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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD,
Patent Owner.

Case IPR2017-01988
Patent No. 8,974,790

PATENT OWNER'S PRELIMINARY RESPONSE

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I. Introduction

AbbVie's U.S. Patent No. 8,974,790 ("the '790 patent") is directed to methods of treating ulcerative colitis with the biologic drug HUMIRA® (adalimumab). Claim 1 requires subcutaneously administering to a human subject having ulcerative colitis a total body fixed dose of 40 mg of a specified human anti-TNFα antibody (adalimumab) once every 13-15 days for a time period sufficient to treat ulcerative colitis. The dependent claims add other important limitations, including a requirement that the human subject has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody (claim 3) and/or that adalimumab is administered for at least 24 weeks (claims 4-6).

For both of its proposed grounds, Petitioner attempts to skirt the required obviousness analysis by using the Board's final written decisions in IPRs relating to a different patent, U.S. Patent No. 8,889,135 ("the '135 patent"), which is directed to rheumatoid arthritis ("RA"), not ulcerative colitis. Instead of comparing the challenged claims to the prior art, Petitioner asserts that the "only difference between claim 1 of the '790 patent and claim 1 of the '135 patent invalidated by the Board, is that 'ulcerative colitis' is substituted for 'RA.'" (Pet., 15; *see also id.*, 2, 25 (same).) Petitioner thus premises its obviousness analysis of the '790

patent on the alleged obviousness of the ’135 patent but never analyzes the ’790 patent claims as a whole.

The Board should deny institution for several reasons:

Most fundamentally, the Petition is legally deficient because Petitioner does not adequately address the differences between the claims and the prior art, as *Graham* requires. The Board’s prior decisions did not address ulcerative colitis, the use of adalimumab to treat ulcerative colitis, or the ’790 patent, and therefore Petitioner’s reliance on them here cannot substitute for a proper *Graham* analysis. Tellingly, Petitioner cites no case that has ever held a claimed invention obvious because one of ordinary skill would have (1) found a different, unclaimed invention obvious based on one set of prior-art references, and then (2) combined that first conclusion of obviousness with additional prior art to reach a second conclusion of obviousness as to the claimed invention. The Board should decline Petitioner’s invitation to create from whole cloth a new theory of obviousness that violates established law.

Petitioner also fails to establish any motivation to combine the asserted references or any reasonable expectation of success. Petitioner frames many of its arguments in terms of the general category of inflammatory bowel disease

("IBD"), which includes Crohn's disease[1] and ulcerative colitis. (*See, e.g.*, Pet., 17 (Crohn's disease and ulcerative colitis are "closely related"), 31 (Table 2).) But attempts to develop new treatments for IBD have frequently failed. Before the June 2001 priority date, for example, the biologic TNFα inhibitor, etanercept (Enbrel®), failed to treat IBD. (*See* Ex. 2015, 6.)[2] Significantly, in its unsuccessful trial, etanercept was administered subcutaneously to Crohn's disease patients using the same fixed dose that the FDA had approved to treat RA. (*Id.*) This refutes any motivation or expectation of success in using a subcutaneous, fixed RA dose (40 mg) of adalimumab to treat IBD. Petitioner not only ignores this critically important prior-art failure, it inaccurately suggests that "there had been no published clinical trials of etanercept for CD [Crohn's disease] or UC [ulcerative colitis]." (Pet., 23 n.19.) Etanercept's failure and other IBD treatment failures

[1] Petitioner has also challenged AbbVie's U.S. Patent No. 8,911,737, which is directed to Crohn's disease, in co-pending IPR2017-01987.

[2] 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.

discussed below establish a high level of unpredictability in the art and contradict Petitioner's hypothesis of an anti-TNFα class effect in IBD.

Importantly, no asserted prior art discloses any clinical testing of adalimumab in ulcerative colitis patients at any dose. In fact, as of the priority date, the FDA had not approved any biologic anti-TNFα drug for treating ulcerative colitis. While Petitioner cites an eleven-patient infliximab study in ulcerative colitis, the doses tested were at least 66% *higher* than infliximab's approved RA dose. The FDA-approved infliximab dose for short-term treatment of Crohn's disease was similarly 66% higher than the RA dose. And for both ulcerative colitis and Crohn's disease, infliximab was administered via intravenous infusion (not subcutaneous injection) using weight-based dosing (not a fixed dose). Petitioner does not explain why one of ordinary skill would have deviated from infliximab's infusion regimen using a weight-based dose well above the RA dose, which worked in Crohn's disease, when etanercept's subcutaneous administration regimen using the same fixed dose approved for RA failed to treat IBD.

Compelling reasons further support denying institution for dependent claims 3-6. Claim 3 requires that the human subject has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody. Petitioner does not address this patient population or analyze how these patients differ from those who

have not had an unwanted immune response to an anti-TNFα antibody. Nor does Petitioner cite any reference that suggests using adalimumab in this patient population. In fact, Petitioner cites multiple references in which patients who had received a chimeric or humanized monoclonal antibody were *excluded* from clinical trials of anti-TNFα antibodies. Petitioner therefore cannot show that one would have had any motivation or reasonable expectation of success in treating a patient who has had an unwanted immune response to an anti-TNFα antibody using the claimed dosing regimen.

Claims 4-6 require administering the adalimumab drug for at least 24 weeks. Petitioner cites no reference that suggests administering adalimumab for at least 24 weeks to treat ulcerative colitis. Instead, Petitioner relies on early *infliximab* studies to assert that the claimed *adalimumab* dosing regimen would have been obvious. But, in 2001, the reported infliximab clinical trial in ulcerative colitis involved only single doses. Similarly, the approved regimen for treating moderately to severely active Crohn's disease provided for only a single intravenous infusion of infliximab, with no repeat dosing, because safety and efficacy beyond a single dose had not been established. (Ex. 1020, 22, 29.) In patients with fistulizing Crohn's disease, the label included additional doses only at weeks 2 and 6 because safety and efficacy beyond three doses had not been

established. (*Id.*) Indeed, as of 2001, longer-term infliximab studies in Crohn's patients were "not definitive" and had failed to achieve statistical significance compared to placebo. (Ex. 1005, 12-13.) Thus, the prior-art infliximab regimens would not have suggested every-other-week subcutaneous administration of adalimumab for a period of at least 24 weeks. Further, claim 4 (which depends from claim 3) includes the limitation requiring at least a 24-week treatment period, the patient population limitation of claim 3, and all of the limitations of claim 1. Petitioner cites no prior art suggesting this novel combination of claim elements.

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

II. Background

A. The Invention of the '790 Patent

The '790 patent is directed to novel methods of treating ulcerative colitis using the biologic drug adalimumab, the active ingredient in HUMIRA®. Many thousands of ulcerative colitis patients have benefited from treatment with HUMIRA®.

The specification describes methods of inhibiting human TNFα activity by subcutaneous, biweekly administration of an anti-TNFα antibody to treat intestinal

diseases, including ulcerative colitis and Crohn's disease. (Ex. 1001, 3:42-52, 27:21-25.) The '790 patent discloses narrowing ranges of therapeutically or prophylactically effective fixed-dosage amounts of adalimumab for use in its novel treatment methods: "10-100 mg, more preferably 20-80 mg and most preferably about 40 mg." (*Id.*, 23:21-33.)

The '790 patent claims are directed to the disclosed methods of treating ulcerative colitis with biweekly, subcutaneous administration of a fixed, 40 mg dose of the fully human anti-TNFα antibody D2E7 (adalimumab):

- Independent claim 1 recites a method of treating ulcerative colitis comprising subcutaneously administering to a human subject having ulcerative colitis a total body dose of 40 mg of adalimumab once every 13-15 days for a time period sufficient to treat ulcerative colitis.
- Claim 3 depends from claim 1 and recites treating a human subject who "has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody."
- Claims 4-6 recite the methods of claims 3, 2, and 1, respectively, wherein the antibody is administered for at least 24 weeks. Claim 4 depends from claim 3 and therefore includes

the limitation requiring at least a 24-week treatment period as well as the patient population limitation of claim 3.

For purposes of this Preliminary Response only, Patent Owner submits that it is unnecessary to construe any claim terms.

B. The Prosecution History of the ’790 Patent

The ’790 patent application was filed on May 30, 2014, as a continuation of application 10/163,657 (now the ’135 patent). (Ex. 2006, 1, 6.) On September 26, 2014, the Applicants filed a preliminary amendment, designating the application as a divisional rather than a continuation of the ’135 patent, because the claims were directed to ulcerative colitis, not RA. (*Id.*, 6.)

On January 2, 2015, the Examiner issued a Notice of Allowance. In the Reasons for Allowance, the Examiner acknowledged that a person of ordinary skill would consider many different factors in contemplating a dosage regimen to treat ulcerative colitis with adalimumab. He provided a nonexhaustive list of such factors, including the biophysical properties of the anti-TNFα antibody; the route of administration (e.g., intravenous vs. subcutaneous); the dosage form (e.g., weight-based vs. fixed dosing); and the frequency of dosage (e.g., weekly vs. biweekly). (Ex. 1010, 6.) He noted that one also would have considered experience treating ulcerative colitis with anti-TNFα antibodies in general. (*Id.*)

At the time, infliximab was the only other anti-TNFα antibody known to be effective for treating IBD patients. (*Id.*) The Examiner recognized that one of ordinary skill would have understood that the FDA-approved infliximab dosage regimen to treat Crohn's disease was higher than the infliximab regimen to treat RA. (*Id.*, 6-7.) The Examiner thus concluded that one of ordinary skill at the time of the invention would have thought that treating another form of IBD (ulcerative colitis) with adalimumab would likely require administering more adalimumab, potentially as much as 66% more than required to treat RA. (*Id.*, 7.)

