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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 IPR2017-01987
Patent No. 8,911,737

PATENT OWNER'S PRELIMINARY RESPONSE

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I. Introduction

AbbVie's U.S. Patent No. 8,911,737 ("the '737 patent") is directed to methods of treating Crohn's disease with the biologic drug HUMIRA® (adalimumab). Claim 1 requires subcutaneously administering to a human subject having Crohn's disease 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 Crohn's disease. 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 Crohn's disease. Instead of comparing the challenged claims to the prior art, Petitioner asserts that the "only difference between claim 1 of the '737 patent and claim 1 of the '135 patent invalidated by the Board, is that 'Crohn's disease' is substituted for 'RA.'" (Pet., 16; *see also id.*, 2, 25 (same).) Petitioner thus premises its obviousness analysis of the '737 patent on the alleged obviousness of the '135 patent but never analyzes the '737 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 Crohn's disease, the use of adalimumab to treat Crohn's disease, or the '737 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. Attempts to develop new treatments for Crohn's disease have frequently failed. Before the June 2001 priority date, for example, the biologic TNFα inhibitor, etanercept (Enbrel®), failed

to treat Crohn's disease. (*See* Ex. 2015, 6.)[1] 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 Crohn's disease. Petitioner not only ignores this critically important prior-art failure, it inaccurately suggests that "there had been no published clinical trials of etanercept for Crohn's or UC [ulcerative colitis]." (Pet., 22 n.17.) Etanercept's failure and other Crohn's treatment failures discussed below establish a high level of unpredictability in the art and contradict Petitioner's hypothesis of an anti-TNFα class effect in Crohn's disease.

Importantly, no asserted prior art discloses any clinical testing of adalimumab in Crohn's patients at any dose. In fact, only one anti-TNFα therapy, infliximab, was approved to treat Crohn's disease as of the priority date. But infliximab's approved dose for short-term treatment of Crohn's disease was 66% *higher* than its approved RA dose. And infliximab was administered via intravenous infusion (not subcutaneous injection) using weight-based dosing (not a

[1] Citations refer to the original page numbering of each exhibit except for references that have been stamped with page numbers. Citations to such references refer to the stamped-on page numbers.

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 Crohn's disease.

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 Crohn's disease. Instead, Petitioner relies on early *infliximab* studies

to assert that the claimed *adalimumab* dosing regimen would have been obvious. But, in 2001, 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 ’737 Patent

The ’737 patent is directed to novel methods of treating Crohn’s disease using the biologic drug adalimumab, the active ingredient in HUMIRA®. Many thousands of Crohn’s disease 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 Crohn’s disease and ulcerative colitis. (Ex. 1001, 3:42-52, 27:21-25.) The ’737 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 ’737 patent claims are directed to the disclosed methods of treating Crohn’s disease 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 Crohn’s disease comprising subcutaneously administering to a human subject having Crohn’s disease a total body dose of 40 mg of

adalimumab once every 13-15 days for a time period sufficient to treat Crohn's disease.

- 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 '737 Patent

The '737 patent application was filed on April 18, 2014, as a continuation of application 10/163,657 (now the '135 patent). (Ex. 2006, 1, 6.) On September 10, 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 Crohn's disease, not RA. (*Id.*, 6.)

On September 23, 2014, 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 Crohn's disease 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, 6-7.) He noted that one also would have considered experience treating Crohn's disease with anti-TNFα antibodies in general. (*Id.*, 7.)

At the time, infliximab was approved by the FDA for the short-term treatment of Crohn's disease and was the only anti-TNFα antibody known to show efficacy for Crohn's disease. (*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.*) Further, although a person of ordinary skill may have "suspected" that an infliximab dose less than the FDA-approved dose "could be useful" to treat Crohn's disease, "it would not have been clear to the ordinarily skilled artisan precisely how much less than the FDA approved dose of infliximab could be administered to effectively treat Crohn's disease." (*Id.*)

The Examiner thus concluded that one of ordinary skill at the time of the invention would have thought that treating Crohn's disease with adalimumab

would likely require administering more adalimumab, potentially as much as 66% more than required to treat RA. (*Id.*)

C. Crohn's Disease Was a Chronic Inflammatory Condition of Unknown Etiology

Crohn's disease and another condition, ulcerative colitis, are related chronic inflammatory disorders of the intestinal tract, which together are known as inflammatory bowel disease ("IBD").[2] (Ex. 2001, 47.)

