) Goodman provides an equation for calculating the magnitude of a loading dose given target steady-state blood concentrations, but warns against using higher doses, particularly if the drug has a long half-life. (Ex. 1030 at 36.) According to Petitioner, adalimumab has a long half-life. (Pet. at 33-34.) None of these references discloses or suggests a *three-tiered* dosing regimen, as recited in claims 2, 3, 5, 6, 8, 15-20, and 22-30.

Further, administering 40 mg every-other-week (as required by claims 3, 6, 18-20, 23, and 27-30) is inconsistent with Petitioner's argument that one of ordinary skill would have used *80 mg* every-other-week as the "basis dose" and, in view of Goodman, Aulton, Ritschel, selected 160 mg as the initial dose to more rapidly obtain steady-state blood levels. (*E.g*. Pet. at 22-23 ("based on well-known dosing equations from prior art texts a double-sized 160 mg dose would achieve the desired blood levels much more rapidly than would 80 mg eow dosing alone").) Even accepting Petitioner's unsupported argument of using an initial dose of 160 mg, nothing in the asserted references suggests administering a *third* dose

that differs from the preceding dose or doses, much less a third dose that is a quarter of the initial dose.

Similarly, Petitioner fails to explain—or identify any prior art support—for selecting a *quadruple-sized* 160 mg initial dose if one of ordinary skill were targeting the steady-state blood levels resulting from administering 40 mg every-other-week instead of 80 mg every-other-week. Nor does Petitioner explain why one would follow this quadruple-sized 160 mg initial dose with a second dose of 80 mg. In sum, Petitioner has not shown a reasonable likelihood that it will prevail in establishing that any of these dependent claims are unpatentable.

2. Achieving a CDAI Score Below 150 Would Not Have Been Obvious

Dependent claims 13, 14, 16, 19, 25, and 28 include the additional limitation that the human subject achieves a CDAI score of <150. A party must "meet a high standard" to rely on inherency in an obviousness analysis—the limitation must be "*necessarily* . . . present, or the natural result of the combination of elements *explicitly disclosed* by the prior art." *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014) (emphasis added). The fact that something "*may* result from a given set of circumstances is not sufficient." *Id.* at 1195 (quoting *In re Rijckaert*, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993)). Petitioner fails to meet this high standard.

First, the combination of asserted references does not disclose or suggest the claimed dosing regimen. In discussing these claims, Petitioner only cites data in the '559 patent. (Pet. at 47, 59.) Having cited no reference to support its argument, Petitioner cannot argue that the CDAI limitation is the "natural result" of the claimed combination of elements disclosed by the prior art. *Par*, 773 F.3d at 1195-96. This is particularly true where, as here, it was unexpected that the claimed dosing regimens yielded the claimed CDAI results. (*See supra* § IV.C.)

Even if Petitioner could identify all the claim elements in the asserted references, it fails to establish that a CDAI score of <150 is *necessarily* present, and thus fails to prove inherency. To the contrary, Petitioner *concedes* that the claimed CDAI score does not necessarily result from the claimed dosing regimen. Petitioner states, for example, that this result is only achieved by "some percentage of patients." (Pet. at 47.) Dr. Bjarnason likewise states only that the data in the patent show that "some patients" achieve the claimed CDAI score. (Ex. 1002 at ¶ 115.) This is legally insufficient as inherency "may not be established by probabilities or possibilities." *Par*, 773 F.3d at 1195 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

The Board should reject Petitioner's improper attempt to use inherency to ignore the CDAI claim limitation. (Pet. at 47.) Petitioner identifies no prior art disclosing or suggesting the CDAI claim limitation, admits that a CDAI score of

<150 does not necessarily occur, and cites no testimony to support its contentions. The Board thus should find that Petitioner has not established a reasonable likelihood that claims 13, 14, 16, 19, 25, and 28 are unpatentable.

V. Petitioner Fails to Establish That the Humira® Label Is a Prior Art Printed Publication

A petitioner, which may only challenge claims based on prior art patents or printed publications, bears the burden to make a threshold showing that an alleged prior art reference was available as a printed publication. 35 U.S.C. § 311(b); *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1379-80 (Fed. Cir. 2015). To qualify as a prior art printed publication, a reference must have been publicly accessible before the critical date such that the document had been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008).