C. Ulcerative Colitis Was a Chronic Inflammatory Condition of Unknown Etiology

Ulcerative colitis and Crohn's disease are related chronic inflammatory disorders of the intestinal tract, which together are known as IBD. (Ex. 2001, 47.)

Ulcerative colitis primarily affects the colon and rectum, which together constitute the large intestine. (Ex. 2007, 361.) It presents with mild to severe mucosal inflammation of the bowel walls. (*Id.*) Ulcerative colitis is a lifelong illness that typically first appears in young adulthood, between the ages of 15 and 30 years, but onset can occur at any age. (Ex. 2003, 3.)

Typical symptoms of ulcerative colitis include diarrhea, rectal bleeding, and abdominal pain. (*Id.*, 6.) Complications may include damage to the intestinal tissues, including ulcers, polyps, bowel perforations, and obstructions, as well as

bowel dilation leading to toxic megacolon (i.e., very thin and severely ulcerated bowel walls). (*Id.*, 7-8.) These symptoms range from mild to severe, on a patient-by-patient basis, and can depend on the part of the colon and/or rectum affected. (*Id.*)

The etiology of ulcerative colitis was unknown in 2001. (*Id.*, 3; Ex. 2001, 33-34.) Manifestations of ulcerative colitis vary widely with severity of the disease and the amount of the colon and/or rectum affected. (Ex. 2003, 6-7.) The disease has a relapsing-remitting course, alternating between active periods of inflammation (known as flares) and short periods of reduced symptoms. (Ex. 2002, 6.)

As of 2001, several interrelated factors were believed to contribute to ulcerative colitis, including genetics, the local enteric environment (e.g., gut bacteria and microflora), and mucosal immunity. (Ex. 2001, 34; *see also* Ex. 2004, 182 (noting the "complex and enigmatic" nature of IBD), 196-98.) Researchers described a multiplicity of paths leading to ulcerative colitis, with these genetic, environmental, and immunological defects each being capable of causing or contributing to the disease. (Ex. 2001, 34, 40-41, 44, 47; Ex. 2005, 296.) Because no single agent or mechanism could explain the etiology of ulcerative colitis (Ex.

2001, 34), researchers found it "naïve" to conclude that ulcerative colitis resulted from a single inflammatory cause or cytokine. (Ex. 2005, 296.)

D. Ulcerative Colitis Was Difficult to Treat and Drug Development Efforts Often Failed

In 2001, ulcerative colitis was difficult to treat. (Ex. 2001, 33.) The most common treatments were the same general immunosuppressant therapies that had existed for over fifty years, such as sulfasalazine and 5-aminosalicylate. (*Id.*, 65.) While these therapies might maintain remission,[3] they had little or no ability to induce remission of moderate or severe ulcerative colitis. (*Id.*, 66.) Instead, physicians used steroids for short-term treatment of acute flares, but with limited efficacy. (*Id.*, 67-68.) Prednisolone and hydrocortisone remained the preferred steroid treatments after more than forty years of use, despite their limited efficacy, severe side effects, and propensity to lead to steroid dependence. (*Id.*) Azathioprine and 6-mercaptopurine were additional options for steroid-resistant patients, but these treatments had a slow onset of action and were often discontinued due to side

[3] In clinical trials, for example, remission has been defined by a patient's Truelove and Witts score falling below a particular threshold (e.g., 4 points). (Ex. 1115, 86.)

effects. (Ex. 2018, S72; Ex. 2001, 70-71.) These general immunosuppressant drugs did not target any particular inflammatory mediator, much less TNFα.

The relapsing/remitting course of ulcerative colitis complicated treatments, because patients with active inflammation could experience periods of reduced symptoms without any therapeutic treatment. (Ex. 2010, 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 the effects of an administered drug or the natural course of the disease. As a result, it was essential to use controlled clinical trials to compare efficacy results against placebo. (*Id.*, 68-69; *see, e.g.*, Ex. 2008, 107 (Table 1 describing placebo rates as high as 35% and 50% in Crohn's disease clinical trials of anti-TNFα drugs).)

A new field of anti-TNFα research for IBD was emerging as of the June 2001 priority date, but the field was in its infancy. Anti-TNFα research and related attempts at drug development were unpredictable and frequently unsuccessful. (Ex. 2011, 54; *see also* Ex. 2008, 109 ("Anti-TNF agents are the first representatives of new biological therapies" for IBD and pose "a challenge for drug development.").) For Crohn's disease, for example, the FDA had approved only one anti-TNFα

drug, infliximab, for short-term treatment. (Ex. 1020, 22.) The approved dose of infliximab for Crohn's disease was administered intravenously based on patient weight (5 mg/kg), which was 66% higher than the approved RA dose (3 mg/kg). (*Id.*, 29.) But infliximab's mechanism of action in Crohn's disease, including its precise mechanism of TNFα inhibition, was unknown. (Ex. 2009, I118.)

For ulcerative colitis, there were no FDA-approved biologic anti-TNFα drugs. (*See* Ex. 2034, 2488-89.) While a small, eleven-patient study of infliximab in ulcerative colitis patients had been reported, the study was terminated prematurely due to slow patient enrollment, and its results were not "definitive." (Ex. 1115, 83, 88; *see also* Ex. 1005, 15.) The sole ulcerative colitis infliximab trial reported as of June 2001 tested single doses of 5, 10, and 20 mg/kg, which were similar to those investigated for Crohn's disease and at least 66% greater than the FDA-recommended dose approved at the time for RA. (Ex. 1005, 15; Ex. 1020, 29.)

In June 2001, the safety and efficacy of infliximab for long-term use in IBD also had not been established. Only single doses of infliximab had been tested in ulcerative colitis (Ex. 1005, 15), and the FDA had not approved infliximab for long-term therapy in Crohn's disease. (Ex. 1020, 22, 29.) Infliximab's package insert stated that moderately to severely active Crohn's disease should be treated

with only a *single* infusion, and further warned that safety and efficacy beyond a single dose had not been established. (Ex. 1020, 22, 29.) In patients with fistulizing Crohn's disease, the package insert included additional doses only at weeks 2 and 6—and again warned that safety and efficacy beyond three doses had not been established. (*Id.*) In fact, it was thought that long-term infliximab use could result in loss of efficacy. (Ex. 1090, 26.) Thus, in 2001, persons skilled in the art believed that infliximab was only "effective for short-term treatment of patients with moderately to severely active Crohn's disease." (Ex. 1023, 3.)

Researchers struggled to understand and explain the role of TNFα in IBD. While they attempted to develop laboratory techniques to correlate disease activity with TNFα levels, the results 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, 823-24 (emphasis added).) Another study sought to evaluate whether heightened serum TNFα levels correlate to Crohn's disease activity. (Ex. 2012, 233.) But it found *no relationship* between disease activity and TNFα levels. (*Id.*, 234-35.) By 2001, attempts to develop cytokine-based correlations with ulcerative colitis and Crohn's disease activity were viewed as "conceptually flawed." (Ex. 2005, 296 (using only

a single inflammatory mediator to "describe what are dynamic and clinically heterogeneous disease processes is probably naïve"); Ex. 2002, 7.)

After initial infliximab clinical trials reported positive results in the short-term treatment of Crohn's disease, researchers attempted to test the hypothesis that other anti-TNFα drugs would have similar efficacy in IBD. As detailed below, each of those attempts failed. (Ex. 2014, 470; Ex. 2015, 6; Ex. 2016, 1092-93.)

1. Oxpentifylline, an Anti-TNFα Drug, Failed to Treat IBD

In 1997, researchers hypothesized that if reducing TNFα was infliximab's exclusive mechanism of action, "other drugs that also reduce TNFα should have similar effects" in treating IBD. (Ex. 2014, 470.) To test this hypothesis, they treated Crohn's disease patients with oxpentifylline, a strong suppressor of TNFα. (*Id.*) They found *no improvement* of any intestinal inflammation or clinical symptoms of Crohn's disease. (*Id.*, 470-71.)

These negative results suggested that mediators other than TNFα may be involved in the inflammatory process in IBD. (*Id.*, 470.) Because TNFα inhibition using oxpentifylline did not treat Crohn's disease, the trial suggested that infliximab achieved its positive results by inhibiting mediators in addition to TNFα. (*Id.*, 473.) Accordingly, by 1997, researchers recognized that anti-TNFα drugs would not predictably treat IBD.