Crohn's disease primarily affects the intestinal tract, presenting with mucosal inflammation of the intestinal walls. (*Id.*, 33; Ex. 2009, I114-15.) It 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 Crohn's disease include diarrhea, severe abdominal pain, weight loss, and malnutrition. (*Id.*, 7-8.) Complications may include damage to the intestinal tissues, including bowel obstructions, strictures, lesions, and ulcers, as well as formation of fistulas (abnormal connections or passageways) between parts of the intestine, or between the intestine and the skin, the bladder, or the stomach. (*Id.*) These symptoms range from mild to severe, on a patient-by-patient basis, and can depend on the part of the gastrointestinal tract affected. (*Id.*)

[2] Petitioner has also challenged AbbVie's U.S. Patent No. 8,974,790, which is directed to ulcerative colitis, in co-pending IPR2017-01988.

The etiology of Crohn's disease was unknown in 2001. (Ex. 2001, 33-34; Ex. 2002, 7.) Manifestations of Crohn's disease vary widely because, among other reasons, it can affect any area of the intestinal tract. (Ex. 2003, 5; Ex. 2007, 361.) 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 Crohn's disease, 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 Crohn's disease, 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 Crohn's disease (Ex. 2001, 34), researchers found it "naïve" to conclude that Crohn's disease resulted from a single inflammatory cause or cytokine. (Ex. 2027, 4; Ex. 2002, 7.)

D. Crohn's Disease Was Difficult to Treat and Drug Development Efforts Often Failed

In 2001, Crohn's disease 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. (Ex. 2001,

65.) While these therapies might maintain remission,[3] they had little or no ability to induce remission of active Crohn's disease. (*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 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 Crohn's disease 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

[3] In clinical trials, for example, remission has been defined by a patient's Crohn's disease activity index ("CDAI") score falling below a particular threshold (e.g., 150 points). (Ex. 1005, 12; Ex. 2016, 1092.)

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 Crohn's disease 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 Crohn's disease and pose "a challenge for drug development.").) The FDA had approved only one anti-TNFα drug, infliximab, for the short-term treatment of Crohn's disease. (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.)

In June 2001, the safety and efficacy of long-term infliximab use had not been established, and the FDA had not approved infliximab for long-term therapy in Crohn's disease. (Ex. 1005, 12-13; Ex. 2008, 107.) 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 Crohn's disease. While they attempted to develop laboratory techniques to correlate Crohn's disease activity with TNFα levels, the results were disappointing. For example, one study 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 Crohn's disease activity and TNFα levels. (*Id.*, 234-35.) By 2001, attempts to develop cytokine-based correlations with 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 Crohn's disease. 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 Crohn's Disease

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." (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 Crohn's disease. (*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 Crohn's disease.

2. Etanercept, Another Anti-TNFα Drug, Failed to Treat Crohn's Disease

Petitioner and its declarants rely on the purported absence of Crohn's disease clinical trial results for etanercept. (Pet. 22, n.17; 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. (*E.g.*, 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 Crohn's disease, making it difficult to compare anti-TNFα agents. (*See* Ex. 2018, S75.) Further, clinical trials seeking to demonstrate an anti-TNFα class effect had failed, including the failure of the FDA-approved *RA dose* of etanercept to treat Crohn's disease.

3. After the Priority Date, Anti-TNFα Drugs Continued to Fail in Clinical Trials for Crohn's Disease

In 2003, the art recognized the failure of another biologic anti-TNFα drug, the humanized monoclonal antibody CDP571. (Ex. 2019.) CDP571 was first tested in a "small" Phase IIa trial. (Ex. 1005, 13.) Sandborn characterizes the results of this 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.) 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 at any dose.

These post-priority date failures of anti-TNFα drugs in Crohn's disease 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 Crohn's Disease 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 Crohn's disease, and that both diseases have different treatment requirements.

RA and Crohn's disease affect different organs. RA is an inflammatory disease of the joints. (Ex. 2023, 1521.) Crohn's disease, by contrast, affects 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.) Combined, the large and small intestines may be longer than eight meters, presenting a vast surface area where Crohn's disease may occur. (Ex. 2025, 3-4.)

The tissues where TNFα is present also differ. In RA, soluble TNFα is present in the synovial fluid of the joints. (Ex. 2023, 1521.) Crohn's disease, by contrast, was understood to include TNFα in the inflamed mucosal tissues of the intestine. (Ex. 2014, 473.) 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 Crohn's disease." (*Id.*)

The diseases also affect different patient populations. Crohn's disease typically first appears in young adulthood and disproportionately affects males. (Ex. 2003, 3 (1.8:1 male-to-female ratio for Crohn's disease).) 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 Crohn's disease. 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 Crohn's disease, 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 too has failed to show efficacy in Crohn's disease. (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 Crohn's disease, as well as the differences in patient demographics, affected organ systems, and TNFα-involved