Petitioner contends that the Humira® Label (Ex. 1026) was posted on the FDA website "no later than March 31, 2003." (Pet. at 10.) As support, Petitioner relies on "the Internet Archive and Wayback Machine service" and cites Exhibits 1031 (a one-page screenshot of a Humira® label from the WayBack Machine) and 1032 (affidavit of Christopher Butler, Office Manager at the Internet Archive, regarding the archiving of a website containing the Humira® Label on March 31,

2003). (*Id*.) At most, these documents establish the existence of the Humira® Label on an FDA website on March 31, 2003. (Ex. 1032.)[5] Existence on an FDA website, however, is insufficient to establish *public* accessibility. *See Celltrion, LLC v. Biogen, Inc.*, IPR2017-01230, Paper 10 at 11-14 (P.T.A.B. Oct. 12, 2017) (holding that Petitioner failed to establish a newsletter as a printed publication despite evidence that it was available on the MD Anderson website because there was insufficient evidence of public accessibility). Critically, Petitioner does not explain what part of the FDA's website this label was part of, or otherwise establish that it was available to one of ordinary skill in the art. *Kyocera*, 545 F.3d at 1350.

Dr. Bjarnason asserts that "[t]he POSA would have accessed the FDA's website and easily found the 2003 Humira™ Package Insert using that website's own search capabilities." (Ex. 1002 at ¶ 77.) He also asserts that physicians knew of the FDA website and accessed drug labels from it. (*Id*. at ¶ 10.) Dr. Bjarnason does not, however, cite any objective evidence to support his conclusory opinions, establish any personal knowledge of the Humira® Label's availability on the FDA website, or cite any evidence establishing that the Humira® Label was actually disseminated to interested artisans. (*See id*. at ¶¶ 10, 77) His unsupported testimony

[5] Patent Owner does not concede that this unexplained evidence establishes that the Humira® Label was on the FDA website as of March 31, 2003.

therefore fails to meet the threshold of establishing the public accessibility of the Humira® Label (Ex. 1026). *Microsoft Corp. v. Bradium Technologies LLC.*, IPR2015-01435, Paper 15 at 11 (P.T.A.B. Dec. 23, 2015) (holding that Petitioner failed to establish an article as printed publication when no evidence supported declarant's assertion that interested persons would have navigated the website to find the article or that the website had any index or catalog that allowed searching); *Coalition for Affordable Drugs IV LLC v. Pharmacylics, Inc.*, IPR2015-01076, Paper 33 at 7 (P.T.A.B. Oct. 19, 2015) (rejecting declarant's conclusory assertion that a clinical trials document was publicly available on www.clinicaltrials.gov, when declarant did not attest to any personal knowledge of the public accessibility or dissemination of the reference as of the critical date).

Petitioner fails to establish whether the FDA indexed drug information in 2003 and, if so, how it was categorized (by trade name, active ingredient, application number, etc.); whether the website had a search capability in 2003 and if so, what that search capability was; what search allegedly would have identified the Humira® Label; and whether there were any "tools for customary and meaningful research" in 2003. *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194-97 (Fed. Cir. 2008) (finding no evidence that an interested person would have freely navigated through the FTP site's directory structure to find the Live Traffic paper); *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349-50

(Fed. Cir. 2016) (holding reference was not publicly accessible because no evidence established that an interested person would be aware of the web address of the reference or that an internet search would have located it). Petitioner also fails to establish that any Internet search engine would have located the Humira® Label or that one could have navigated the FDA website to locate it.

Petitioner has therefore failed to establish that the reference was sufficiently accessible to the public. *See Microsoft Corp.*, IPR2015-01435 Paper 15 at 11; *Celltrion*, IPR2017-01230, Paper 10 at 11-14. This is fatal because the Petition relies on the label for several arguments, including its allegation that "adalimumab exhibited linear pharmacokinetics." (*See, e.g.*, Pet. 22 at 40-41, 51.) Because Petitioner's sole ground of unpatentability relies on the Humira® Label, this failure warrants denial of institution. (*Id.* at 10.) *Ford Motor Co. v. Versata Dev. Grp., Inc.*, IPR2016-01012, Paper 12 at 3, 11-12 (P.T.A.B. Nov. 4, 2016).

VI. Conclusion

Petitioner has not established a reasonable likelihood of prevailing as to any challenged claim of the '559 patent. The Board should therefore deny institution of the Petition.

Respectfully submitted,

Dated: March 7, 2018

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** contains 12,685 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and Exhibits 2001-2021, 2024, and 2026-2034 were served electronically via email on March 7, 2018, in their entirety on the following:

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