2. Etanercept, Another Anti-TNFα Drug, Failed to Treat IBD

Petitioner and its declarants rely on the purported absence of clinical trial results for etanercept in IBD. (Pet. 23, n.19; Ex. 1008, ¶ 38 n.2.) But in April 2001, two months before the '737 patent's priority date, Sandborn et al. reported the failure of the biologic anti-TNFα drug etanercept in Crohn's disease. (Ex. 2015, 6.) The FDA had approved etanercept to treat RA with a fixed subcutaneous dose of 25 mg twice weekly. (*Id.*) Investigators selected this *same dose* for a clinical trial with Crohn's disease patients. (*Id.*) The results, however, demonstrated that the 25 mg fixed, subcutaneous RA dose of etanercept was "not an effective therapy" for Crohn's disease. (*Id.*)

A follow-up publication by the clinical trial investigators explained that they hoped to find an "anti-TNF-α class effect" for treating Crohn's disease with etanercept in view of its efficacy for RA, since infliximab had obtained FDA approval for both diseases. (Ex. 2016, 1092-93.) But etanercept's failure contradicted any anti-TNFα class effect. Moreover, the investigators could not explain why etanercept failed. (*Id.*) Clinical trial design, for example, was not responsible for the differing results between etanercept and infliximab, since the clinical endpoints and patient-selection criteria were "nearly identical" to those used in infliximab's clinical trials. (*Id.*) Instead, the investigators speculated that

greater doses of etanercept were required for Crohn's disease than for RA. (*Id.*) Ultimately, however, etanercept has never been shown to treat Crohn's disease or ulcerative colitis. (Ex. 2017, S33 (investigation of etanercept to treat Crohn's disease was "discontinued by the manufacturer").)

Thus, as of 2001, 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, I116 (comparing infliximab and oxpentifylline clinical study results).) The target populations, study designs, and endpoints also varied widely among clinical studies for IBD, making it difficult to compare anti-TNFα agents. (*See* Ex. 2018, S75.) Further, clinical trials seeking to demonstrate an anti-TNFα class effect in IBD had failed, including the failure of the FDA-approved *RA dose* of etanercept to treat IBD.

3. After the Priority Date, Anti-TNFα Drugs Continued to Fail in Clinical Trials for IBD

In 2003, the art recognized the failure of another biologic anti-TNFα drug, the humanized monoclonal antibody CDP571. (Ex. 2019.) CDP571 had undergone small pilot studies in IBD. For example, CDP571 was tested in a fifteen-patient Phase I trial in ulcerative colitis patients. (Ex. 1005, 15.) Sandborn characterizes the results of this trial as "suggest[ing] a possible short-term benefit" in ulcerative

colitis. (*Id*. ("Additional studies are needed to prove efficacy . . . .").) CDP571 had also been tested in a "small" Phase IIa trial in Crohn's disease patients. (*Id.*, 13.) Sandborn similarly characterized the Crohn's trial as "suggest[ing] that CDP571 5 mg/kg may have short-term efficacy" in Crohn's disease. (*Id.*)

After unsuccessful testing in larger Phase III clinical trials, however, CDP571's developer abandoned the drug because "it was shown to have no discernible benefits" for patients. (Ex. 2019.) Based on this failure, CDP571's developer dismissed proposals for additional clinical trials. (*Id.*) News reports 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.*)

Between late 2001 and early 2003, researchers conducted a clinical trial of another biologic anti-TNFα drug, onercept, for Crohn's disease. (Ex. 2028, 888, 892.) This drug also failed. (*Id.*, 888 (onercept was "not effective").) And, like etanercept, the investigators *could not explain* the failure. (*Id.*, 892 ("The reason why onercept was not efficacious in the present study is unclear.").) Despite testing four different dose levels, the investigators postulated that even higher doses of onercept may be necessary for Crohn's disease. (*Id.*, 893.) To date, onercept has not been shown to treat Crohn's disease or ulcerative colitis.

These post-priority date failures of anti-TNFα drugs in IBD trials demonstrate the continued unpredictability in the art. Indeed, Petitioner's own expert, Dr. Bjarnason, reported in 2005 that the etiology of IBD remained "inadequately understood" and drug therapy was still "*empirical* rather than based on sound understanding of the disease mechanism." (Ex. 2021, 179 (emphasis added).)

E. Rheumatoid Arthritis and Ulcerative Colitis Are Different Diseases with Different Treatment Requirements

As of June 2001, RA was a poorly understood disease with an "unresolved" etiology. (*See* Ex. 2022, 202.) Persons skilled in the art nevertheless recognized that RA is a significantly different condition than ulcerative colitis, and that both diseases have different treatment requirements.

RA and ulcerative colitis affect different organs. RA is an inflammatory disease of the joints. (Ex. 2023, 1521.) Ulcerative colitis, by contrast, affects the colon and rectum, a significant part of the largest organ of the immune system—the intestines. (Ex. 2007, 361; Ex. 2024, 660.) Indeed, the intestines contain up to 40% of the body's immune-system cells. (Ex. 2024, 660.) The large intestine, which includes the colon and rectum, may be longer than one and half meters, presenting a large surface area for ulcerative colitis to occur. (Ex. 2025, 1137

(depicting the ascending, transverse, descending, and sigmoid colon and the rectum).)

The tissues where TNFα is present also differ. In RA, soluble TNFα is present in the synovial fluid of the joints. (Ex. 2023, 1521.) IBD, by contrast, was understood to include TNFα in the inflamed mucosal tissues of the intestine. (Ex. 1124, 3.) These differences led to the "frustrating" conclusion that although basic inflammatory mechanisms may have similarities, the *blockade* of inflammatory processes (e.g., TNFα activity) may be "tissue specific." (Ex. 2026, 2.) As a result, it was understood that a biologic drug for RA "may be of limited or no use in" IBD. (*Id.*)

The diseases also affect different patient populations. Ulcerative colitis typically first appears in young adulthood and affects both genders equally. (Ex. 2003, 3 (1:1 male-to-female ratio for ulcerative colitis).) RA, by contrast, typically appears in patients aged 35 to 50 and disproportionately affects females. (*Id.*, 9 (1:3 ratio male-to-female ratio for RA).)

Several other biologics approved to treat RA have also failed to show efficacy in IBD. For example, anakinra (Kineret™), a recombinant IL-1 receptor antagonist, received FDA approval to reduce the signs and symptoms of moderately to severely active RA. (Ex. 2029, 3.) In IBD, however, anakinra has

not been shown to be effective. (Ex. 2030, 4 ("[N]o clinical trials have been reported for IL-1 antagonists in IBD, but one case of *IBD worsening* with anakinra treatment has been described." (emphasis added)).) Abatacept (Orencia®), a soluble fusion protein that inhibits T cell activation, was approved to reduce the signs and symptoms of moderately to severely active RA. (Ex. 2031, 3.) But it has failed to show efficacy in ulcerative colitis. (Ex. 2032, 62.)

Several conventional RA drug therapies have likewise failed to treat IBD. For example, indomethacin was known to effectively control acute flares in RA (Ex. 2033, 14), but proved ineffective in (and worsened) IBD. (Ex. 1066, 3.) Parenteral or oral gold was a long-used RA therapy. (Ex. 2033, 19-20.) But side effects such as diarrhea and inducement of enterocolitis made gold unsuitable for IBD treatment. (Ex. 2020, 758.)

Thus, the failures of RA therapies to treat IBD, as well as the differences in patient demographics, affected organ systems, and TNFα-involved tissues, illustrate that RA and ulcerative colitis are distinct conditions with different treatment requirements.

F. The Asserted References

1. Salfeld (Ex. 1006)

The Salfeld PCT publication discloses human antibodies, including adalimumab, that bind to TNFα. It broadly identifies disorders for which the antibodies and antibody portions of the invention could be used, including sepsis, autoimmune diseases, infectious diseases, transplantation, malignancy, pulmonary disorders, intestinal disorders, cardiac disorders, and others. (Ex. 1006, 7:33-8:4, 38:5-42:17.) Salfeld discloses an exemplary, nonlimiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of 0.1-20 mg/kg, more preferably 1-10 mg/kg, representing a 200-fold range of weight-based doses. (*Id.*, 35:31-33.) It further discloses that dosage regimens may include a single bolus, several divided doses over time, or proportionally reduced or increased doses "as indicated by the exigencies of the therapeutic situation." (*Id.*, 35:17-21.)

Salfeld does not disclose fixed dosing of adalimumab for any purpose, and thus does not disclose a fixed dose of 40 mg. Nor does it disclose dosing once every 13-15 days.

2. Sandborn (Ex. 1005)

Sandborn, a 1999 review article, discusses three anti-TNFα drugs—etanercept, infliximab, and CDP571—in the context of RA and IBD. It describes

chimeric monoclonal antibodies like infliximab as the first generation of anti-TNFα drugs; humanized monoclonal antibodies like CDP571 as the second generation of anti-TNFα drugs; and fusion proteins like etanercept as the third generation of anti-TNFα drugs. (Ex. 1005, 6-8 (Fig. 4).) Petitioner does not acknowledge that two of these three anti-TNFα drugs were ultimately abandoned in IBD after unsuccessful clinical trials—specifically, the *later-generation* etanercept and CDP571 drug candidates. (Ex. 2015, 6; Ex. 2019.)