tissues, illustrate that RA and Crohn's disease 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 Crohn's disease 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 '737 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 Crohn's disease, by contrast, 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, 12-13.) 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 Crohn's disease. (Pet., 14.) 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 Crohn's disease 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 Crohn's disease patients. Such a physician would have an MD, a gastroenterology fellowship, and at least three years of experience treating Crohn's disease 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 Crohn's disease, 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 Crohn's disease. (*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., 25-53, 58-64.) 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 '737 patent;
- Sandborn (Ex. 1005) does not disclose adalimumab, using adalimumab to treat Crohn's disease, any dosing regimen for adalimumab to treat Crohn's disease, or any subcutaneous treatment of Crohn's disease as required by each claim of the '737 patent;
- Kempeni (Ex. 1004) does not disclose fixed dosing for any disease, using adalimumab to treat Crohn's disease, or any dosing regimen for adalimumab to treat Crohn's disease as required by each claim of the '737 patent;
- VDP1999 (Ex. 1003), VDP2000 (Ex. 1107), and Rau (Ex. 1017) do not disclose using adalimumab to treat Crohn's disease or any dosing regimen for adalimumab to treat Crohn's disease as required by each claim of the '737 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 ’737 Patent Claims as a Whole

Instead of presenting a complete *Graham* obviousness analysis of the ’737 patent claims as a whole, for both of its proposed grounds Petitioner improperly conflates its obviousness analysis of the ’737 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 Crohn’s disease. (*E.g.*, Pet., 25-26, 39-45 (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 ’737 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 ’737 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 Crohn's disease using the '135 patent's allegedly obvious RA dosing regimen. (*See*, *e.g.*, Ex. 1008, ¶¶ 109-11 (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 Crohn's disease 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 '737 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 '737 patent's different claimed method of using adalimumab to treat Crohn's disease, 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 Crohn's disease, the use of adalimumab to treat Crohn's disease, or the '737 patent.[4]

[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.

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 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.

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filed Dec. 29, 2015); *AbbVie Biotechnology Ltd v. Boehringer Ingelheim Int'l GmbH*, No. 17-2363 (Fed. Cir. filed Dec. 29, 2015).

Id. at 1141. By cobbling together the alleged obviousness of the ’135 patent with its incomplete analysis of the ’737 patent’s claimed inventions (Pet., 2, 16, 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.*, 25-53.) Nor does Petitioner offer expert testimony that connects its bifurcated arguments. This fractured legal analysis fails to analyze the claimed subject matter of the ’737 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 Crohn’s Disease

The treatment method of claim 1 of the ’737 patent requires a combination of several features: (1) subcutaneously administering (2) to a subject having Crohn’s disease, (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 Crohn's disease. 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., 45-46.) In particular, Petitioner asserts that Sandborn establishes that anti-TNF antibodies are effective in treating both RA and Crohn's disease using the same doses and dosing regimens, and that Salfeld teaches that D2E7 (adalimumab) can be used to treat both RA and Crohn's disease 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 Crohn's disease 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.

3-4 (relying on the '737 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, 11-15.) Two of these anti-TNFα drugs, etanercept and CDP571, were ultimately abandoned as Crohn's disease 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., 22-24.)

Petitioner instead asserts that Sandborn reported that there had been no published clinical trials of etanercept for Crohn's disease or ulcerative colitis. (*Id*., 22 n.17.) This is both irrelevant and misleading because etanercept's failure as a treatment for Crohn's disease was published after Sandborn but *before* the '737 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 Crohn's disease. (*Id.*)

Sandborn's discussion of infliximab also fails to provide motivation. 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.) And by the priority date of the '737 patent, the FDA had approved infliximab only for short-term treatment of Crohn's disease. (*Id.*, 22.) In light of these fundamental differences, infliximab's short-term effectiveness in treating Crohn's disease would not have established any motivation to treat 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, after initial clinical testing of infliximab in Crohn's disease patients, 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 '737 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 Crohn's." (Pet., 35 (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. (*E.g.*, Ex. 1005, 11-12.)

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 Crohn's disease and RA. (Pet., 33.) Sandborn merely 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. (Ex. 1005, 13.) This tentative conclusion hardly supports 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.*, 10, 13.) Nor does CDP571's potential

"short-term efficacy" suggest the invention of claims 4-6, which require administering adalimumab for at least 24 weeks. (*Id.*, 13.) Furthermore, CDP571 ultimately failed as a Crohn's disease 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 Crohn's disease; 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 Crohn's disease 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 Crohn's disease 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 Crohn's disease, and (2) extrapolating from the clinical results of *other drugs* to predict adalimumab's efficacy and dosing for treating Crohn's disease. (Pet., 3, 46-47.) 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 Crohn's disease 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 Crohn's Disease 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 Crohn's disease. *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 Crohn's disease. 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.*) But they found no improvement in Crohn's patients, which cast doubt on the relevance of TNFα for Crohn's disease 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 treat Crohn's disease. (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 Crohn's disease or that experiences treating RA with an anti-TNFα drug would provide a reasonable expectation of success in treating

Crohn's disease). (Pet., 22 n.17 (inaccurately suggesting that "there had been no published clinical trials of etanercept for Crohn's 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 Crohn's disease posed "a challenge for drug development").) Moreover, the art recognized even after the '737 patent's priority date that a biologic drug for RA "may be of limited or no use in Crohn's disease." (Ex. 2026, 2.)