Sandborn summarizes preliminary clinical results for infliximab, CDP571, and etanercept in RA. (Ex. 1005, 13-15.) For Crohn's disease and ulcerative colitis, preliminary results are reported only for infliximab and CDP571, as the failed etanercept trial had not yet been reported in 1999 (but was published before the '790 patent's priority date). (*Id.*, 11-13, 15.) Sandborn does not refer to adalimumab or the use of adalimumab to treat any disease.

Sandborn describes infliximab clinical studies testing 1, 3, 5, 10, and 20 mg/kg doses in RA patients. (*Id.*, 13-14.) The studies demonstrated that one of the lower doses, 3 mg/kg, was the optimal dose for RA. (*Id.*) For ulcerative colitis, only single doses of 5, 10, and 20 mg/kg were investigated in an eleven-patient study. (*Id.*, 15.) For Crohn's disease, a lower dose of 1 mg/kg was abandoned in favor of higher 5, 10, and 20 mg/kg doses during clinical trials. (*Id.*, 11-12.)

Sandborn states that 5 mg/kg of infliximab was the "best dose" tested for Crohn's disease. (*Id.*, 12; *see also* Ex. 1020, 29 (recommending 3 mg/kg for RA and 5 mg/kg for Crohn's disease).)

Only one of the infliximab studies in Crohn's disease reported in Sandborn involved dosing beyond week 6. (Ex. 1005, 11-12.) In a Phase IIb/III study in chronically active Crohn's patients, selected patients were re-randomized after 12 weeks to treatment with placebo or infliximab (10 mg/kg) at weeks 12, 20, 28, and 36, and followed through 48 weeks. (*Id*., 12.) The study "results were not definitive." (*Id*., 12-13.) According to Sandborn, the "failure to achieve statistical significance due to wide confidence intervals and questions regarding concomitant medications led the FDA to withhold a maintenance claim for infliximab." (*Id*., 13.)

3. Kempeni (Ex. 1004)

Kempeni, a review article, reports preliminary results from several early weight-based RA clinical trials with adalimumab in which subjects received anywhere from 0.5 mg/kg up to 10 mg/kg in a single dose, in weekly doses, or at a dosing frequency dependent on clinical response. (Ex. 1004, 2-3.) Kempeni does not suggest using adalimumab at a fixed dose for RA or any other disease, or using adalimumab to treat any condition other than RA.

4. VDP1999 (Ex. 1003)

The VDP1999 abstract reports data from a Phase II RA clinical trial with adalimumab at 3 months, in which subjects received *weekly* doses at 20 mg, 40 mg, or 80 mg. (Ex. 1003, 3.) VDP1999 discloses using adalimumab for RA. (*Id.*) It does not suggest every-other-week dosing or using adalimumab for any other condition.

5. VDP2000 (Ex. 1107)

The VDP2000 abstract reports data at 6 months from the same RA clinical trial reported in VDP1999. (Ex. 1107, 2.) VDP2000 does not suggest using every-other-week dosing or adalimumab for any condition other than RA.

6. Rau (Ex. 1017)

Rau, a review article, discusses the same RA studies reported in Kempeni and the VDP1999 and VDP2000 abstracts. (*See generally* Ex. 1017.) Rau does not disclose using adalimumab for any purpose other than to treat RA.

III. The Level of Ordinary Skill in the Art

Petitioner proposes a person of ordinary skill having the skill sets of a pharmacologist and of physicians treating patients for RA and IBD. (Pet., 13.) The person of ordinary skill, however, necessarily depends on the art of the claimed invention. *E.g.*, *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007) (holding that where the claims concerned a method for treating bacterial ear

infections, one of ordinary skill would be a developer of ear treatments or an ear treatment specialist with training in pharmaceutical formulations, not a general practitioner).

Here, the claimed method treats ulcerative colitis by administering 40 mg of adalimumab subcutaneously once every 13-15 days. (Ex. 1001, claim 1.) Thus, a person of ordinary skill in this art would have the skill sets of a physician treating ulcerative colitis patients. Such a physician would have an MD, a gastroenterology fellowship, and at least three years of experience treating ulcerative colitis patients, including experience with the available anti-TNFα agent, infliximab. For purposes of this Preliminary Response, Patent Owner does not dispute that one of ordinary skill could also have the skills of a pharmacokineticist with experience related to monoclonal antibodies.

But because they typically do not treat ulcerative colitis, rheumatologists would not qualify as ordinary skilled artisans. Petitioner's RA expert, Dr. Helfgott, states only that he has "training, knowledge, and experience in the field of rheumatology, including treating patients with RA." (Ex. 1002, ¶ 14.) He does not state that he has any experience in treating ulcerative colitis. (*See, e.g.*, *id.*, ¶¶ 3-16.) Therefore, Dr. Helfgott is not a person of ordinary skill and is not

qualified to provide relevant expert testimony from the perspective of a person of ordinary skill. *E.g.*, *Daiichi Sankyo*, 501 F.3d at 1257.

IV. Petitioner Has Not Established a Reasonable Likelihood of Prevailing as to Any Challenged Claim

A. Petitioner's Obviousness Theory for Both Grounds Is Legally Deficient

1. Petitioner Does Not Adequately Address the Differences Between the Claims and the Prior Art as Required by the Statute and *Graham*

An obviousness challenge requires determining whether the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time of the invention to a person having ordinary skill in the art. 35 U.S.C. § 103(a) (pre-AIA).

Obviousness is a legal conclusion based on underlying facts of four general types: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) any objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

The *Graham* factors are mandatory: *all* of them "must be considered by the trier of fact." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998). As the Supreme Court held in *KSR*: "While the sequence of these questions might be

reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 407 (2007).

Petitioner, however, does not perform an adequate *Graham* analysis. (*See, e.g.*, Pet., 25-52, 57-63.) To illustrate, the Petition (including its claim chart) does not address *any* of the following nonexhaustive differences between the challenged claims and the asserted prior art:

- Salfeld (Ex. 1006) does not disclose fixed dosing, a 40 mg fixed dose of adalimumab, or dosing 40 mg of adalimumab every 13-15 days as required by each claim of the '790 patent;
- Sandborn (Ex. 1005) does not disclose adalimumab, using adalimumab to treat ulcerative colitis, any dosing regimen for adalimumab to treat ulcerative colitis, or any subcutaneous treatment of ulcerative colitis as required by each claim of the '790 patent;
- Kempeni (Ex. 1004) does not disclose fixed dosing for any disease, using adalimumab to treat ulcerative colitis, or any dosing regimen for adalimumab to treat ulcerative colitis as required by each claim of the '790 patent;

- VDP1999 (Ex. 1003), VDP2000 (Ex. 1107), and Rau (Ex. 1017) do not disclose using adalimumab to treat ulcerative colitis or any dosing regimen for adalimumab to treat ulcerative colitis as required by each claim of the '790 patent.

(*See supra* § II.F.)

Because Petitioner does not adequately address these differences between the challenged claims and the prior art, both proposed obviousness grounds are legally deficient. *KSR*, 550 U.S. at 407; *ATD Corp.*, 159 F.3d at 546; *Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00443, Paper 9 (PTAB July 9, 2015).

In *ContentGuard*, for example, the Board denied institution of an IPR where the petition "fail[ed] to identify sufficiently the differences between any claim of the [challenged] patent and the asserted prior art references." IPR2015-00443, Paper 9, at 10. Rather than performing the required *Graham* analysis, the petition "obscure[d] any comparison of the individual prior art references to the claim limitations" and did "not explain with any particularity which claim limitations [were] absent from the asserted references." *Id.* at 10-11. The Board therefore denied institution. *Id*. The same rationale supports denying institution here. *See id*.

Petitioner's failure to adequately address the differences between the claims and the prior art also means that the Petition does not comply with the PTO's

regulations on IPR petitions. *See, e.g.*, 37 C.F.R. § 42.104(b)(4) (a petition must identify how the challenged claims are unpatentable and specify where each claim element is found in the prior art); *ContentGuard*, IPR2015-00443, Paper 9, at 5, 10-11 (denying institution because the Petition's deficient *Graham* analysis provided insufficient information regarding the grounds of unpatentability).

2. Petitioner Improperly Bifurcates Its Obviousness Analysis, Failing to Address the '790 Patent Claims as a Whole

Instead of presenting a complete *Graham* obviousness analysis of the '790 patent claims as a whole, for both of its proposed grounds Petitioner improperly conflates its obviousness analysis of the '790 patent with the '135 patent. Petitioner first focuses on the alleged obviousness of the '135 patent's biweekly administration of 40 mg adalimumab to treat an unclaimed disease (RA)—not ulcerative colitis. (*E.g.*, Pet., 26, 39-44 (obviousness analysis of the '135 patent).) Petitioner then combines its conclusion of obviousness as to the '135 patent with additional prior art to reach a second conclusion of obviousness as to the claimed invention. In this way, Petitioner attempts to stack one obviousness conclusion on top of another, never addressing the '790 patent claims as a whole. (*Id.*, 4. ("Therefore, it would have been *obvious* for a POSA to have used the prior art D2E7 dosing regimen that the Board *found obvious* to treat RA . . . ." (emphases added)).)

Petitioner's piecemeal approach to the '790 patent claims is confirmed by its declarants. Petitioner's pharmacokinetic and RA experts, Drs. Posner and Helfgott, exclusively discuss the alleged obviousness of the subject matter of the '135 patent (i.e., using a 40 mg every-other-week adalimumab dosing regimen to treat RA). (*See generally* Ex. 1015; Ex. 1002.) Then, separately, Petitioner's IBD expert, Dr. Bjarnason, only asserts, in a wholly conclusory manner, that it would have been obvious to treat ulcerative colitis using the '135 patent's allegedly obvious RA dosing regimen. (*See, e.g.*, Ex. 1008, ¶¶ 122-24 (basing his opinion on the assumption that methods of treating RA would have been obvious).)

The '135 patent, however, does not concern a method of treating ulcerative colitis and is not the challenged patent in this IPR. Neither Petitioner nor its experts address all of the prior art in combination with respect to the claimed invention of the '790 patent, as required by § 103 and *Graham*. Instead, Petitioner improperly attempts to use the Board's decisions on the '135 patent as a shortcut to avoid addressing as a whole the '790 patent's different claimed method of using adalimumab to treat ulcerative colitis, as the statute requires. 35 U.S.C. § 103. The Board's decisions on the '135 patent are legally irrelevant here because they did

not address ulcerative colitis, the use of adalimumab to treat ulcerative colitis, or the '790 patent.[4]

The Federal Circuit has rejected the type of shortcut, obviousness-stacking analysis that Petitioner presents here. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1141 (Fed. Cir. 1985). In *Interconnect Planning*, a district court held certain patent claims invalid for obviousness on summary judgment. *Id.* at 1134. The PTO then resumed examination of a reissue application corresponding to the same patent and subsequently granted a reissue patent with amended claims. *Id*. at 1134-35. The district court later held the reissue patent claims obvious after comparing "the differences between the original and the reissue claims" with the

[4] Patent Owner disagrees that the methods of treating RA claimed in the '135 patent would have been obvious and has appealed the Board's final written decisions regarding the '135 patent. *AbbVie Biotechnology Ltd v. Coherus BioSciences Inc.*, No. 17-2304 (Fed. Cir. filed Nov. 9, 2015); *AbbVie Biotechnology Ltd v. Boehringer Ingelheim Int'l GmbH*, No. 17-2362 (Fed. Cir. filed Dec. 29, 2015); *AbbVie Biotechnology Ltd v. Boehringer Ingelheim Int'l GmbH*, No. 17-2363 (Fed. Cir. filed Dec. 29, 2015).

prior art. *Id*. at 1137. On appeal, the Federal Circuit rejected the district court's stacking of one obviousness conclusion on another as legally improper:

> The original claim is not prior art against the reissue claim. It is not correct to weigh the reissue claim against the original claim. It is not correct to weigh the changes in the reissue claim against the original claim. It is the reissue claim alone that is to be analyzed in accordance with the *Graham* guidelines, and the differences to be considered are the differences between the reissue claim as a whole and the prior art.

Id. at 1141. By cobbling together the alleged obviousness of the '135 patent with its incomplete analysis of the '790 patent's claimed inventions (Pet., 2, 15, 25), Petitioner asks the Board to engage in precisely the same sort of flawed obviousness-on-obviousness analysis that the Federal Circuit rejected in *Interconnect Planning*.

Importantly, Petitioner cites no case-law support for its obviousness theory that one of ordinary skill would have (1) found a different, unclaimed invention obvious based on one set of prior-art references and then (2) combined that first conclusion of obviousness with additional prior art to reach a second conclusion of obviousness as to the claimed invention. (*See, e.g.*, *id.*, 25-52.) Nor does Petitioner offer expert testimony that connects its bifurcated arguments. This fractured legal

analysis fails to analyze the claimed subject matter of the '790 patent as a whole against the prior art, and cannot comport with § 103 or *Graham*. The Board should therefore deny institution because the proposed grounds are not legally viable. *See, e.g.*, *KSR*, 550 U.S. at 407; *Interconnect Planning*, 774 F.2d at 1136-41.

B. Petitioner Fails to Establish Any Motivation to Combine the Cited References to Achieve the Claimed Method of Treating Ulcerative Colitis

The treatment method of claim 1 of the '790 patent requires a combination of several features: (1) subcutaneously administering (2) to a subject having ulcerative colitis, (3) a specific fixed total body dose (40 mg), (4) of adalimumab, (5) once every 13-15 days, (6) for a time period sufficient to treat ulcerative colitis. The dependent claims add other significant limitations. Claim 3, for example, further requires (7) that the human subject has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody. Claim 4 includes limitations (1)-(7) plus a limitation (8) that the anti-TNFα antibody (adalimumab) is administered for at least 24 weeks. Petitioner must establish that each of these claimed inventions "as a whole" would have been obvious. 35 U.S.C. § 103.

Petitioner contends that Sandborn and Salfeld provide the requisite motivation to combine the teachings of Salfeld with Kempeni and VDP1999. (Pet., 44-45.) In particular, Petitioner asserts that Sandborn establishes that anti-

TNF antibodies are effective in treating both RA and ulcerative colitis using the same doses and dosing regimens, and that Salfeld teaches that D2E7 (adalimumab) can be used to treat both RA and ulcerative colitis with a single dosage range for both indications. (*Id*.) The claimed dosing regimen, however, was not disclosed in the prior art to treat any condition. Therefore, Petitioner relies on the Board's prior decisions on the '135 patent and contends that one would have been motivated to treat ulcerative colitis with the same 40 mg D2E7 every-other-week subcutaneous dosing regimen for RA that the Board found obvious over Kempeni and VDP1999. (*Id*.) Neither Sandborn nor Salfeld, however, supports Petitioner's assertions, which reflect an improper hindsight reconstruction of the challenged claims. (Pet. 4 (relying on the '790 patent's examples to "confirm" a motivation and reasonable expectation of success)); *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).

1. Sandborn Does Not Support a Motivation to Combine

Sandborn does not refer to adalimumab or the use of adalimumab to treat any disease. Rather, Sandborn discusses three other anti-TNFα drugs—etanercept, infliximab, and CDP571—in the context of RA and IBD. (Ex. 1005, 1.) Two of these anti-TNFα drugs, etanercept and CDP571, were ultimately abandoned as IBD

treatments after unsuccessful clinical trials. (Ex. 2015, 6; Ex. 2016, 1092-93; Ex. 2019.) Petitioner fails to address (or even acknowledge) either of these failures. (*E.g.*, Pet., 21-24.)

Petitioner instead asserts that Sandborn reported that there had been no published clinical trials of etanercept for Crohn's disease or ulcerative colitis. (*Id.*, 23 n.19.) This is both irrelevant and misleading because etanercept's failure as a treatment for Crohn's disease was published after Sandborn but *before* the '790 patent's priority date. (*See supra* § II.D.2.) The investigators could not explain why etanercept failed to treat Crohn's disease and proposed that *higher* or more frequent doses than the RA dose may be required. (Ex. 2016, 1092-93.) This failed study, which used the same FDA-approved RA dose (a subcutaneous, fixed 25 mg dose), directly refutes Petitioner's assertion that one of ordinary skill would have been motivated to use the *same* dose for treating both RA and IBD. (*Id.*)

Sandborn's discussion of infliximab also fails to provide a motivation to combine. Infliximab is a different biologic drug than adalimumab, dosed on a *patient-weight basis* (not as a fixed dose) via *intravenous infusion* (not by subcutaneous administration). (Ex. 1020, 29; Ex. 1005, 15.) And by the priority date of the '790 patent, the FDA had approved infliximab only for short-term treatment of Crohn's disease. (Ex. 1020, 22.) In light of these fundamental

differences, infliximab's short-term effectiveness would not have established any motivation to treat ulcerative colitis or Crohn's disease by subcutaneously administering a fixed dose (40 mg) of adalimumab every 13-15 days, or for a period of at least 24 weeks, as claimed.

Moreover, as Sandborn discloses, investigators had only tested single doses of 5, 10, and 20 mg/kg of infliximab in patients with ulcerative colitis. (Ex. 1005, 15.) Those doses were at least 66% greater than the FDA-approved dose for RA (Ex. 1020, 29.) And the study terminated prematurely due to slow patient enrollment, leading the investigators to conclude that the results were not "definitive." (Ex. 1115, 83, 88; Ex. 1005, 15.)

Similarly, after initial clinical testing of infliximab in Crohn's patients, the investigators quickly *abandoned* low doses of infliximab (i.e., 1 mg/kg) in favor of higher doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg, which were selected for the Phase IIb/Phase III placebo-controlled clinical trials of infliximab in Crohn's patients. (*E.g.*, Ex. 1005, 11-12.) As the Examiner correctly recognized during prosecution of the '790 patent, infliximab's 5 mg/kg approved dose for treating Crohn's disease was *66% higher* than its 3 mg/kg approved dose for treating RA. (Ex. 1010, 7.)