Additional failures of anti-TNFα biologics to treat Crohn's disease 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 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. (*E.g.*, Pet., 23-24, 33-34.)

Between 2001 and 2003, yet another anti-TNFα biologic drug, onercept, failed a clinical trial in Crohn's disease. (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 for Crohn's disease. (*Id.*, 893.) Onercept, however, has never been shown to treat Crohn's disease.

Other biologic drugs, like anakinra and abatacept, have been approved to treat RA while failing to treat Crohn's disease, 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 Crohn's disease despite FDA approval for RA show the difficulty and unpredictability of developing Crohn's disease 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 Crohn's disease 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 Crohn's disease 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 Crohn's Disease or the Significant Differences Between Crohn's Disease and Rheumatoid Arthritis

Petitioner also ignores the significant differences between RA and Crohn's disease, which refute its theory that because TNFα is "implicated" in both RA and

Crohn's disease, one would have had a reasonable expectation of success in achieving the claimed invention. (Pet. 46.) As noted above, these diseases affect different organs. RA manifests in the joints, whereas Crohn's disease affects the intestines—the largest organ of the immune system with a vast surface area for inflammation to occur. (Ex. 2024, 660; Ex. 2025, 3-4 (the large and small intestines may be longer than eight meters in total length).) Because these diseases are so different, two distinct medical specialties treat them: rheumatologists treat RA, while gastroenterologists treat Crohn's disease. Petitioner's rheumatologist, for example, does not state that he has ever treated Crohn's disease. (*See* Ex. 1002 ¶¶ 3-16.)

Petitioner cannot bridge these differences by pointing to any common cause of Crohn's disease and RA. The etiology of Crohn's disease was unknown in June 2001, as was the etiology of RA. (Ex. 2001, 33-34; Ex. 2022, 202; Ex. 1008 ¶ 58.) Petitioner tacitly admits the uncertainties in the separate fields of treatments for Crohn's disease and RA by stating only that TNFα was "implicated" in both diseases, rather than a known cause. (Pet., 46; *see also* Ex. 2027, 4 (deeming it "naïve" to believe that Crohn's disease resulted from a single inflammatory cytokine, TNFα).)

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), Crohn's disease was known to include TNFα in the cells of the mucosa of the intestinal walls (Ex. 2014, 473). 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 Crohn's disease." (*Id.* (emphasis added).)

The diseases also affect different patient populations. Crohn's disease typically first appears between the ages of 15 and 30, and disproportionately affects males. (Ex. 2003, 3.) RA, by contrast, typically appears in patients aged 35 to 50 with a high 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 Crohn's disease, 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., 37-38; Ex. 1008, 37-38.) 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. 37-38) largely contradicts Petitioner's allegation that the same dose was used to treat Crohn's disease 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., 37.)
- 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. 37.)
- 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, ¶ 86.)

- For penicillamine, Petitioner does not even allege that it has been used to treat IBD. (Pet., 38.) 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., 38.) Thus the same doses were not used in RA and PSC, let alone RA and Crohn's disease. 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., 38), 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, ¶ 85; 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, ¶ 86; 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 Crohn's disease or suggested the claimed dosing regimen for Crohn's disease. The state of the art at the time of the invention demonstrated that anti-TNFα therapies other than infliximab had failed in Crohn's disease despite showing efficacy in RA. Petitioner ignores these failures, which contradict its anti-TNFα class-effect theory. Moreover, the only approved anti-TNFα drug for treating 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 Crohn's disease 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., 47, 63-64 (citing Ex. 1006).) But Salfeld does not suggest using adalimumab to treat Crohn's disease 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 a Crohn's disease study using infliximab); Ex. 1023, 4 (patients who received prior anti-TNFα therapies were excluded from a Crohn's disease 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, ¶ 118.) 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., 47, 63-64.) 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

Crohn's disease 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 two early *infliximab* studies disclosed in Sandborn as evidence that the claimed *adalimumab* dosing regimen for at least 24 weeks would have been obvious. (Pet., 48; *id.*, 64; Ex. 1008, ¶ 120.) 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 Crohn's disease 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. In 2001, 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 two early infliximab studies reported in Sandborn do not establish otherwise. In the first 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." (Ex. 1005, 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 infliximab study relied on by Petitioner (Pet., 48) 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 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 Crohn's disease 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 '737 patent. The Board should therefore deny institution of the Petition.

Respectfully submitted,

Dated: December 13, 2017

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** contains 11,844 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*/
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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and Exhibits 2001-2033 were served electronically via email on December 13, 2017, in their entirety on the following:

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