Petitioner criticizes the Examiner for focusing on infliximab's FDA-approved RA dose and allegedly "ignoring the prior art teaching that the *higher* doses of 5 and 10 mg/kg were also effective to treat RA and CD." (Pet., 33-34 (emphasis added).) But Petitioner misses the point. That *higher* infliximab doses than the approved RA dosing regimen—66% higher at 5 mg/kg and 233% higher at 10 mg/kg—showed short-term efficacy in both Crohn's disease and RA patients does not mean that one would have expected the *lower* RA dose (3 mg/kg) to also treat Crohn's disease, let alone ulcerative colitis. (*E.g.*, Ex. 1005, 11-12, 15.)

Sandborn's discussion of CDP571 also provides no motivation for achieving the claimed treatment method. Petitioner overstates Sandborn's disclosure, asserting that one would conclude that a 5 mg/kg dose of CDP571 is effective in treating RA and IBD. (Pet., 31-32.) Sandborn merely states that a small fifteen-patient, single dose, Phase I trial in ulcerative colitis patients "suggest[ed] a possible short-term benefit," while recognizing that additional studies were needed to prove efficacy. (Ex. 1005, 15.) Similarly, for Crohn's disease, Sandborn states that the results of a "small" clinical trial "suggested" that a CDP571 single dose of 5 mg/kg "may have" short-term efficacy in Crohn's disease. (*Id.*, 13.) These tentative conclusions hardly support applying these preliminary results to a different biologic drug such as adalimumab, especially where CDP571 (like

infliximab) was dosed on a *patient-weight basis* (not as a fixed dose) via *intravenous* infusion (not by subcutaneous administration). (*Id.*, 13, 15.) Nor does CDP571's "possible short-term benefit" in ulcerative colitis patients suggest the invention of claims 4-6, which require administering adalimumab for at least 24 weeks. (*Id.*, 15.) Furthermore, CDP571 ultimately failed as an IBD treatment when larger trials showed "no discernible benefits" for patients. (Ex. 2019.) Like the etanercept failure in Crohn's disease, Petitioner and its experts omit any mention of this failure.

In view of etanercept's failure and experiences with infliximab, Sandborn would not have motivated one of ordinary skill to select an anti-TNFα RA dosing regimen to treat ulcerative colitis; nor would Sandborn have motivated one to select a fixed-dose, subcutaneous dosing regimen.

2. Salfeld Does Not Support a Motivation to Combine

Salfeld fails to remedy the deficiencies of Sandborn. Salfeld identifies dozens of diseases for which the disclosed anti-TNFα antibodies could theoretically be used. (Ex. 1006, 7:33-8:4, 38:5-42:17.) Salfeld discloses a broad *weight-based* dose range of 0.1-20 mg/kg, without identifying particular doses for any of the listed diseases. (*Id.*, 35:31-33.) And, contrary to Petitioner's assertion that Salfeld's broad, weight-based disclosure of 0.1-20 mg/kg taught that

adalimumab can treat ulcerative colitis with the same dose used to treat RA (*e.g.*, Pet., 26-27), Salfeld also states: "It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated." (Ex. 1006, 35:33-34.) Thus, Salfeld does not supply motivation to treat RA and ulcerative colitis with the same dose of adalimumab.

C. Petitioner Fails to Establish a Reasonable Expectation of Success

Relying again principally on Sandborn and Salfeld, Petitioner asserts that one would have had a reasonable expectation of success of achieving the claimed invention based solely on (1) TNFα being "implicated" in both RA and ulcerative colitis, and (2) extrapolating from the clinical results of *other drugs* to predict adalimumab's efficacy and dosing for treating ulcerative colitis. (Pet., 3, 45-46.) But just as Sandborn and Salfeld do not establish any motivation to combine the prior art to achieve the claimed invention, they similarly fail to establish any reasonable expectation of success. Additional reasons detailed below—including failures in the art and important differences between RA and ulcerative colitis that Petitioner completely ignores—confirm that Petitioner's assertions of a reasonable expectation of success lack merit.

1. The Failures of Etanercept and Other Drugs to Treat IBD Disprove Petitioner's Obviousness Theory

Numerous failures in the art, which Petitioner and its experts do not address, refute Petitioner's position that one would have had an expectation of success in using the same fixed dose of an anti-TNFα drug to treat both RA and ulcerative colitis. *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)).

Before the June 2001 priority date, it was established that no anti-TNFα "class effect" existed for treating IBD. After infliximab exhibited positive results for short-term treatment in Crohn's disease, researchers hypothesized that other drugs that reduce TNFα should have similar effects. (Ex. 2014, 470-71 (identifying infliximab as "cA2 antibody").) Researchers thus tested the small-molecule drug oxpentifylline, a "strong suppressor of TNFα." (*Id.*, 470.) But they found no improvement in Crohn's patients, which cast doubt on the relevance of TNFα for IBD and suggested the involvement of other causal factors. (*Id.*, 470-71, 473.) Moreover, in view of oxpentifylline's failure, it appeared that infliximab's positive results in Crohn's disease could be due to its ability to inhibit inflammation mediators apart from TNFα. (*Id.*, 473.)

Subsequently, investigators also 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 RA would also treat IBD. (Ex. 2016, 1092-93.) Their efforts also failed. (*Id.*) Petitioner does not identify these failed studies, which contradict its theory of a reasonable expectation of success (i.e., that any anti-TNFα drug would treat IBD or that experiences treating RA with an anti-TNFα drug would provide a reasonable expectation of success in treating IBD). (Pet., 23 n.19 (inaccurately suggesting that "there had been no published clinical trials of etanercept for CD or UC"); Ex. 1008, ¶ 38 n.2.) Thus, the failed etanercept and oxpentifylline trials illustrated the unpredictability in the art as of June 2001. (Ex. 2008, 109 (applying anti-TNFα drugs to IBD posed "a challenge for drug development").) Moreover, the art recognized even after the '790 patent's priority date that a biologic drug for RA "may be of limited or no use in" IBD. (*See* Ex. 2026, 2.)

Additional failures of anti-TNFα biologics to treat IBD continued long after the priority date, further confirming the unpredictability in the art and demonstrating that Petitioner's allegations of a reasonable expectation of success lack merit. *See Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.*, IPR2017-01009, Paper 11, at 18 (PTAB 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 (CCPA 1977))).

In 2003, CDP571 was abandoned by its developer after it was shown to have "no discernible benefits" for 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.*) Petitioner misleadingly relies on published preliminary results with CDP571 without acknowledging that the drug ultimately failed and was abandoned for IBD. (*E.g.*, Pet., 22-24, 31-32.)

Between 2001 and 2003, yet another anti-TNFα biologic drug, onercept, failed an IBD clinical trial. (Ex. 2028, 888, 892.) When the results were published years later, the investigators still could not explain why it failed. (*Id.*, 892 (it was "unclear" why onercept was ineffective).) Despite testing four different doses, the investigators postulated that even higher doses of onercept may be necessary. (*Id.*, 893.) Onercept, however, has never been shown to treat either Crohn's disease or ulcerative colitis.

Other biologic drugs, like anakinra and abatacept, have been approved to treat RA while failing to treat IBD, further illustrating unpredictability in the art. (Ex. 2029, 3; Ex. 2031, 3; Ex. 2030, 4; Ex. 2032, 62.) Although these biologic

drugs are not TNFα inhibitors, their failures to treat IBD despite FDA approval for RA show the difficulty and unpredictability of developing IBD treatments. *Cyclobenzaprine*, 676 F.3d at 1081 (failed attempts to make a therapeutically effective product negate a reasonable expectation of success). In fact, in 2005, Petitioner's own expert, Dr. Bjarnason, reported that the etiology of IBD was "inadequately understood" and thus drug therapy was "*empirical* rather than based on sound understanding of the disease mechanism." (Ex. 2021, 179 (emphasis added).)

Accordingly, Petitioner's theory that one would have had a reasonable expectation of success in treating ulcerative colitis using an RA dose of an anti-TNFα drug is unsupported and fails to justify institution. In *Tomlinson*, for example, the CCPA rejected an analogous class-effect obviousness theory. *In re Tomlinson*, 363 F.2d 928, 932-33 (CCPA 1966). The PTO rejected a claim to a stabilized polypropylene composition based on the prior-art use of a stabilizer for a different polymer, polyethylene. *Id.* The PTO asserted that because polyethylene and polypropylene were closely related, one would have expected that a stabilizer useful for one polymer would be useful for the other. *Id.* The court reversed because the art recognized that determining the ability of compounds to stabilize polymers was "quite empirical," rendering the PTO's obviousness theory deficient.

Id. Here, because the art of treating IBD was similarly empirical and unpredictable, as Petitioner's own expert admitted (Ex. 2021, 179), Petitioner's unsupported class-effect theory of obviousness provides no basis to institute an *inter partes* review. *See also In re Mercier*, 515 F.2d 1161, 1167-68 (CCPA 1975) (holding that mere allegations of a known relationship between compounds does not provide the "necessary predictability of success" of using them interchangeably for a specific use).

2. Petitioner Does Not Address the Unknown Etiology of Ulcerative Colitis or the Significant Differences Between Ulcerative Colitis and Rheumatoid Arthritis

Petitioner also ignores the significant differences between RA and ulcerative colitis, which refute its theory that because TNFα is "implicated" in both RA and ulcerative colitis, one would have had a reasonable expectation of success in achieving the claimed invention. (Pet. 45-46.) As noted above, these diseases affect different organs. RA manifests in the joints, whereas ulcerative colitis affects the colon and rectum, a significant part of the largest organ of the immune system, with a large surface area for inflammation to occur. (Ex. 2024, 660; Ex. 2025, 3, 4 (the large intestine, which includes the colon and rectum, may be longer than one and a half meters).) Because these diseases are so different, two distinct medical specialties treat them: rheumatologists treat RA, while gastroenterologists treat

ulcerative colitis. Petitioner's rheumatologist, for example, does not state that he has ever treated ulcerative colitis. (*See* Ex. 1002, ¶¶ 3-16.)

Petitioner cannot bridge these differences by pointing to any common cause of ulcerative colitis and RA. The etiology of ulcerative colitis was unknown in June 2001, as was the etiology of RA. (Ex. 2004, 182; Ex. 2022, 202; Ex. 1008 ¶ 61.) Petitioner tacitly admits the uncertainties in the separate fields of treatments for ulcerative colitis and RA by stating only that TNFα was "implicated" in both diseases, rather than a known cause. (Pet., 45; *see also* Ex. 2005, 296 (deeming it "naïve" to believe that ulcerative colitis resulted from a single inflammatory cause or cytokine).)

Petitioner's reliance on TNFα as the sole commonality between the two diseases also ignores the art's understanding of the significant tissue differences where TNFα is active in each disease. Whereas soluble TNFα is present in the joints in RA (Ex. 2023, 1521), IBD was known to include TNFα in the cells of the mucosa of the intestinal walls (Ex. 1124, 3). The differences between soluble and mucosal TNFα led to the "frustrating" conclusion that the blockade of inflammatory processes, such as TNFα-mediated inflammation, was tissue specific. (Ex. 2026, 2.) As a result of these tissue and organ differences, it was

known that a biologic agent that is highly effective in treating RA "may be of *limited or no use* in" IBD. (*Id.* (emphasis added).)

The diseases also affect different patient populations. Ulcerative colitis typically first appears between the ages of 15 and 30, and affects both genders equally. (Ex. 2003, 3.) RA, by contrast, typically appears in patients aged 35 to 50 with a disproportionate prevalence in females. (*Id.*, 9.)

When a party presents conclusory, oversimplified arguments attempting to extrapolate from a treatment in one disease to another, as Petitioner does here, it is appropriate to deny institution. *Dr. Reddy's Labs., Ltd. v. Galderma Labs., Inc.*, IPR2015-01777, Paper 12, at 18 (PTAB Feb. 16, 2016). In *Dr. Reddy's*, for example, the Board denied institution because one would not have reasonably expected to successfully use a specific dose of a periodontal-disease drug to treat a different condition, rosacea, based on an allegedly common inflammatory pathway. *Id.* at 15-16. These two different conditions affected distinct organ systems: periodontal disease affected the gums in the mouth while rosacea affected the skin. *Id.* at 18. Each disease required a different medical specialty for treatment. *Id.* And the etiology of rosacea was unknown. *Id.* at 16. Thus, the Board found no reasonable expectation of success for applying a treatment from one

disease "to a different disease in a different tissue type." *Id.* at 19-21. The same reasoning supports denying institution here.

The Federal Circuit has similarly rejected conclusory obviousness arguments that attempt to extend a treatment from one disease to another. In a case involving a method of treating osteoporosis, for example, the court rejected broad allegations that one could have used an autoimmune drug to treat osteoporosis, finding the claims nonobvious. *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1337-38 (Fed. Cir. 2010). Significantly, Petitioner cites no case finding a reasonable expectation of success by extrapolating from a treatment in one disease to a different disease.

Petitioner's conclusory analysis fails to account for any of the differences between RA and ulcerative colitis, and therefore cannot establish a reasonable expectation of success.

3. Small-Molecule Drug Dosing Does Not Support Obviousness

Dosing of nonanalogous small-molecule drugs also fails to support any reasonable expectation of success. (Pet., 35-37; Ex. 1008, ¶ 92.) As an initial matter, small-molecule drugs directed to targets other than TNFα are inapposite here because the claims concern a biologic inhibitor of TNFα. Moreover, to the extent any relevance exists, Petitioner's cherry-picked table of small-molecule

drugs (Pet. 35-37) largely contradicts Petitioner's allegation that the same dose was used to treat IBD and RA. For example:

- Petitioner's table shows a wide 7.5-20 mg/day range of prednisolone doses for RA, from which Petitioner selects 20 mg/day as a common dose for ulcerative colitis, ignoring the vast majority of the range where the doses are not the same. (Pet., 35-36.)
- Also, for the prednisolone RA dose range, Petitioner relies on a study investigating a *different drug* (auranofin (gold)) in RA. (Ex. 1056, 7.) Prednisolone was merely permitted as a rescue therapy if gold treatment resulted in "intolerable joint pain and stiffness." (*Id*.)
- For cyclosporine, Petitioner's table shows that *no common dose* was used to treat both RA and ulcerative colitis. (Pet. 36.)
- For flurbiprofen, a nonsteroidal anti-inflammatory drug ("NSAID"), Petitioner omits that its underlying reference describes the drug as "unlikely to prove a useful alternative to conventional [ulcerative colitis] treatment." (Ex. 1064, 12.) In fact, Petitioner's reference questioned the rationale for continuing any further trials with flurbiprofen in ulcerative colitis. (*Id*.) For RA, by contrast, flurbiprofen was reported as a powerful anti-inflammatory drug.

(Ex. 1063, 6.) Petitioner also omits Dr. Bjarnason's testimony that using NSAIDs to treat IBD had been "discontinued," and that NSAIDs may exacerbate, rather than treat, IBD. (Ex. 1008, ¶ 97.)

- For penicillamine, Petitioner does not even allege that it has been used to treat IBD. (Pet., 36-37.) Instead, Petitioner's table indicates that while up to 1000-1800 mg/day doses were used for RA, a dose of 750 mg/day was tested in patients with a different disease, primary sclerosing cholangitis ("PSC"). (Pet., 36-37.) Thus the same doses were not used in RA and PSC, let alone RA and UC. Furthermore, Petitioner omits that penicillamine "had *no beneficial effect* on the course, complications, and survival of patients with PSC." (Ex. 1079, 7 (emphasis added).)
- For methotrexate, Petitioner relies on early pilot-study results (Pet., 37), ignoring later publications closer to the priority date that recognized contradictory results in Crohn's disease. (*Compare* Ex. 1082, 3 (reporting "encouraging" results from a pilot study in 1989), *with* Ex. 2008, 104 (cautioning in 2000 that methotrexate should only be considered "experimental" due to contradictory reports).)

Furthermore, Petitioner's table selectively omits examples of small-molecule drugs that failed to treat both IBD and RA. Gold, for example, was a common RA treatment at the time of invention. (Ex. 2033, 10-11.) Yet it failed to show efficacy in—and worse, could exacerbate—IBD. As early as 1995, cases of gold therapy-induced ulcerative colitis had been reported. (Ex. 2020, 758.) Likewise, as Petitioner's expert concedes, NSAIDs were and continue to be a mainstay treatment for RA. (Ex. 1008, ¶ 96; *see also* Ex. 2033, 10-11, 14 (identifying NSAIDs, including indomethacin, as a recommended treatment for mild, moderate, and severe RA).) In IBD, on the other hand, NSAIDs may exacerbate, rather than treat it. (Ex. 1008, ¶ 97; Ex. 1066, 3 (indomethacin resulted in no improvement or worsening of ulcerative colitis).)

In summary, no asserted prior-art reference disclosed any clinical evaluation of adalimumab in ulcerative colitis or suggested the claimed dosing regimen for ulcerative colitis. The state of the art at the time of the invention demonstrated that anti-TNFα therapies had failed in IBD despite showing efficacy in RA. Petitioner ignores the reported failures in the art, which contradict its anti-TNFα class-effect theory. Moreover, there were no FDA-approved biologic anti-TNFα drugs for ulcerative colitis, as infliximab trials had generated only inconclusive results. For Crohn's disease, infliximab was approved for short-term treatment only and used

weight-based dosing administered via intravenous infusion rather than a fixed dose administered by subcutaneous injection, as claimed. By contrast, the only prior-art anti-TNFα biologic drug that had been tested in IBD using a fixed dose and subcutaneous administration (etanercept) failed for lack of efficacy. Because Petitioner has failed to establish that one would have had any reason or motivation to combine the cited references with a reasonable expectation of success, it has not met its burden for any challenged claim, and institution should be denied.

D. Petitioner Has Not Established a Reasonable Likelihood of Prevailing for Dependent Claims 3-6

1. Petitioner Fails to Address the Specific Patient Population Recited in Dependent Claims 3 and 4

Dependent claim 3 recites the method of claim 1, wherein the human subject has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody. Dependent claim 4 incorporates the same limitation. Petitioner does not address this specific patient population, offering no analysis of how these patients differ from patients who have not previously had an unwanted immune response to a chimeric or humanized anti-TNFα antibody. Petitioner likewise cites no reference that suggests using adalimumab in this patient population. Petitioner therefore cannot establish that one of ordinary skill would have had any motivation or a reasonable expectation of success in treating such a patient using the claimed

dosing regimen, and the Board should deny institution on claims 3 and 4 for this additional reason. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006) (motivation and reasonable expectation of success are considered only if all the claim elements are found in a combination of prior-art references).

Petitioner relies solely on Salfeld to support its obviousness argument for claim 3. (Pet., 46, 63 (citing Ex. 1006).) But Salfeld does not suggest using adalimumab to treat ulcerative colitis in patients who *previously* had an unwanted immune response to a chimeric or humanized anti-TNFα antibody. Rather, Salfeld makes the unremarkable and irrelevant statement that because "chimeric and humanized antibodies still retain some murine sequences, they still may elicit an unwanted immune reaction, the human anti-chimeric antibody (HACA) reaction." (Ex. 1006, 4:8-13.) Salfeld then states that an entirely human anti-TNFα antibody would be preferred since such an antibody should not elicit the HAMA (human anti-mouse antibody) reaction. (*Id.*, 4:14-17.) But Salfeld nowhere suggests using an entirely human anti-TNFα antibody in a patient *after* the patient has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody, as claims 3 and 4 require.

Petitioner's own references undercut its argument. Patients who had received monoclonal antibody treatment (regardless of whether the patient

experienced an unwanted immune response) were regularly excluded from clinical trials of anti-TNFα antibodies. (Ex. 1052, 6 (patients who previously received treatment with murine, chimeric, or humanized monoclonal antibodies were excluded from an IBD study using infliximab); Ex. 1023, 4 (patients who received prior anti-TNFα therapies were excluded from an IBD study using CDP571); *see also* Ex. 1016, 8 (patients with a history of treatment with any murine, chimeric, or humanized monoclonal antibody were excluded from an RA study using infliximab).)

In similar circumstances, the Board has denied institution where the challenged claims were directed to a method of treating a specific patient population or characteristic, and the petitioner cited no prior art that disclosed or suggested treating the claimed patient population or characteristic. In *Roxane Laboratories*, for example, the challenged claims recited a method of treating neuroendocrine tumors by administering everolimus after failure of cytotoxic chemotherapy. *Roxane Labs., Inc. v. Novartis AG*, IPR2016-01461, Paper 9, at 3 (PTAB Feb. 13, 2017). The cited references, however, did not suggest treatment after failure of cytotoxic chemotherapy. *Id.* at 9. The petitioner argued that the reference *inferred* treatment after failure of cytotoxic chemotherapy, based on unsupported expert testimony. *Id.* The Board concluded that the petitioner had not

established a reasonable likelihood of prevailing and denied institution. *Id.* at 10; *see also Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01094, Paper 12, at 15-16 (PTAB Oct. 2, 2017) (denying institution where claims recited a method of treating diffuse large-cell lymphoma in patients having bulky disease, but no references disclosed treating patients having bulky disease). Similarly, here, Petitioner relies only on Salfeld, but Salfeld does not suggest using adalimumab in a patient *after* the patient has had an unwanted immune response to a chimeric or humanized anti-TNFα antibody.

Petitioner's IBD expert, Dr. Bjarnason, offers a one-paragraph opinion that Salfeld supposedly provides motivation and an expectation of success to practice claim 3, but he cites no support. (Ex. 1008, ¶ 131.) Like the expert testimony in *Roxane*, Dr. Bjarnason's unsupported and conclusory testimony is entitled to no weight. 37 C.F.R. § 42.65(a); *Roxane*, IPR2016-01461, Paper 9, at 10 ("As the Board has stated repeatedly, conclusory expert testimony is entitled to little or no weight."). Moreover, Petitioner does not discuss or cite Dr. Bjarnason's testimony on claim 3 in the Petition. (*E.g.*, Pet., 46, 63.) Thus, the Board should not consider it. *Conopco, Inc. v. Procter & Gamble Co.*, IPR2013-00510, Paper 9, at 8-9 (PTAB Feb. 12, 2014) (declining to "consider information presented in a supporting

declaration, but not discussed in a petition"). The Board should therefore deny institution as to claims 3 and 4.

2. Petitioner Fails to Address the "At Least 24 Weeks" Treatment Period Recited in Dependent Claims 4-6

Dependent claims 4-6 define the methods of claims 3, 2, and 1, respectively, wherein the anti-TNFα antibody is administered for a period of at least 24 weeks. Petitioner cites no reference that suggests administering adalimumab to treat ulcerative colitis using the claimed dosing regimen for at least 24 weeks. Moreover, dependent claim 4 recites not only the "at least 24 weeks" limitation but also requires the patient population limitation of claim 3, and all of the limitations of claim 1. Petitioner cites no prior art suggesting this novel combination of claim elements.

Petitioner relies on *infliximab* studies disclosed in Sandborn as evidence that the claimed *adalimumab* dosing regimen for at least 24 weeks would have been obvious. (Pet., 47-48; *id.*, 63; Ex. 1008, ¶ 133.) But as discussed above, experience with infliximab or other anti-TNFα drugs would not have allowed one of ordinary skill to predict whether adalimumab would successfully treat ulcerative colitis using the claimed dosing regimen. (*See supra* §§ IV.B.1, C.1.) Moreover, Petitioner fails to show that, in 2001, one would have expected success by administering *infliximab* for a period of at least 24 weeks. Infliximab had only

been tested in ulcerative colitis patients with single doses. (Ex. 1005, 15.) And the FDA-approved infliximab dose for treating moderately to severely active Crohn's disease directed only an initial infusion, with no repeat dosing, warning that "[**t**]**he safety and efficacy of therapy continued beyond a single dose have not been established**." (Ex. 1020, 22, 29 (emphasis in original).) In patients with fistulizing Crohn's disease, the label included additional doses only at weeks 2 and 6—again emphasizing that "[**t**]**he safety and efficacy of therapy continued beyond three doses have not been established**." (*Id.*, 22, 29 (emphasis in original).) In fact, it was thought that long-term infliximab use could result in loss of efficacy. (Ex. 1090, 26.) Thus, in June 2001, the safety and efficacy of long-term infliximab use was not established. Rather, it was believed that infliximab was only "effective for *short-term treatment* of patients with moderately to severely active Crohn's disease." (Ex. 1023, 3 (emphasis added).)

The early infliximab studies reported in Sandborn do not establish otherwise. In the ulcerative colitis trial, patients received only a single dose. (Ex. 1005, 15.) Neither the appropriate dose nor the appropriate dosing intervals had been determined for ulcerative colitis. (*Id.*) In the first Crohn's disease study that Petitioner relies on, infliximab was administered at weeks 0, 12, 20, 28, and 36, but "because the confidence intervals were wide and the life-table analyses were not

statistically significant, the results were not definitive." (*Id.*, 12-13 ("The failure to achieve statistical significance due to wide confidence intervals and questions regarding concomitant medications led the FDA to withhold a maintenance claim for infliximab.").) The second Crohn's disease infliximab study relied on by Petitioner (Pet., 47) was "a small case series" that reported that infliximab may be useful in closing nonhealed perineal wounds in Crohn's disease after proctocolectomy. (Ex. 1005, 12.) The study involved only two patients. (Ex. 1022, 2-4.) Each patient received a "single" infliximab infusion and, in an effort to heal persistent perineal wounds, received one or two additional infusions several months later, at no fixed or specific interval, contrary to the claimed every-other-week dosing regimen for at least 24 weeks. (*Id.*)

Both Sandborn and the FDA label show that repeat dosing had not been attempted in ulcerative colitis, and that the safety and efficacy of repeat infliximab dosing beyond 6 weeks in Crohn's disease had not been established. Thus, experience with infliximab would not have motivated one of ordinary skill to treat ulcerative colitis by administering adalimumab every other week for at least 24 weeks or have provided a reasonable expectation of success in doing so. Having identified no prior art suggesting the "at least 24 weeks" limitation, Petitioner cannot establish a reasonable likelihood of prevailing as to claims 4-6, and

institution should be denied on those claims for this additional reason. *Hopkins Mfg. Corp. v. Cequent Performance Prods., Inc.*, IPR2015-00616, Paper 9, at 7 (PTAB Aug. 17, 2015) (citing 37 C.F.R. § 42.104(b)(4)).

V. Conclusion

Petitioner has not established a reasonable likelihood of prevailing as to any challenged claim of the '790 patent. The Board should therefore deny institution of the Petition.

Respectfully submitted,

Dated: December 13, 2017

By: /*Michael J. Flibbert*/
Michael J. Flibbert, Reg. No. 33,234
William B. Raich, Reg. No. 54,386
Maureen D. Queler, Reg. No. 61,879
Pier D. DeRoo, Reg. No. 69,340
Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP

Counsel for Patent Owner
AbbVie Biotechnology Ltd

CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** contains 12,268 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: December 13, 2017 By: /*Michael J. Flibbert*/
Michael J. Flibbert, Reg. No. 33,234

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and Exhibits 2001-2026 and 2028-2034 were served electronically via email on December 13, 2017, in their entirety on the following:

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

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

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

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

Petitioner has consented to service by email.

Date: December 13, 2017 By: /William Esper/
William Esper
Legal Assistant

Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP