UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ, INC.,
Petitioner

v.

GENENTECH, INC.,
Patent Owner

Case IPR2017-02036
Patent 7,976,838 B2

PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107

LIST OF EXHIBITS

Exhibit[1]	Description
Ex.2001	International Application Publication No. WO 00/74718 A1 to David M. Goldberg *et al.* ("Goldenberg")
Ex.2002	Boardside "Chat with the Chief" presentation by Chief Administrative Patent Judge David P. Ruschke, titled "An Analysis of Multiple Petitions in AIA Trials," dated Oct. 24 2017
Ex.2003	J.K. Jenkins & K.J. Hardy, *Biological Modifier Therapy for the Treatment of Rheumatoid Arthritis*, 323(4) Am. J. Med. Sci. 197-205 (2002) ("Jenkins")
Ex.2004	Rituxan® (Rituximab) Prescribing Information dated February 2010
Ex.2005	Stanley B. Cohen et al., *Rituximab for Rheumatoid Arthritis Refractory to Anti-Tumor Necrosis Factor Therapy*, 54(9) Arthritis & Rheumatism, 2793-2806 (Sept. 2006) ("Cohen")
Ex.2006	"Arthritis Foundation Statement on Rituximab for Rheumatoid Arthritis" submitted, on May 10, 2012, by Genentech, Inc. to the European Patent Office as an exhibit (D61) to an appeal in the Opposition Proceedings in EP 1613350
Ex.2007	Boardside Chat presentation by Judges Lora Green & Brian McNamara, titled "Best Practices For Proving A Document Is A Printed Publication," dated December 7, 2017
Ex.2008	Declaration of Megan Raymond
Ex.2009	Peter McLaughlin et al., *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program*, 16(8) J. of Clinical Oncology, 2825-33 (Aug. 1998) ("McLaughlin")

[1] Consistent with Petitioner's citation format, citations herein are to the original page numbers.

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Patent Owner Genentech, Inc. ("Genentech") submits this 37 C.F.R. § 42.107[2] Patent Owner Preliminary Response ("POPR") to the above-captioned Petition ("Petition" or "Pet."), which should be denied for failure to show a reasonable likelihood of prevailing on any asserted ground.

I. Introduction

The present Petition is one of an onslaught of *six petitions* filed against U.S. Patent No. 7,976,838 (the "'838"), together with four others filed against a patent identified by one '838 petitioner as "related." Three of the six '838 IPRs are currently pending as the latest wave of a systematic attempt to invalidate claims 1–14 ("the Challenged Claims") through iterative attacks, each making minor adjustments from the last in hopes of finding a challenge that will yield a different result. All six petitions, including a second petition by this same Petitioner, rely on overlapping art and arguments, including those already rejected by the original Examiner and this Board. Indeed, Petitioner here fails to present *any* art or argument that is not the same or substantially the same as those previously considered by the Office. But Petitioner never acknowledges this overlap, let alone explains how its art or arguments are unique, or why the Board should devote its finite resources to another do-over. This alone is fatal to the Petition and

[2] Unless otherwise stated, all emphasis/annotations added, and all statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates.

the Board should deny institution under §§ 314(a) and 325(d) for this repetitive attack of the same patent—a problem that has been repeatedly criticized as improper "gang tackling."

Even if Petitioner's rehashed arguments were considered on their merits, Petitioner fails to meet its burden. Petitioner fails to establish that various of its cited references (Edwards 2001 and De Vita 2001) are, in fact, prior art printed publications. And even if they were, Petitioner's cited art fails to teach or suggest key limitations of every Challenged Claim, including, *e.g.*, the treatment of TNFα-inhibitor inadequate-responders ("TNFIRs") with two intravenous doses of 1000 mg of an antibody that binds to CD20 (claims 1, 2, and 4–7) or rituximab (claims 3, 8, and 9–14), and the specific clinical responses required by claims 2-7 and 10–14, namely an "ACR50 response," an "ACR70 response," and "no erosive progression." For at least these reasons, the Petition should be denied.

II. The Challenged Claims are Directed to a Non-Obvious Invention

Rheumatoid arthritis ("RA") is an autoimmune disorder. RA patients "suffer a chronic course of disease that, even with therapy, may result in progressive joint destruction, deformity, disability and even premature death." Ex.1001 4:4-7.

The goals of RA therapy are preventing or controlling joint damage, preventing loss of function, and decreasing pain. *Id*. 4:8-10. While RA patients are often initially treated with nonsteroidal anti-inflammatory drugs ("NSAIDs"),

glucocorticoids, and/or low-dose prednisone, most patients are treated with synthetic disease-modifying antirheumatic drugs ("DMARDs") such as methotrexate or cyclosporine within three months of diagnosis. *Id*. 4:11-24. Prior to the claimed invention, if patients failed synthetic DMARDs, they could be treated with biologic drugs that inhibited tumor necrosis factor alpha ("TNFα") including etanercept (ENBREL®), infliximab (REMICADE®), and adalimumab (HUMIRA™). *Id*. 4:25-56. However, not all RA patients respond to TNFα-inhibitors which also have side-effects including infections, sepsis, and heart failure. *Id*. 4:28-40. These hard-to-treat RA patients needed other treatment options. Ex.2006 at 1; Ex.1042 at 665 (¶7).

Rituximab is an antibody that binds a B-cell-surface antigen, CD20, leading to the depletion of B cells. Ex.1001 2:32-48. Genentech originally obtained FDA approval of rituximab for B-cell non-Hodgkin's lymphoma ("NHL"), a cancer. Ex.1026 at 1. In treating NHL, rituximab was administered in body surface area ("BSA")-based doses of 375 mg/m^2 per week for four weeks. *Id*. at 2. The '838 inventors, though, saw the potential for rituximab to be used for treating other diseases.

The '838 discloses treating RA patients who have experienced an inadequate response to TNFα-inhibitors due to toxicity and/or inadequate efficacy (TNFIRs) with rituximab. Ex.1001 4:60-65, 5:25-29. However, every Challenged Claim

requires an anti-CD20 antibody/rituximab be administered in two doses of 1000 mg each to treat TNFIRs, rather than the dosing required to treat NHL. *Id*. 37:40-38:64.

In obtaining FDA approval of rituximab for treating RA, Genentech conducted a two-year double-blind Phase III clinical trial called "REFLEX" in more than 500 TNFIRs. Ex.2005. REFLEX patients showed marked improvements in ACR scores, which use a scale developed by the American College of Rheumatology. Ex.1011 at 735, Table 5. An ACR score generally corresponds to a percentage improvement in certain signs and symptoms of the disease.[3] *See* Ex.1010 at 332. Although the REFLEX trial patients were particularly hard to treat, many achieved ACR50 and ACR70 responses. Ex.2005 at 2793. More surprisingly, a substantial number of patients had no progression in joint erosion at 24 weeks and beyond, even after two years. Ex.2004 at 27-28. The Challenged Claims refer to these important clinical outcomes, respectively, as an "ACR50 response," an "ACR70 response," and "no erosive progression." Ex.1001 37:40-38:64.

III. Petitioner's Cited Art

Petitioner relies on three references it argues render the Challenged Claims unpatentable: Edwards 2001 (Ex.1006), De Vita 2001 (Ex.1005), and Curd

[3] For example, ACR50 corresponds to 50% improvement, and ACR70 to 70%.

(Ex.1016). Pet. at 5. But none of Petitioner's references renders the Challenged Claims unpatentable.[4]

A. Edwards 2001

Edwards 2001 reports the results of an "open-label" study (where it is known which patients received the drug), using rituximab to treat five RA patients who did not respond to synthetic DMARDs such as gold, methotrexate or prednisolone. Ex.1006 at 205-06. ***None*** of the patients in Edwards 2001 were TNFIRs. *Id*. at 206, Table 1 n.b.

Edwards 2001 used a protocol "based on the type of combination therapy used in B-cell lymphoma": Four rituximab infusions of 300 mg, 600 mg, 600 mg, and 600 mg administered on days 2, 8, 15 and 22, as well as oral prednisolone and cyclophosphamide. *Id*. All five patients achieved ACR50 at six months, and patients 1–3 achieved ACR70. *Id*. at 207. However, because patients were treated with a drug combination, it could not be confirmed that the results were due to rituximab alone. Instead, "[t]he further possibility, that steroid and cyclophosphamide contributed to the results, at least in part, through actions other than on B lymphocytes, seems very plausible." *Id*. at 210.

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[4] Moreover, as set forth below, neither Edwards 2001 nor De Vita 2001 was established as prior art. *Infra* § VI.

B. De Vita 2001

De Vita 2001 is an abstract regarding a study treating four female RA patients who "did not respond to a combination therapy with methotrexate and cyclosporine-A" using rituximab. Ex.1005 at 1. While the target population was methotrexate- and cyclosporine-A-non-responders, two women (patients 3 and 4), were also TNFIRs. *Id*. The study used the rituximab protocol approved to treat NHL—four weekly infusions of 375 mg/m^2 of rituximab. *Id*. While De Vita 2001 reported patients 1 and 2 saw ACR50 and ACR70 responses at six months, patients 3 and 4—the two TNFIRs—had significantly *less* improvement. *Id*. One saw only an ACR 20 response at month 5, while the other saw *no* response. *Id*. In other words, the TNFIRs reacted *differently* than those RA patients who were not TNFIRs.

In 2002, De Vita published additional data in De Vita 2002.[5] Ex.1060. Regarding patient 4, De Vita 2002 explained the ACR20 response was transient (from month 3 to 5 only) followed by subsequent relapse. *Id*. at 2030-2032. De Vita 2002 also reported the TNFIRs, patients 3 and 4, saw an ***increase*** in the

[5] De Vita 2001 reports both that patient 4 achieved an ACR20 response in month 5 and that patient 4 did not respond. It reports no results for patient 3. Ex.1005 at 1. Petitioner asserts this was an error and that it was patient 3 who saw no response. (Pet. at 29, n.3).

number of eroded joints following rituximab treatment. *Id*. at 2032. Thus, De Vita 2002 confirmed that TNFIRs responded differently and less well to rituximab than other RA patients.

C. Curd

Curd discloses treating RA with rituximab in size-adjusted (varying based on BSA) and often dose-escalating regimens—all involving at least four doses of the drug. For instance, Example 1 teaches dosing using (1) 50 mg/m^2 on day 1, followed by 150 mg/m^2 on days 8, 15 and 22; (2) 150 mg/m^2 on day 1, followed by 375 mg/m^2 on days 8, 15 and 22; and (3) 375 mg/m^2 on days 1, 8, 15 and 22. Ex.1016 at 25:9-23. Curd notes adjunct therapies may be combined with rituximab, but "[p]referably however, the patient is only treated with RITUXAN®." *Id*. at 25:9-16. Curd says nothing about targeting or treating TNFIRs.

IV. The Petition Should Be Denied Under 35 U.S.C. § 325(d)

In deciding whether to institute *inter partes* review, "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the [Patent and Trademark] Office," § 325(d), and the Board has repeatedly denied institution when—as here—the petition fails to explain why this discretion to deny should not be exercised. *See, e.g.*, *Unified Patents, Inc. v. Berman*, IPR2016-01571, Pap. 10 at 11-12 (Dec. 14, 2016) (informative).

Notwithstanding Petitioner's conclusory assertion that the "grounds, evidence, and/or arguments relied upon in this Petition are different than what was relied upon" during prosecution and in previously-filed petitions (Pet. at 3)[6], the Petition relies on identical (or at minimum substantially the same) prior art and arguments previously presented in *both* original prosecution and earlier IPRs (IPR2015-00417 by Boehringer; IPR2015-01733 and IPR2016-01667 by Celltrion). Yet Petitioner never mentions § 325(d), despite the PTO's prior consideration of the same art. Regardless, Petitioner's substantive arguments here fare no better than those the Board rejected in IPR2016-01667, despite Petitioner's having the benefit not only of the original prosecution and the three prior IPR petitions filed against the '838, but also of Genentech's POPRs, as well as Board institution decisions.

[6] In failing to identify what is allegedly "different," Petitioner improperly asks the Board and Genentech to "play archeologist with the record." *ZTE (USA), Inc. v. Elecs. & Telecomms. Research Inst.*, IPR2015-00029, Pap. 12 at 6 (Mar. 20, 2015) (internal quotation omitted); *see also A.C. Dispensing Equip. Inc. v. Prince Castle LLC*, IPR2014-00511, Pap. 16 at 5–6 (Sept. 10, 2014).

A. The Petition Should be Denied for Relying On Substantially the Same Art and Arguments Already Rejected by the Examiner and Board

In situations far less egregious than here, the Board routinely denies institution where a petition recycles substantially the same previously-considered art and arguments. For example, in applying § 325(d), the Board has repeatedly denied institution where, like here, the same or similar art was *either* before the original examiner *or* before the Board. *See Cultec, Inc. v. Stormtech LLC*, IPR2017-00777, Pap. 7 at 7-14 (Aug. 22, 2017) (informative) (previously considered by examiner); *Hospira, Inc. v. Genentech, Inc*., IPR2017-00739, Pap. 16 at 17-19 (July 27, 2017) (informative); *NetApp Inc. v. Crossroads Sys. Inc.*, IPR2015-00777, Pap. 12 at 7-8 (Sep. 3, 2015) (previously considered by Board); *Unilever Inc. v. Procter & Gamble Co.*, IPR2014-00506, Pap. 17 at 6-8 (July 7, 2014). But here, *both* the Examiner *and* the Board have rejected the same or substantially the same art and arguments.

The Board has also been critical of petitioners who fail to offer any explanation why § 325(d) should not apply. *See, e.g.*, *Unified Patents*, IPR2016-01571, Pap. 10 at 11-12. Here, Petitioner fails to mention that its art (or, in the case of De Vita 2001, De Vita 2002's disclosure of the same results, but in greater detail) was before the Examiner, who issued the Challenged Claims over this art. Petitioner also fails to mention that the same or substantially the same art and

arguments were previously before—and rejected by—the Board. Instituting trial on these same arguments—in the face of Petitioner's silence regarding § 325(d)—would both waste the Board's limited resources and invite substantial abuses of *inter partes* review. For example, it would encourage petitioners to scour prior proceedings to mix and match previously-rejected material, using the Office's prior decisions as a roadmap to try to avoid the same fate.

Section 325(d) is meant to prevent just the sort of inefficiencies, harassment of patent owners, and abuse of process Petitioner invites here in repeating arguments already *twice* overcome by Genentech. The Board should exercise its discretion under § 325(d) and deny institution.

B. The Patent Examiner Considered and Rejected the Art Cited in the Petition

Petitioner relies entirely on Edwards 2001, De Vita 2001, and Curd. Pet. at 5. But the disclosures of *each piece of art* were before the Examiner who allowed the Challenged Claims over them during prosecution.

Edwards 2001: Edwards 2001 was specifically relied upon during original prosecution by the Examiner who allowed the Challenged Claims. In particular, the pending claims were initially found obvious in light of *Edwards 2001*, Jenkins (Ex.2003) and Goldenberg (Ex.2001). Ex.1042 at 402-405. The Examiner asserted Edwards 2001 disclosed using rituximab in four infusions, at a total dose of 2100 mg, as a safe and effective for treating RA. *Id*. at 403. Further, the

Examiner asserted Jenkins taught stopping TNFα-inhibitor therapy in RA patients who develop serious side effects, and Goldenberg taught that a patient experiencing only minor relief when treated with TNFα-inhibitor ENBREL® achieved improvement with rituximab. *Id*. at 403-404. The Examiner concluded Edwards 2001, combined with Jenkins and Goldenberg, rendered the claims obvious. *Id*. at 403-405. In particular, the Examiner found it obvious to treat patients who did not respond to TNFα-inhibitor therapies with rituximab, and that obtaining the claimed dosing regimen would be obvious dose optimization. *Id*. at 404-405.

The patentee overcame this rejection, pointing out that *none of the Edwards 2001 patients had been previously treated with a TNFα-inhibitor* and thus *none were TNFIRs*. *Id*. at 428. The patentee further distinguished Edwards 2001 based on its use of four rituximab doses of 300 mg, 600 mg, 600 mg and 600 mg, not the two claimed doses of 1000 mg, explaining the claimed dosing regimen was not merely optimization. *Id*. at 428-429. The Examiner thereafter withdrew the § 103 rejection and allowed the Challenged Claims. *Id*. at 985.

De Vita: During prosecution, the pending claims were also initially rejected as anticipated by De Vita 2002. *Id*. at 400-401. As Petitioner explains, De Vita

2002 is a more detailed publication of the results reported in De Vita 2001.[7] Pet. at 43 n.6. Thus, while De Vita 2001 itself was not before the Examiner, the results it summarized and that Petitioner relies on were, along with De Vita 2002's more fulsome discussion.

The Examiner found De Vita 2002 taught methods of treating RA using rituximab in patients who did not respond to TNFα-inhibitor therapy. Ex.1042 at 401. But in overcoming the rejection, the patentee noted De Vita *failed to disclose* both the *claimed dosing regimen* of two doses of 1000 mg (instead using four doses of 375 mg/m^2) as well as the *claimed clinical responses* of ACR50, ACR70, and no erosive progression. *Id*. at 423-424, 430. Indeed, the patentee noted, of De Vita 2002's two reported TNFIRs, one achieved only an ACR20 response and one "exhibited no improvement," while both actually saw an increase in the number of eroded joints. *Id*. at 423-424; Ex.1060 at 2030-2032. The Examiner withdrew the rejection and allowed the Challenged Claims. Ex.1042 at 927, 985.

[7] In relying on De Vita 2001, Petitioner attempts to avoid De Vita 2002's additional disclosure of an ***increase*** in erosive progression in the joints in the two TNFIRs discussed during prosecution. Ex.1060 at 2032. Petitioner does not acknowledge this increase, let alone explain it.

Curd: The '838 identifies Curd as art "concerning CD20 antibodies," and it was cited in an IDS and reviewed by the Examiner during prosecution. Ex.1001 2:60-3:32; Ex.1042 at 410. The Examiner did not reject any Challenged Claim in light of Curd, either alone or in combination.

The Examiner also considered substantially the same arguments about the prior art. The Petition uses the same disclosures in Edwards 2001 and De Vita 2001 (as presented and elaborated in De Vita 2002), in substantially the same way as they were initially argued by the Examiner, but before the Examiner *ultimately reversed course*.

In arguing obviousness, Petitioner—like the Examiner did—relies on Edwards 2001 for disclosure of treating RA patients with four infusions totaling 2100 mg of rituximab to obtain ACR50 and ACR70 responses. *See, e.g.*, Pet. at 31-33, 48. Petitioner then swaps De Vita 2001 for Goldenberg (in the Examiner's combination) for alleged disclosure of treating TNFIRs. *Id*. at 31-32. Petitioner next relies on the same De Vita disclosures (citing De Vita 2001) that the Examiner used in initially finding anticipation by De Vita 2002. Then Petitioner argues De Vita 2001 disclosed treating two TNFIRs with four doses of 375 mg/m^2 of rituximab and obtained "marked clinical improvement" in two patients—*ignoring De Vita 2001 and De Vita 2002's explicit teaching to the contrary*. *See, e.g.*, Pet. at 31-33, 48. Further, acknowledging as the Examiner did that *none of*

the cited art discloses the claimed dosage amounts, Petitioner makes the same argument initially made by the Examiner—that dose optimization would have been obvious. *See, e.g.*, Pet. at 2, 33-34. But, Petitioner never addresses the fact that the Examiner ultimately abandoned this argument and allowed the Challenged Claims.

Petitioner's reliance on Curd also does not change the arguments previously considered and ultimately rejected by the Examiner, who relied on Goldenberg (methotrexate) and Edwards 2001 (prednisolone) for the same disclosures of the co-administration of rituximab with methotrexate and corticosteroids, including prednisone, that Petitioner cites from Curd. Ex.1042 at 403-404; Pet. at 53-55.

Petitioner never reconciles its use of Edwards 2001, De Vita 2001, or Curd with the fact that the Challenged Claims were specifically allowed over them. Further, nowhere does Petitioner confront the additional unfavorable results for De Vita's TNFIRs reported in De Vita 2002—results presented to the Examiner and known to a person of ordinary skill in the art ("POSITA") that directly conflict with Petitioner's assertions here. Nor does Petitioner identify any disclosure in its cited art that was not previously before the Examiner, let alone how its arguments differ from those the Examiner abandoned. This is no surprise, because in acknowledging these facts, Petitioner would be conceding that its Petition should be denied.

C. The PTAB Considered and Rejected the Same (or Substantially the Same) Prior Art and Arguments in the *Celltrion* IPR

While Petitioner's "Related Matters" disclosure identifies three prior '838 IPRs and notes the earliest, filed by Boehringer, was instituted (Pet. at 3), nowhere does Petitioner disclose that the most recent was *denied in its entirety* at institution, as was rehearing. *Celltrion, Inc. v. Genentech, Inc*., IPR2016-01667, Pap. 15 at 2 (Mar. 2, 2017); *id*., Pap. 19 at 6 (Aug. 18, 2017). Petitioner's silence regarding the *Celltrion* denial is telling, given that Petitioner relies on art and arguments considered and rejected there as the basis for its arguments here.

In IPR2016-01667, Celltrion unsuccessfully asserted obviousness in light of De Vita 2001, Curd, and Goldenberg. *Celltrion*, IPR2016-01667, Pap. 15 at 15-18. Petitioner rehashes essentially identical arguments here, just substituting Edwards 2001 for Goldenberg to give the appearance of presenting something "different" (Pet. at 3) and avoid repeating Celltrion's failure.[8] But Edwards 2001 offers

[8] As Petitioner notes (Pet. at 3, 36), in *Boehringer* the Board instituted claim 6 based on Edwards 2001, De Vita 2001 and Curd, but without the benefit of Genentech's fuller discussion of flaws in the dose optimization arguments underlying that combination as provided in, *e.g.*, Genentech's later POPR in *Celltrion*. As detailed *infra* § VIII(A)(3)(a), when provided that information the Board *denied* institution.

nothing new: unlike Goldenberg, it never even addresses TNFIRs. And Petitioner fails to explain how Edwards 2001 provides disclosure different from (let alone superior to) the combinations the Board already rejected.

Petitioner relies on the same teachings in De Vita 2001 and Curd the Board acknowledged and rejected in *Celltrion*. In particular, like Petitioner, the Board noted De Vita 2001 disclosed treating two TNFIRs with four doses of 375 mg/m^2 rituximab and that one TNFIR achieved an ACR20 response in month 5. *Compare Celltrion*, IPR2016-01667, Pap. 15 at 15, *with* Pet. at 29. The Board noted—like Petitioner—that Curd disclosed treating RA using various rituximab dosing schedules and optional further treatment with methotrexate and corticosteroids. *Compare Celltrion*, IPR2016-01667, Pap. 15 at 15, *with* Pet. at 30. And unlike Edwards 2001 (which does not address TNFIRs), the Board found Goldenberg disclosed treating RA in a patient that obtained only minor relief from TNFα-inhibitor ENBREL® with five 300 mg doses of rituximab.[9] *Celltrion*, IPR2016-01667, Pap. 15 at 15.

[9] Goldenberg and Edwards 2001 do have in common disclosing different dosing regimens from the Challenged Claims. Ex.1006 at 206; Ex.2001 at 21 (Example 3).

Ultimately, the *Celltrion* Board found none of the art taught the claimed dosing regimen. The Board rejected Celltrion's argument, repeated by Petitioner here, that a POSITA would have arrived at the claimed dosing regimen through routine optimization. *Compare Celltrion*, IPR2016-01667, Pap. 15 at 16-18, *with* Pet. at 33-41. In particular, the Board found the claimed dosing regimen differed from the art based on numerous variables, including fixed dosing (as opposed to BSA-based dosing), total dose administered, the amount of rituximab per infusion, and the number of infusions. *Celltrion*, IPR2016-01667, Pap. 15 at 16-18. Thus, Celltrion did not "demonstrate[] that each of those parameters represents a result-effective variable, such that a [POSA] would have had a reason to optimize it." *Id*. at 17. The Board also highlighted Celltrion's failure to explain why a POSITA would not have tried other options, like three doses or escalating doses. *Id*. at 18.

Here, Petitioner relies on the same disclosures of De Vita 2001 and Curd that the Board rejected. Petitioner relies on Edwards 2001 for the disclosure of treating RA using four doses of rituximab (300 mg, 600 mg, 600 mg, and 600 mg). Pet. at 28-29. But this disclosure is substantially the same as that in the combination with Goldenberg that the Board already rejected. *Celltrion*, IPR2016-01667, Pap. 15 at 15. In particular, like Goldenberg, De Vita, and Curd, Edwards 2001 discloses using four doses of rituximab to treat RA and, like Goldenberg, it uses four fixed doses. *Id*.; Ex.1006 at 206; Ex.1005 at 1; Ex.1016 at 25:9-23. Yet,

unlike Goldenberg, Edwards 2001 did not treat TNFIRs. Ex.1006 at 206, Table 1; *Celltrion*, IPR2016-01667, Pap. 15 at 15. Thus, far from providing a stronger combination, Edwards 2001 is *further away* from the claimed invention than Goldenberg. It offers nothing more than the art rejected by the Board in *Celltrion*.

Nowhere does Petitioner reconcile its use of De Vita 2001 or Curd with the fact that institution was rejected based on these references in *Celltrion*. IPR2016-01667, Pap. 15 at 18. Petitioner does not and cannot identify any disclosure in its art, including Edwards 2001, that was not before the Board when it last rejected essentially the same argument. Nor does (or can) Petitioner explain how its arguments are not "the same or substantially the same" as those rejected by the Board six months before the present Petition.

V. Petitioner's Unfair Use of the Office's Prior Decisions and Patent Owner's Arguments to Frame Its Challenge Warrants Denial Under § 314(a)

Even if the Petition did not raise substantially the same art and arguments as were raised by the Examiner and rejected in *Celltrion* (it does), the Board should separately deny institution under § 314(a). Petitioner is unfairly taking advantage of the PTO's prior actions and decisions, along with the Patent Owner's prior responses, using them as a "roadmap" to repeat and tweak previously-rejected arguments as part of a deliberate serial attack on the '838.

The Board applied both § 314(a) and § 325(d) to deny repetitive petitions long before its precedential decision in *General Plastic Industrial Co., Ltd. v. Canon Kabushiki Kaisha*.[10] And, as the Board has repeatedly indicated, the Petition should have affirmatively addressed these issues. The Board in *General Plastic* explained "[a]lthough … an objective of the AIA is to provide an effective and efficient alternative to district court litigation, we also recognize the potential for abuse of the review process by repeated attacks on patents." IPR2016-01357, Pap. 19 at 16-17 (Sept. 6, 2017) (precedential). The Board cautioned against allowing petitioners "the opportunity to strategically stage their prior art and arguments in multiple petitions, using our decisions as a roadmap, until a ground is found that results in the grant of review," *id*. at 17—the very same opportunity Petitioner attempts to exploit here. The Board set forth a "non-exhaustive list of factors … the Board[] consider[s] in evaluating follow-on petitions," taking into account "undue inequities and prejudices to Patent Owner." *Id*. at 16-17. The *General Plastic* factors include:

[10] *See Alarm.com Inc. v. Vivint, Inc.*, IPR2016-01124, Pap. 11 at 5-7 and n.3 (Dec. 5, 2016); *Nora Lighting, Inc. v. Juno Mfg., LLC*, IPR2015-00601, Pap. 13 at 11-12 (Aug. 12, 2015); *Conopco, Inc. v. Procter & Gamble Co*., IPR2014-00507, Pap. 17 at 7-8 (July 7, 2014).

1. whether the same petitioner previously filed a petition directed to the same claims;
2. whether at the time of filing of the first petition the petitioner knew or should have known of the prior art asserted in the second petition;
3. whether at the time of filing of the second petition the petitioner already received the POPR or Board's institution decision for the first petition;
4. the time between the petitioner learning of the prior art in the second petition and the filing of the second petition;
5. whether the petitioner provides adequate explanation for the time between the filings of the multiple petitions;
6. the Board's finite resources; and
7. the requirement under § 316(a)(11) to issue a final determination not later than one year after the date on which the Director notices institution.

See id. at 16.

While *General Plastic* involved follow-on petitions by the same petitioner, the Board has applied these factors to petitions by separate petitioners. For example, in *Samsung Electronics Co. v. Elm 3DS Innovations, LLC*, the Board applied the *General Plastic* factors and denied institution where a new petitioner

relied on three of the four references, as well as evidence and rulings, from prior proceedings. IPR2017-01305, Pap. 11 at 8-12, 16-23 (Oct. 17, 2017) (informative). Recognizing that not all factors might be as directly applicable to new petitioners, *id*. at 20-23 (finding factors 2, 6, and 7 had little probative value), the Board considered the availability of prior petitions, patent owner responses, and Board decisions on the same and related patents, which the petitioner unfairly used to "improve its position." *Id*. at 21. In addition, the Board emphasized the petitioner's reliance on substantially the same art, in substantially the same manner, evidenced the unfair "benefit" petitioner derived from the prior proceedings. *Id*. at 20. Just as the *Samsung* Board found these factors warranted denial under § 314(a), the *General Plastic*/*Samsung* framework confirms the Petition here should also be denied.

A. Factor One: Same Petitioner

While not a party to the earlier '838 petitions, Petitioner is now an active party to a second wave of three petitions, filed over three days. These newest petitions include a second, concurrently-filed petition by Petitioner (IPR2017-02042) and a petition by Pfizer (IPR2017-01923), both using overlapping art. In filing its petitions, Petitioner puts before the Board still more permutations of previously-considered art and arguments, hoping something will stick after six

'838 attacks.[11] This is the very abuse § 314(a) is meant to curb and exemplifies the type of repeated petitioning activity that has led to scrutiny by the Board itself. *See, e.g.*, Ex.2002 at 36.

Moreover, as in *Samsung*, the Petition here has a "high degree of similarity" with the four previously-filed '838 petitions. IPR2017-01305, Pap. 11 at 19; *supra* § IV(C). This is not surprising: the same lawyers representing Petitioner here (including lead attorney Gutman) represented Boehringer in its '838 petition and in its simultaneously-filed petition against U.S. Patent No. 7,820,161 ("the '161"),[12] which is also directed to methods of treating RA using rituximab and has itself been subjected to repeated attacks in petitions by Boehringer (IPR2015-00415), Celltrion (IPR2015-01744 and IPR2016-01614) and Pfizer (IPR2017-

[11] Petitioner's separate petitions are likely an attempt to hedge its bets given that the art in the 2042 Petition is not actually prior art, as Patent Owner will show in the event of institution. *Infra* § VIII(A)(3)(c)(iv).

[12] Pet. at 4; *Boehringer Ingelheim Int'l GmbH v. Genentech, Inc*, IPR2015-00417, Pap. 3 at 4 (Dec. 15, 2014); *Boehringer Ingelheim Int'l GmbH v. Genentech, Inc*., IPR2015-00415, Pap. 3 at 4 (Dec. 15, 2014).

01115).[13] In other words, Petitioner has effectively taken advantage of 10 opportunities to test, assess, and triangulate its arguments—leading to unfairness that should not be rewarded with institution.

B. Factor Two: Knowledge of Prior Art

Given that every reference relied on by Petitioner (or, in the case of De Vita 2001, the more fulsome De Vita 2002 article with additional disclosures) was both before the original Examiner and this Board in prior '838 petitions, Petitioner, like the Office, was unquestionably aware of this art. However, as in *Samsung*, because Petitioner was not involved in prior '838 petitions, this factor may have less probative value. IPR2017-01305, Pap. 11 at 20.

C. Factor Three: Availability of Information From Prior Proceedings

As in *Samsung*, this factor weighs strongly in favor of denying institution. *Id*. at 20-21.

[13] Despite being aware of these challenges based on its counsel's involvement in the '161 proceedings and Pfizer's identification of, and reliance on statements made in, those proceedings in its parallel petition, *Pfizer, Inc. v. Genentech, Inc*., IPR2017-01923, Pap. 2 at 65 (Aug. 29, 2017), nowhere does Petitioner acknowledge these '161 attacks.

Petitioner had the benefit of four other '838 petitions and Genentech's POPRs in *Boehringer* and *Celltrion* (along with multiple papers involving the '161 Patent) in preparing the present Petition. The fact that Petitioner relies on substantially the same art in substantially the same manner (*see supra* § IV(C)), "evinces benefit Petitioner [ ] derived from those prior proceedings." *Samsung*, IPR2017-01305, Pap. 11 at 20. And Petitioner clearly used Genentech's prior POPRs to try to preempt Genentech's arguments and strengthen Petitioner's position here. *See, e.g.*, Pet. at 5-6 (Petitioner arguing that "[i]n a previous IPR, Genentech did not dispute" that Edwards 2001 and De Vita 2001 were publicly accessible); *id*. at 43 ("Genentech has previously argued [in *Celltrion*]" that De Vita 2002 teaches away); *id*. at 46 (discussing Genentech's prior arguments regarding "'hardest-to-treat' patients"); *id*. at 64 (discussing secondary considerations raised by Genentech "[i]n response to Boehringer Ingelheim's" petition" and noting "Genentech did not advance any arguments regarding secondary considerations in response to Celltrion's petition."). As the Board explained in *Samsung*, "[t]he *availability* of the Patent Owner's Response and Patent Owner's expert testimony from other proceedings also weights strongly in favor of exercising our discretion, as does Petitioner's *use* of such information in its Petition." IPR2017-01305, Pap. 11 at 21.

Petitioner also had available two prior '838 institution decisions and a decision denying reconsideration. As in *Samsung*, Petitioner used those prior decisions to try to improve its position here and would be able to do so further were the Board to institute review. "This also strongly weighs in favor of exercising [the Board's] discretion." *Id*.

Petitioner's ability to leverage prior statements by Genentech and the Board is not limited to those in the '838 IPRs. As discussed above, the '161, directed to methods of treating RA using rituximab, has been subject to four petitions. Petitioner should not be allowed to pick through 10 IPRs to strengthen its case here and try still more permutations of these arguments.

D. Factor Four: Prior Art Asserted in Instant Petition

While Petitioner knew or should have known of the art cited in its Petition because it was expressly cited before both the Examiner and Board in prior proceedings, *supra* §§ IV(B)-(C), the Board in *Samsung* found this factor to have little, if any, probative value where Petitioner had not filed prior petitions. IPR2017-01305, Pap. 11 at 22.

E. Factor Five: Petitioner's Explanation

Because Petitioner failed to mention, let alone address, § 314(a), it provided *no explanation* for its failure to file its Petition sooner. Thus, unlike in *Samsung*,

where petitioner explained its delay, this factor weighs heavily in favor of denying institution. IPR2017-01305, Pap. 11 at 22-23.

F. Factors Six and Seven: Board Considerations of Finite Resources/One-Year Timeline

These related factors consider the "finite resources of the Board" and the timing requirement for the Board's final determination. *Id*. at 17. As detailed *supra* §§ IV(B)-(C), the Examiner and the Board have already expended significant effort to consider and reject the same art and arguments. Asking the Board to do so again does not conserve the Board's finite resources, and the Petition offers no justification. Thus, while factor seven (concerning the one-year timeline) may not weigh significantly for or against institution, factor six weighs in favor of denying institution.

G. The Equities Support Denying Institution

For the reasons above, when all seven factors are considered, the balance of the equities clearly supports denying institution under § 314(a). This is a textbook example of Patent Owner harassment with iterative attacks superficially and incrementally tweaked to see what might stick.

VI. The Petition Should be Denied Because Petitioner Failed to Demonstrate a Reasonable Likelihood That Its References Qualify as Prior Art Printed Publications

Petitioner has not made even the barest attempt to establish Edwards 2001 and De Vita 2001 are actually prior art printed publications. Petitioner merely

asserts this is so, concluding without support that the references are "printed publication[s]" published in 2001. Pet. at 5-6. But Petitioner says nothing about where the pages it attaches as exhibits were found or generated. For instance, Petitioner presents no evidence establishing the exhibits were from regularly published journals, and no explanation for the asserted 2001 date. Even if Petitioner took the date from the articles (which it does not assert), Petitioner provides no explanation as to why such dates are not hearsay. Petitioner thus failed to meet its burden on a basic element of obviousness: establishing its references are prior art printed publications and are authentic. *See, e.g.*, *Teva Pharms. USA, Inc. v. Indivior UK Ltd*., IPR2016-00280, Pap. 23 at 10 (June 10, 2016) (finding insufficient "threshold evidence" to justify institution; "even assuming Patent Owner stipulated regarding the prior art status . . . in a co-pending district court litigation, that fact, by itself, also would be insufficient to provide a threshold showing."); *TRW Auto. v. Magna Elecs.*, IPR2014-01347, Pap. 25 at 8-9 (Jan. 6, 2016) ("[C]opyright notice is … not probative that the article was ever published by IEEE or anyone else.").

Further, Petitioner's attempt to shift the burden of persuasion by asserting Genentech did not dispute the prior art status of these references in another proceeding is misguided and irrelevant—and certainly does not relieve *this* Petitioner of satisfying *its* burden. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d

1364, 1375 (Fed. Cir. 2016) ("[T]he burden of persuasion is on the petitioner … and …never shifts to the patentee."); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) ("[P]etitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable."); Ex.2007 at 4-5; § 316(e). Furthermore, the "previous IPR" referenced by Petitioner terminated before Genentech filed a POPR. *See Boehringer*, IPR2015-00417, Pap. 18 (Oct. 1, 2015).

For similar reasons, Petitioner has also not established its various background references (*e.g.*, Exs.1009-1015, 1017-1018, 1022-1025, 1027-1039, 1047, 1050-1055, 1057-1058, 1060) are actually prior art. For example, Petitioner cites various drug labels (Exs.1019-1021) and includes the Rituxan® label (Exs.1026, 1056) in its filings, without providing information to establish what they are or when they published. *See Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01166, Pap. 9 at 13-17 (Nov. 13, 2017) (finding Rituxan® Label fails to qualify as prior art); *Mylan Pharm. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01566, Pap. 15 at 10-12 (Feb. 3, 2017) (finding that purported "printed package insert" was not a printed publication); *Frontier Therapeutics, LLC v. Medac Gesellschaft Fur Klinische Spezialpraparate MBH*, IPR2016-00649, Pap. 10 at 22 (Sept. 1, 2016) (same). Thus, such background references should be ignored, including with respect to any analysis regarding the level of skill in the art.

VII. Claim Construction

A. Every Claim Requires the Recited Patient has Been, or is Being, Treated With a TNFα-Inhibitor

Every Challenged Claim requires treating a "patient who experiences an inadequate response to a TNFα-inhibitor." Ex.1001 37:40-38:64. The Board correctly construed this as a substantive limitation requiring the patient have experienced an inadequate response to a previous or current TNFα-inhibitor, not merely that such a person would experience such a result if treated. *Celltrion*, IPR2016-01667, Pap. 15 at 6-7; *see also Boehringer*, IPR2015-00417, Pap. 11 at 8-10 (July 14, 2015). Petitioner does not challenge—or even address—this construction, but contradicts it in describing the specification and prosecution. *See* Pet. at 20 ("invention is not limited to a prior therapy step . . ."); *id*. at 23 ("[A]ccording to the patent, TNFIRs did not need to actually be treated with TFNα inhibitors to be considered TNFIRs."). To the extent Petitioner is arguing an implicit construction that the claims do not require prior or current treatment with a TNFα-inhibitor, such construction is contrary to the claims' plain meaning and the express definition in the specification, previously adopted by the Board. Ex.1001 5:25-29, 5:37-41, 28:45-55; Ex.1042 at 426, 428; *see also* § 42.104(b)(3) (requiring Petitioner to construe necessary claim terms).

B. The Clinical Response Limitations Cannot be Read Out

Claims 2–7and 10–14 require achieving one of three clinical responses: ACR50 at week 24, ACR70 at week 24, and no erosive progression at weeks 24 and beyond. Petitioner mischaracterizes these limitations as merely "intended results of the administered doses" and argues they are not limitations. Pet. 25-27. In doing so, Petitioner revives the same arguments presented by challengers in prior petitions and countered by Genentech, without addressing Genentech's prior responses. The Board did not accept those previous improper invitations to read out limitations of the Challenged Claims, and should not do so now. *Texas Instruments Inc. v. ITC*, 988 F.2d 1165, 1171 (Fed. Cir. 1993).

1. "achieving a clinical response selected from" (claims 11-14)

(a) The Applicant Used Both the Preamble and Body of Claim 11 to Define the Claimed Subject Matter

All words in a claim, whether in the preamble or body, may have patentable significance. "[W]hen the claim drafter chooses to use *both* the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects." *Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995) (emphasis in original). In general, when a preamble recites essential structures or steps, it limits the invention. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999).

The body of claim 11 recites steps of administering rituximab and methotrexate in a specific dosing regimen. Ex.1001 38:51-58. The preamble recites an additional step of "achieving a clinical response selected from the group consisting of ACR50 response at week 24, ACR70 response at week 24, and no erosive progression at weeks 24 and beyond." *Id*. This step is not a necessary consequence or inherent result of the treatment set forth in the other claimed steps.

The fact that the additional step in the preamble necessary to achieve the intended response contains a Markush group further supports that it is limiting. *Abbott Labs. v. Andrx Pharm., Inc.*, 473 F.3d 1196, 1210 (Fed. Cir. 2007) ("A Markush group … limit[s] the claim to a list of specified alternatives.").

(b) The Applicant Relied on the Clinical Response Limitations to Distinguish Art

That the claimed clinical responses limitations are limiting is further confirmed by Genentech's reliance on them in distinguishing art during prosecution, including art cited by Petitioner. Ex.1042 at 424, 426-27, 429-31 (distinguishing De Vita 2002, the Tuscano protocol, Edwards 2001, Jenkins, and Goldenberg based on failure to disclose claimed clinical responses in TNFIRs). In doing so the Applicant argued "these features of the invention … represent independently patentable features that further distinguish the claimed invention over the cited art." *Id.* at 429. This clear reliance on the preamble to distinguish the claimed invention from the prior art confirms it is limiting. *Bristol-Myers*

Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1375 (Fed. Cir. 2001); *see also Invitrogen Corp. v. Biocrest Mfg. LP*, 327 F.3d 1364, 1370 (Fed. Cir. 2003); *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003) (giving weight to preamble phrases added to gain allowance); *Smith & Nephew, Inc. v. Bonutti Skeletal Innovations, LLC*, IPR2013-00605, Pap. 9 at 8-9 (Feb. 26, 2014). Nowhere does Petitioner address this prosecution history, in spite of being on clear notice of it through prior POPRs. *Boehringer*, IPR2015-00417, Pap. 9 at 20 (Apr. 15, 2015); *Celltrion*, IPR2016-01667, Pap. 13 at 13-14 (Dec. 6, 2016).

(c) Claims 12–14 Rely Upon, and Derive Antecedent Basis From, the Clinical Responses in Claim 11

That the clinical response limitations of claim 11 are limiting is further confirmed by dependent claims 12–14.

First, claims 12–14 each derive antecedent basis from the "achieving a clinical response" language of the claim 11 preamble by referring to "***the clinical response***": "The method of claim 11 wherein ***the*** clinical response is" one of the three alternatives set forth in claim 11. Ex.1001 38:59-64. Preamble language is limiting when, as here, "limitations in the body of the claim rely upon and derive antecedent basis from the preamble." *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003).

In addition, the claim differentiation doctrine further confirms the clinical response language is limiting. The only difference among claims 12–14 is that

each requires a different clinical response. If the clinical response limitations were ignored, claims 12–14 would be identical, reading "[t]he method of claim 11." Ex.1001 38:59-64. This would not only violate claim differentiation principles but would also be nonsensical. *Versa Corp. v. Ag-Bag Int'l Ltd.*, 392 F.3d 1325, 1330 (Fed. Cir. 2004).

2. "wherein the patient has no erosive progression …" (Claim 10)

Petitioner's suggestion that claim 10's limitation "wherein the patient has no erosive progression at weeks 24 and beyond" (Ex.1001 38:45-50) is non-limiting is without merit.

Again, "wherein" clauses like this are regularly found limiting. For example, in *BioDelivery Sciences International, Inc. v. RB Pharmaceuticals Ltd.*, claim 15 recited "an orally dissolving film formation, 'wherein said formulation provides' specific pharmacokinetic profiles." IPR2014-00325, Pap. 43 at 4 (June 30, 2015). The Board agreed "that the pharmacokinetic ranges recited in the wherein clause 'give crucial meaning to, and provide defining characteristics provided by the film formulation at issue.'" *Id.* at 5. This language required a formulation "capable of producing the pharmacokinetic profile recited in the wherein clause of the claim." *Id.* at 6 (citing *Griffin v. Bertina*, 285 F.3d 1029, 1033-34 (Fed. Cir. 2002)); *see also 10X Genomics, Inc. v. Univ. of Chicago*, IPR2015-01162, Pap. 14 at 12-13 (Nov. 16, 2015) ("wherein" clause limiting

because it was informative about how steps were performed) (citing *Griffin*, 285 F.3d 1033-34); *US Endodontics, LLC, v. Gold Standard Instruments, LLC*, PGR2015-00019, Pap. 17 at 22-24 (Jan. 29, 2016) ("wherein" clause limiting because it set forth a "specific, quantitative test" for determining if process fell within scope of claim).

The "wherein" clause's limiting nature is further confirmed by its giving "meaning and purpose" to the step of administering two intravenous doses of 1000 mg. *See, e.g.*, *Griffin*, 285 F.3d 1033-34 ("wherein" clause limiting where it gave "meaning and purpose to the manipulative steps"). Claim 10 is directed to a "method of treating rheumatoid arthritis." Thus, like claims 11-14, its method is used to achieve a therapeutic effect or invoke a clinical response in a TNFIR patient, rather than just administration of an antibody as intravenous doses. And the "wherein" clause defines a specific, quantitative test for determining what that therapeutic effect or clinical response is, requiring achievement of "no erosive progression at 24 weeks and beyond." The '838 explicitly states a "primary endpoint" of treatment is "the portion of patients with an ACR20 response at Week 24"; "secondary endpoints" include "[p]roportion of patients with ACR50 and 70 responses at Week 24"; and "[e]xploratory endpoints" involve "ACR(20/50/70 and ACR n) . . . over Weeks 8, 12, 16, 20, 24, and beyond . . . non erosive progression . . . at weeks 24 and beyond." Ex.1001 31:42-32:34. It further teaches that

beneficial clinical response is determined "according to one or more of the[se] endpoints." *Id*. 32:40-43. This determination is a fundamental characteristic of the claimed invention, as evidenced by the patentee's reliance on endpoint limitations in distinguishing art during prosecution. *Supra* § VII(B)(1)(b). Claim 10, like claims 11–14, requires a specific endpoint. Like those claims, its antibody administration step would have little meaning or utility, and would be a mere academic exercise, unless placed within the context of the specific purpose of achieving the endpoints, defined by its wherein clause.

3. "an amount that is effective to provide" (Claims 2-7)

Claim 2 recites administering an antibody which binds to CD20 in "an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond." Ex.1001 37:46-52. Claims 3-7 depend from claim 2. *Id*. 37:53-65. In asking the Board to ignore this limitation, Petitioner attempts to equate two different terms in the same claim: the clinical response limitation ("in an amount that is effective to provide an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond") and the administering limitation ("the antibody is administered as two intravenous doses of 1000 mg"). Pet. at 25-26; Ex.1001 37:46-52. This invitation to error should be rejected: "In the absence of any evidence to contrary, we must presume that the use of [] different terms in

claims connotes different meanings." *CAE Screenplates Inc. v. Heinrich Fiedler GmbH Co. Kg*, 224 F.3d 1308, 1317 (Fed. Cir. 2000). There is no contrary evidence.

Furthermore, the claim language demonstrates that the "amount that is effective to provide [a clinical response]" clarifies the "two intravenous doses of 1000 mg" phrase. Petitioner ignores that an amount of antibody cannot be "effective to provide" the recited clinical responses unless administering the antibody to the patient actually provides such a response. Indeed, as prior petitioners admitted, the claimed treatment produces a clinical response in "some but not all patients." *Celltrion, Inc. v. Genentech, Inc*., IPR2015-01733, Pap. 2 at 48 (Aug. 14, 2015). Merely claiming "two intravenous doses of 1000 mg" would not have required any particular clinical response be achieved. Thus, Petitioner's argument should be rejected.

VIII. The Petition Fails to Establish that the Challenged Claims are Obvious

To justify institution, Petitioner must make a *prima facie* showing that, as a factual and legal matter for its asserted grounds, Petitioner's submitted evidence and arguments have a reasonable likelihood of proving at least one Challenged Claim unpatentable. § 314. Even if Edwards 2001 and De Vita 2001 were assumed to be prior art, the Petition fails to establish a *prima facie case* that Edwards 2001, De Vita 2001, and Curd render obvious each and every limitation

of *any* Challenged Claim. Thus, Petitioner has failed again to meet its burden for institution.

A. The Petition Fails to Demonstrate that it Would Have Been Obvious to Treat TNFIRs Using Two 1000 mg Doses of Rituximab

Every challenged claim requires treating RA "in a human patient who experiences an inadequate response to a TNFα-inhibitor" by administering "two intravenous doses of 1000 mg" of "an antibody that binds to CD20" (claims 1, 2, and 4–7) or of "rituximab" (claims 3, 8, and 9–14). Ex.1001 37:40-38:64. Petitioner fails to establish that its asserted art combination renders these claim limitations obvious.

1. The Cited Art Does Not Teach or Suggest Treating TNFIRs with Rituximab

While Petitioner's cited art does disclose attempts to treat RA using rituximab, Petitioner failed to show that any art targeted the hard-to-treat TNFIRs that are the focus of the Challenged Claims. Indeed, Curd says nothing about TNFIRs of any sort. Ex.1016. And while Edwards 2001 targeted patients whose RA was not adequately controlled using at least five synthetic DMARDs, it said *nothing about TNFIRs*. Ex.1006 at 206, Table 1. In fact, Edwards 2001 explicitly listed the DMARDs previously tried by each of its patients—*none is a TNFα-inhibitor*. *Id*.

The only art cited by Petitioner that even mentions TNFIRs is De Vita 2001, but such patients were not the target of De Vita's study. Instead, De Vita targeted RA patients who "did not respond to a combination therapy *with methotrexate and cyclosporine-A*." Ex.1005 at 1. And, in fact, the De Vita 2001 results showed that rituximab was significantly *less effective* in treating RA in TNFIRs than in other RA patients. Indeed, the TNFIRs, patients 3 and 4, saw only (1) a transient ACR20 response, and (2) no response, as compared to ACR50 and ACR70 responses in other patients. *Id*. at 1.

Petitioner argues that because TNFα-inhibitors and rituximab have "a different mechanism of action," a patient's inadequate-response to an inhibitor would not suggest that they would respond differently from other RA patients to rituximab, and thus a POSITA would treat TNFIRs with rituximab in the same way, and expect the same response, as other RA patients. *See* Pet. at 43-45, 50, 59. But De Vita 2001 and De Vita 2002 flatly contradict this assumption that is the foundation of all of Petitioner's arguments here.[14] Contrary to Petitioner's

[14] Petitioner's argument that De Vita 2002 does not "teach away" (Pet. at 43-45) misses the point. The immediate question is what De Vita 2002 taught a POSITA about the likelihood of success in treating TNFIRs with rituximab: Petitioner ignores its teaching that they reacted differently (and worse).

suggestion that a POSITA would have assumed there was no functional connection between being a TNFIR, on the one hand, and response to rituximab, on the other, De Vita 2001's results told a POSITA that different patient populations do *not* respond the same way to rituximab. Ex.1005 at 1. In particular, the TNFIRs who are the focus of the Challenged Claims and Petitioner's flawed arguments respond differently. *Id*. Indeed, in light of the art cited by Petitioner, there is nothing to suggest to a POSITA that TNFIRs should be treated with rituximab, let alone that they would respond the same way to rituximab as other patients. De Vita 2001 reported that they would *not*, and De Vita 2002 provided still further confirmation, reporting additional data showing that TNFIRs actually saw an *increase* in their number of eroded joints. Ex.1005 at 1; Ex.1060 at 2032.

2. The Cited Art Does Not Teach or Suggest the Claimed Dosing Regimen

Even assuming it would have been obvious to treat TNFIRs using rituximab to begin with (it was not), Petitioner failed to show it would have been obvious to treat these patients using the particular dosing regimen—two fixed intravenous doses of 1000 mg—required by every Challenged Claim.

It is undisputed that ***none*** of Petitioner's cited art disclosed using *two fixed doses of 1000 mg* to treat RA at all, let alone hard-to-treat TNFIRs. Instead, all three cited references disclose using a *four dose* regimen to treat RA in which each individual dose is less than 1000 mg. Moreover, De Vita 2001 and Curd teach

using variable dosing, based on the patient's BSA, rather than the claimed fixed dosing. And Curd and Edwards 2001 disclose using escalating doses rather than doses of the same amount, as claimed. As detailed further below, it is only through impermissible hindsight that a POSITA would arrive at the claimed dosage from Petitioner's cited art.

Moreover, Petitioner fails to address that its reliance on De Vita 2001 to obviate the claimed dosing regimen ignores what De Vita 2001 actually reported. In De Vita 2001, TNFIRs saw no response or only a short-lived ACR20 response when administered four rituximab doses of 375 mg/m^2, while other RA patients saw ACR50 and ACR70 responses. Ex.1005 at 1. While De Vita does not disclose the BSA of any participant or the total rituximab dosage administered to any patient, Petitioner states the average female BSA is 1.6 m^2. Pet. at 17 n.3. On this basis, De Vita's patients would have received a total rituximab dose of approximately 2400 mg (375 mg/m^2 x 1.6 m^2 x 4 doses), not 2000 mg (2 x 1000 mg) as claimed. Petitioner offers *no explanation* of how or why De Vita's results would suggest to a POSITA that the key to successfully treating TNFIRs, which De Vita itself showed were *more difficult* to treat, would be to (1) start with the dose that did not successfully treat TNFIRs, (2) reduce the number of doses of rituximab by 50% (from four to two), and, at the same time (3) reduce the total dosage of rituximab by 400 mg (from 2400 mg to 2000 mg) or nearly 20%. The

reason is simple: they would not, and Petitioner's failure to explain this means it has failed to make the threshold showing required for institution.

Petitioner's arguments with respect to Edwards 2001 similarly defy logic. Petitioner's suggestion that Edwards 2001's statement that "the protocol used, or a modification thereof, may be of major benefit to subjects with RA" would motivate a POSITA to arrive at the *specific claimed dosing regimen* for *TNFIRs* with a *reasonable expectation of success* (Pet. at 33) ignores that Edwards 2001 was *silent as to TNFIRs*.[15] It also ignores the dosing actually used in Edwards 2001. Tellingly, as with De Vita 2001, Petitioner offers no explanation why a POSITA, reading Edwards 2001, would determine the key to successfully treating TNFIRs would, again, be to (1) decrease the number of rituximab doses given to non-TNFIRs by 50% (from four to two) and to (2) decrease the total amount of rituximab given (from 2100 mg (300 mg + 600 mg + 600 mg + 600 mg) to 2000 mg (2 x 1000 mg)). Ex.1006 at 206; Ex.1001 at 37:40-38:64.

[15] It also completely ignores the teachings of Petitioner's relied-on De Vita 2001 reference, which—as discussed above—reported to a POSITA that there were problems using rituximab in TNFIRs. Petitioner makes no attempt to explain how or why a POSITA would overlook this.

Petitioner's argument that Curd discloses a "broad range" of dosages from about "20 mg/m^2 to about 1000 mg/m^2" (Pet. at 37) simply underscores the hindsight underlying Petitioner's obviousness analysis. First, what Curd repeatedly teaches in terms of subsequent dosage amounts is the use of *smaller initial treatments* followed by *escalating doses*—not two identical doses as claimed. *See, e.g.*, Ex.1016 at 23:23-27. But even if Petitioner's reading of Curd were correct, Petitioner fails to explain why, absent hindsight, a POSITA would arrive at the claimed dosing regimen from Curd's "broad" disclosure, especially given that Curd nowhere discloses any dosing that is not based on the BSA of the patient.

For example, Curd's Example 1 discloses three RA dosing regimens, all of which are four-dose regimens that vary based on the BSA of the patient. Example 1 includes individual doses of 50 mg/m^2, 150 mg/m^2, and 375 mg/m^2. Ex.1016 at 25:9-23. Two of the three Example 1 regimens (A and B) involve escalating dosing, and the third (C) is the same 375 mg/m^2 dosing disclosed in De Vita 2001 and used for treating NHL.[16] *Id.*; Ex.1005 at 1. Even if one ignores that Curd is

[16] While Curd does not disclose the actual amount of any individual dose or total final dosage of any proposed BSA-based regimen, using Petitioner's asserted BSA averages for men and woman (Pet. at 17 n.3), the lowest total dose in Curd's Example 1 would be 809.6 mg (dosing A for a female ((50 mg/m^2 x 1.6

silent as to the treatment of TNFIRs, what it discloses about the treatment of RA is not the dosing claimed in the '838.

3. Petitioner's Routine Optimization Arguments Fail

Faced with the fact that none of its cited art teaches or suggests the claimed dosing regimen, Petitioner argues a POSITA would have arrived at the claimed dosing regimen as a matter of "routine optimization." Pet. at 35. In doing so, however, Petitioner ignores the Examiner's and Board's prior rejection of this same argument, as well as the case law on "routine optimization," which was cited by the *Celltrion* Board.

(a) Petitioner's Routine Optimization Arguments Have Already Been Properly Rejected

Although Petitioner repeats the same routine optimization arguments advanced by Celltrion, and touts statements made by the Board in *Boehringer*, Petitioner fails to disclose that these routine optimization arguments were rejected

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m^2) + (150 mg/m^2 x 1.6 m^2 x 3) = 809.6 mg)) and the highest disclosed would be 2850 mg (dosing C for a male ((375 mg/m^2 x 1.9 m^2 x 4) = 2850 mg)). Picking a total dose of 2000 mg from this range—especially in the claimed *two fixed 1000 mg doses*, where *no fixed dosing is disclosed in Curd*—is pure, unsupported hindsight, and a choice for which Petitioner fails to offer any explanation.

both before and after the *Boehringer* decision: first by the Examiner during prosecution, and then by the Board in *Celltrion*, with the benefit of further discussion of this issue in Genentech's POPR.

During prosecution, the Examiner rejected the pending claims under § 103 based on Edwards 2001, Jenkins, and Goldenberg. Ex.1042 at 402-405. While none of the cited art disclosed the claimed dosing regimen, the Examiner initially argued that regimen was obvious as a matter of routine optimization. *Id*. at 404-405. However, the Examiner ultimately withdrew those rejections, allowing the Challenged Claims. *Id*. at 985-987.

In *Boehringer*, the Board accepted Boehringer's routine optimization argument in instituting claim 6. IPR2015-00417, Pap. 11 at 20-22. The Board's opinion, however, focused only on Boehringer's argument that the number of doses would be reduced from the four in the prior art to the two claimed to "solve the problem of patient compliance." *Id*. at 22. Nowhere did the Board specifically address how or why the other dosing parameters—*e.g*., fixed v. BSA-based dosing, total dosage amount, number of doses, and amount of rituximab per dose—would be arrived at as a matter of routine optimization. However, when the Board examined these additional parameters two years later in *Celltrion* with the benefit of briefing on the facts and law concerning "optimization" in Genentech's POPR,

it came to the opposite conclusion, *rejecting* the idea that the claimed dosing regimen would result from mere routine optimization:

> [T]he claimed dosing regimen involves a number of variables that differ from the cited prior art, such as: dose-sizing option, i.e., fixed dosing vs. dosing based on body surface area (Curd and De Vita); total dose; number of infusions; and amount of each infusion. [ ] Petitioner has not demonstrated that each of those parameters represents a result-effective variable, such that a person of skill in the art would have had a reason to optimize it. . . . . Moreover, Petitioner has not explained adequately that the alleged routine optimization would result in modifying each parameter in a manner so as to arrive at the claimed dosage regimen.

Celltrion, IPR2016-01667, Pap. 15 at 17. For the same reasons, the same argument now repeated in this Petition should be rejected.

(b) The Petition Fails to Address the Requirements For "Routine Optimization" Arguments

In spite of having in hand Genentech's *Celltrion* POPR (of which Petitioner was aware, Pet. at 3), Petitioner fails to address these requirements in the case law. For Petitioner to show "routine optimization" applies, and thus to argue that some "optimum value" of "a result effective variable" in a "known process" or composition is obvious, *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977), Petitioner must show at least five requirements are satisfied. But Petitioner (like Celltrion before it) fails to address any of these requirements with respect to any of the four variables reflected in the claimed dosing regimen (discussed *supra* § VIII(A)(3)(a) and *infra* § VIII(A)(3)(c)).

First, for "routine optimization" to apply, the resulting value must be the "*optimum value*" for the variable. *In re Antonie*, 559 F.2d at 620; *In re Aller*, 220 F.2d 454, 458 (C.C.P.A. 1955) ("No invention is involved in discovering *optimum* ranges of a process by routine experimentation."). Nowhere, though, does Petitioner even assert that any of the four dosing variables is, in fact, an "optimum." To the contrary, Petitioner argues *they are not*: Petitioner repeatedly asserts that the clamed dosing regimen is "*interchangeable*" and "*equivalent* for therapeutic purposes" with four BSA-based doses of 375 mg/m^2. *See* Pet. at 32-33. As set forth *supra* § VIII(A)(2) (discussing De Vita 2001), such a dose differs from the claimed dosing regimen *in all four of the relevant dosing variables* (*i.e.*, (i) dose-sizing (fixed v. BSA-based dosing); (ii) total dosage amount; (iii) number of doses; and (iv) amount per dose). Thus, by Petitioner's own arguments, *none* of the dosing variables that lead to the claimed dosing regimen would be an *optimum* because each would be *interchangeable* with other alternatives.

Second, the variable being optimized must have been *"known" to be "result-effective." In re Antonie*, 559 F.2d at 620; *In re Yates*, 663 F.2d 1054, 1056 (C.C.P.A. 1981) (rejecting routine optimization argument where allegedly optimized variable "*was not recognized* to be a result-effective variable"). Nowhere does Petitioner assert that any, let alone every one, of the four dosage variables were "result-effective," or that a POSITA would have known by the '838

's priority date how each of these variables would interact in treating TNFIRs. In fact, the words "result-effective" appear nowhere in the Petition. But the Board highlighted *this same deficiency* in *Celltrion*, noting "Petitioner has not demonstrated that each of those parameters represents a result-effective variable, such that a person of skill in the art would have had a reason to optimize it." *Celltrion*, IPR2016-01667, Pap. 15 at 17. Despite having this decision, Petitioner repeats that same failure here, and the same rejection from the Board is warranted.

Third, for "routine optimization" to apply, the evidence must show the *experimentation needed to optimize the variable was known* in the art. *In re Fay*, 347 F.2d 597, 602 (C.C.P.A. 1965). Nowhere does Petitioner present evidence describing the experimentation process that would have allegedly been needed to arrive at the claimed dosing regimen, let alone evidence that such experimentation was known as of the '838's priority date.

Fourth, the *prior art* must "have *suggested to one of ordinary skill in the art that this [experimentation] process should be carried out* and would have a *reasonable likelihood of success*, viewed in light of the prior art." *Merck & Co. v. Biocraft Labs., Inc*., 874 F.2d 804, 809 (Fed. Cir. 1989). Petitioner identifies no such suggestion. Indeed, as discussed *supra* § VIII(A)(1), the only prior art relied on by Petitioner that discusses TNFIRs is De Vita 2001, which indicates the contrary. De Vita 2001 reported that *more frequent dosing* and a *higher total dose*

than claimed in the '838 resulted in *worse* results for TNFIRs who had no response or only an ACR20 response, while other RA patients saw ACR50 and ACR70 responses. Ex.1005 at 1. Moreover, De Vita 2002, which Petitioner attempts to avoid by citing the earlier publication, explained these TNFIRs saw an *increase* in joint erosion. Ex.1060 at 2032. Petitioner has not attempted to, and cannot, reconcile its assertions of a reasonable expectation of success from *decreasing* the total amount and frequency of dosing for TNFIRs with the teachings of its own cited art.

Fifth, the ***experimentation required*** to arrive at the claimed optimum must be "***nothing more than routine***." *Merck & Co*, 874 F.2d at 809. But nowhere does Petitioner provide evidence that any required experimentation—which it never describes to begin with—would have been merely routine.

In sum, because Petitioner has failed to show a POSITA would have arrived at the claimed dosing regimen through "routine optimization," just as in *Celltrion*, this argument fails, and Petitioner has failed to show that the claimed dosing regimen—required in every Challenged Claim—would have been obvious.

(c) Petitioner's Routine Optimization Arguments are Impermissible Hindsight

Petitioner's dosage optimization arguments fail for the additional, independent reason that they are the result of impermissible hindsight.

Arriving at the claimed dosage requires making choices about at least four variables. As set forth below, the dosing in ***every one of Petitioner's prior art references differs from the claimed dosing regimen in at least three of the four dosing variables***. Indeed, De Vita 2001 and Curd differ in ***all four*** variables. Thus, arriving at the claimed dosing regimen would require the POSITA to *ignore* the disclosed dosing and instead pluck out and combine elements in a way that contradicts the very references on which Petitioner relies.

Dosing Variables	**'838 Claimed Dosing Regimen**	**Edwards 2001**	**De Vita 2001**	**Curd**
Dose-Sizing (Fixed v. BSA-Based Dosing)	Fixed	Fixed	BSA	BSA
Total Dosage Amount	2000 mg	2100 mg	Not disclosed ~2400 mg	Not disclosed ~ 809.6 mg to ~2850 mg
Total Number of Doses	2	4	4	4
Amount Per Dose	1000 mg	300 mg, 600 mg, 600 mg, 600 mg	375 mg/m^2	(1) 50 mg/m^2, 150 mg/m^2, 150 mg/m^2, 150 mg/m^2 (2) 150 mg/m^2 375 mg/m^2, 375 mg/m^2, 375 mg/m^2 (3) 375 mg/m^2

As set forth in detail below, looking at this art together, it is only through the use of impermissible hindsight using the '838 as a roadmap that Petitioner, from this art,

purports to "optimize" the dosing to arrive at the claimed dosing regimen. This cannot support obviousness. *See In re NTP, Inc.*, 654 F.3d 1279, 1298-99 (Fed. Cir. 2001) (reversing obviousness finding based on improper "hindsight reasoning to piece together elements to arrive at the claimed invention"); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); *Janssen Pharms., Inc. v. Watson Labs., Inc.*, No. 08-cv-5103, 2012 WL 3990221, at *24 (D.N.J. Sept. 11, 2012) (finding claimed dosing regimen non-obvious where obviousness argument "appears persuasive only from the perspective of the rear-view mirror" and "appears to start with the invention and work backwards").

(i) Dose-Sizing

Under Petitioner's theory, to arrive at the claimed dosing regimen, there is first a choice among dose-sizing options. Among the available options are (i) fixed dosing for all patients as claimed in the '838; (ii) size-based (*i.e.*, variable) dosing based on, *e.g.*, a patient's BSA as was used for treating NHL and taught in De Vita 2001 and Curd for treating RA; or (iii) a combination of the two.

While Petitioner asserts a POSITA would prefer fixed dosing (Pet. at 35 (arguing "fixed dosing was generally used for biologic drugs in the RA field")), the totality of Petitioner's art overwhelmingly suggests otherwise: of Petitioner's three references, only one, Edwards 2001, uses fixed dosing. Ex.1006 at 206. And De Vita 2001, the single cited reference discussing the treatment of TNFIRs (the

relevant population for the Challenged Claims) used *only* BSA-based dosing. Ex.1005 at 1. Curd similarly teaches *only* BSA-based dosing for treating RA.[17] Ex.1016. Petitioner fails to explain why or how, if it is correct that the "prefer[ence]" was for *fixed* dosing (Pet. at 35), most of its cited art, including the only reference that mentions TNFIRs, used *BSA-based* dosing instead.

Petitioner's attempt to justify the selection of fixed dosing based on an alleged concern for operator error in calculating BSA, or based on the way in which TNFα-inhibitors ENBREL® and HUMIRA™ are administered, similarly falls flat. Pet. at 35. Petitioner failed to cite any evidence that a concern of miscalculating BSA existed for the administration of anti-CD20 antibodies generally, or rituximab specifically—the relevant drugs for the '838. Indeed, rituximab was already being administered in BSA-based dosing for treating NHL. Ex.1026 at 2. Moreover, while Petitioner cites the ENBREL® and HUMIRA™ labels to suggest a preference existed for fixed dosing when using biologics to treat RA (Pet. at 35 (citing Exs.1019, 1020)), Petitioner fails to acknowledge that REMICADE®, the third TNFα-inhibitor discussed in the '838, is administered

[17] Contrary to Petitioner's assertion that the dosing ranges disclosed in Curd "includes fixed doses of 1,000 mg" (Pet. at 37), nowhere does Curd disclose "fixed doses." Instead, Curd's dosing is all BSA-based.

using weight-based dosing, not fixed dosing. Ex.1001 4:41-48; Ex.1021 at 21. Petitioner makes no attempt to reconcile REMICADE®'s dosing with its tale of a supposed "prefer[ence]" for fixed dosing.

(ii) Total Dose

Second, for Petitioner to achieve the claimed dosage regimen, the proper total dose of the claimed anti-CD20 antibody or of rituximab must be selected. Even assuming a POSITA would have gone against the majority of Petitioner's own relied-upon art to select fixed dosing to the exclusion of any BSA-based dosing, it is undisputed that *none of the cited art actually teaches the claimed 2000 mg total dose*. Petitioner does not specifically address how or why a POSITA (without the benefit of the '838) would select the total dosage administered to match the '838 claims. Instead Petitioner jumps to its unsupported conclusion that a POSITA would have selected two doses of 1000 mg (and thus, coincidentally, the total dosage claimed in'838 but wholly absent from Petitioner's prior art). And as discussed *supra* §§ VIII(A)(1)-(2) and *infra* § VIII(B), Petitioner fails to reconcile its conclusion with its own cited art, including De Vita 2001, which teaches that harder-to-treat TNFIRs were achieving a less-favorable response at even higher doses.

(iii) Number of Doses

Third, arriving at the claimed dosage regimen as Petitioner suggests would additionally have required determining the number of doses over which to divide the total dose. While each Challenged Claim requires ***two*** infusions, *every one of Petitioner's cited references teaches using at least* ***four*** *infusions*. Ex.1005 at 1; Ex.1006 at 206; Ex.1016 at 25:17-23. Petitioner's assertion that a POSITA would be motived to use fewer infusions (Pet. at 34-35) is thus belied by the very art it cites, *none* of which identified such a need, let alone acted on it.

Petitioner's attempts to justify its hindsight-based selection of two doses by arguing that reducing the number of doses would improve patient compliance and the patient experience (*id*.) are without merit. Nowhere does Petitioner identify any actual patient compliance problem with RA drugs, let alone with those administered intravenously. Indeed, the '838 claims are directed to patients that had previously taken, but did not adequately respond to, TNFα-inhibitor injections and were now trying the claimed therapy. That these patients continue to seek treatment after an inadequate response to prior TNFα-inhibitor treatment suggests they are complying with attempts to treat their RA. This is particularly true given that the very ENBREL® and HUMIRA™ labels Petitioner cites show that both TNFα-inhibitors were administered using significantly more than four doses. Pet. at 35; Ex.1019 at 3, 14; Ex.1020 at 3, 23; *see also* Ex.1021 at 21. Regarding

alleged patient experience improvements, Petitioner fails to explain how subjecting a patient to two infusions—each using significantly more drug than any single infusion in the cited art, thus lengthening the already hours-long infusion time—improves the patient's experience over receiving four smaller infusions. Unlike oral drugs that can be swallowed in an instant, infused therapies like rituximab are administered slowly, with duration depending on the amount administered. Indeed, one article reports the mean time required for a first infusion of only 375 mg/m^2 of rituximab in cancer patients (well below what Petitioner argues would be obvious) was 5.2 hours, with values ranging from 2.5 to 20 hours. Ex.2009 at 2828-2829.

And even if it were assumed that a POSITA would be motivated to decrease the total number of doses from the four in Petitioner's art, Petitioner does not explain why or how a POSITA would have selected exactly two doses instead of three doses or even a single dose. Indeed, by Petitioner's logic a drive to "improve[e] patient compliance by reducing the number of trips that the patient makes to the clinic to treat his or her RA" (Pet. at 35) would actually suggest a single, massive dose. But this is not what Petitioner argues or attempts to explain. This same deficiency was identified by in *Celltrion* where the Board rejected petitioner's dose optimization arguments: "[Petitioner] has not explained why a skilled artisan would not have considered an optimized dose to include three

infusions or some number of infusions with differing, e.g., escalating, dosage amounts." IPR2016-01667, Pap. 15 at 18. Once more, even with that decision in hand, Petitioner does nothing to address this same shortcoming, and this new Petition should similarly be rejected.

(iv) Amount of Each Dose

Finally, arriving at the claimed dosing regimen under Petitioner's argument requires selecting the amount of each infusion: While every Challenged Claim requires two doses of 1000 mg, *none of the cited art identifies a specific initial dose* of an anti-CD20 antibody or rituximab for treating RA *greater than 375 mg/m^2* which, assuming an average BSA of 1.6 m^2 (females) and 1.9 m^2 (males) as Petitioner does, would be 600 mg and 712.5 mg respectively. This is not surprising given that 375 mg/m^2 is the individual infusion dosage for treating NHL and, Petitioner's Edwards 2001 reference explained that it based its protocols using rituximab for treating RA on the type of therapy used for treating NHL. Ex.1006 at 206. Petitioner has not explained why a POSITA would increase the maximum disclosed individual dose for rituximab in treating RA, as well as the maximum individual dose approved to treat cancer (NHL), by more than 40% to arrive at the claimed dosage sizes. Nor has Petitioner explained why a POSITA would have used two infusions of equal size instead of escalating dosage amounts as taught in Edwards 2001 and Curd to avoid adverse reactions. Indeed, in

Celltrion there was additional evidence (which Petitioner ignores) regarding the risk of adverse reactions during initial dosing of rituximab. IPR2016-01667, Pap. 10 at 55-56, Exs. 2066, 2077, 2079, and 2090.

Petitioner argues a POSITA would have modified the *four*-dose, *2100* mg total rituximab regimen in Edwards 2001 to arrive at *two 1000 mg doses* with an expectation of success. Pet. at 36. To begin, Petitioner's analysis ignores that simply changing Edwards 2001 from four doses to two does not result in the claimed dosing regimen. If one simply combined the Edwards 2001 doses together, it would result in one dose of *900* mg and one dose of *1200* mg—not two doses of *1000* mg. Petitioner's analysis also ignores that Edwards 2001 said nothing about treating TNFIRs, while De Vita 2001 indicated that such patients responded differently—and more poorly—to rituximab treatment than other RA patients, like the patients in Edwards 2001. Ex.2005 at 1. It also ignores that, as discussed *supra* § VIII(A)(2), De Vita 2001 obtained these poor results using more frequent doses and a higher total dosage than claimed in the '838. Nowhere does Petitioner cite art suggesting that treating these harder-to-treat patients with less frequent dosing and less total drug would obtain a better result.

Petitioner's additional assertion that two doses of 1000 mg were an obvious choice because rituximab was already supplied in 500 mg and 100 mg vials (Pet. at 37) ignores (1) Petitioner's own prior art, which includes references teaching

dosages that conflict with this argument,[18] and (2) that intermediate dosage amounts—including amounts that were actually used in Petitioner's cited references—can be obtained by combining vials of 100 mg or of 100 mg and 500 mg. For example, the four doses disclosed in Edwards 2001 (300 mg, 600 mg, 600 mg, and 600 mg) can all be obtained using these vial amounts. Nothing about these vial sizes (or about Edwards 2001's actual use of 300 mg and 600 mg dosages that contradict Petitioner's arguments here) suggests the claimed 1000 mg doses.

Faced with the inadequacies in the art it actually relies on, Petitioner attempts to argue that the fact that a 2002 publication by Edwards (Ex.1038) used two doses of 1000 mg to treat RA patients suggests that the claimed dosage for treating TNFIRs was obvious. Pet. at 17-18, 34. Setting aside that Petitioner has conspicuously not relied on Edwards 2002 here as prior art (Pet. at 5)—likely

[18] For example, in dosing schedule A of Curd's Example 1 (Ex.1016 at 25:19-23), the 50 mg/m^2 dosage would be an 80 mg dose for a 1.6 m^2 woman (50 mg/m^2 x 1.6 m^2) and the 150 mg/m^2 dosage would be a 243.2 mg dose for a 1.6 m^2 woman (150 mg/m^2 x 1.6 m^2).

because Petitioner knows it is not[19]—this Board has ***twice*** held that Edwards 2002 does not disclose the treatment of TNFIRs. *See Boehringer*, IPR2015-00417, Pap. 11 at 14; *Celltrion*, IPR2016-01667, Pap. 15 at 10. And correctly so: Edwards 2002 says nothing about how one would treat such patients. Accordingly, the Board in *Celltrion* rejected petitioner's claim that a POSITA would use the dosing disclosed in Edwards 2002 to treat TNFIRs. *Celltrion*, IPR2016-01667, Pap. 15 at 12-13. Along with attempting to bootstrap the Edwards 2002 document into its prior art analysis without being willing to include it as part of any cited prior art combination, Petitioner simply does not address this finding.

Finally, Petitioner's argument that two doses of 1000 mg were obvious because they would produce an "equivalent blood plasma profile" as four doses of 375 mg/m^2 (Pet. at 38) is, at best, improper hindsight. Even assuming a POSITA

[19] Should this petition be instituted, in addition to addressing the numerous other substantive errors and shortcomings that underlie Petitioner's arguments and purported evidence, Genentech anticipates showing the claimed invention was reduced to practice earlier. *See, e.g.*, *Celltrion*, IPR2016-01667, Pap. 13 at 19 (Dec. 6, 2016); *see also id*. at 20-29, Exs.2001-2004, 2007, 2010, 2023, 2036-37, 2041, 2057, 2061-62, 2085, 2088, 2089, 2091-2096, 2098-99. Thus, Edwards 2002 would not be prior art to at least claims 1–3 and 7–9.

would have considered such a calculation in determining dosing— and nothing in Petitioner's POSITA definition (*id*. at 7) suggests a POSITA would possess such pharmacokinetic expertise—Petitioner failed to allege, let alone show, that any such equivalence was known prior to '838. That the '838's own specification references both dosing regimens as therapeutically effective (*Id*. at 40-41) is of no moment here except to confirm Petitioner's improper use of hindsight *from the very '838 Petitioner is challenging*. It says nothing about what a POSITA would have known *prior* to the inventors' disclosure of the claimed invention.

Even assuming (as Petitioner does) that a POSITA would have understood four doses of 375 mg/m^2 to be therapeutically equivalent to two doses of 1000 mg, *De Vita 2001 taught that four doses of 375 mg/m^2 was not effective* for the TNFIRs who are the subject of the Challenged Claims, producing only an ACR20 response in one patient and no response at all in the second. Ex.1005 at 1. Indeed, a POSITA would also know De Vita 2002 further taught, at this dosage, both TNFIRs experienced the further negative result of increased joint erosion. Ex.1060 at 2032. Petitioner fails to explain how this would motivate any POSITA to use "equivalent" dosing to four doses of 375 mg/m^2 or expect a different response in TNFIRs using this "equivalent" dosing.

Because Petitioner failed to show the cited art teaches or suggests treating TNFIRs with the claimed dosing regimen of two 1000 mg doses, Petitioner's obviousness claims fail and institution should be denied.

B. The Petition Fails to Establish that the Claimed Clinical Response Limitations Were Obvious

Claims 2-7 and 10-14 each require an "ACR50 response at week 24," an "ACR70 response at week 24," or "no erosive progression at weeks 24 and beyond." Ex.1001 37:40-38:64; *supra* § VII(B).[20] However, none of Petitioner's art teaches or suggests the claimed clinical responses in TNFIRs, and the Petition should be denied for this additional reason.

No Disclosure of ACR50 or ACR70 Responses: While apparently acknowledging Curd discloses *no clinical response whatsoever*, Petitioner misleadingly argues Edwards 2001 and De Vita 2001 "disclose ACR50 and ACR70 responses." Pet. at 50. What Petitioner omits, of course, is that these responses were ***not*** reported ***in the claimed TNFIR population***. Indeed, Edwards

[20] Petitioner's suggestion that the claimed clinical responses should be ignored because the '838 does not disclose clinical data demonstrating these responses (Pet. at 50-51) is, *inter alia*, meritless. The '838 describes these clinical outcomes in the specification and claims them in the Challenged Claims. Ex.1001 31:42-32:34, 37:40-38:64.

2001 is silent as to whether the patients were TNFIRs. Ex.1006. And De Vita 2001's two TNFIRs achieved only (1) a transient ACR20 response followed by relapse and (2) no response at all, respectively. Ex.1005 at 1; Ex.1060 at 2030-32. It was the *other* patients in De Vita 2001—not the TNFIRs—who achieved ACR50 and ACR70 responses. Ex.1005 at 1. Indeed, contrary to Petitioner's argument that a POSITA would expect the same responses in both populations or would have a reasonable expectation of success in achieving the same responses in both populations (Pet. at 50-51), De Vita 2001 itself reported that TNFIRs respond differently (and less well) to rituximab than other RA patients, such that obtaining ACR50/ACR70 responses in certain RA patients *did not correlate to achieving those responses in TNFIRs*. Nowhere does Petitioner explain this inconsistency in its arguments with De Vita 2001.

No Disclosure of No Erosive Progression: Tellingly, Petitioner also remains silent regarding any alleged teaching or suggestion in the art of the claimed "no erosive progression at 24 weeks and beyond," as specifically required by claims 10 and 14. Curd and Edwards 2001 are silent as to erosive progression, and the TNFIRs in De Vita 2001 (as explained in De Vita 2002) actually saw an ***increase*** in joint erosion. Ex.1060 at 2032. Even if one were to accept Petitioner's argument that the cited art rendered obvious the claimed dosing regimen (and, as set forth above, it does not), Petitioner makes no attempt to explain why a POSITA

would have a reasonable expectation of success in obtaining no erosive progression in the very patients De Vita 2002 reported as experiencing an increase.

Finally, in an attempt to avoid the lack of disclosure in its cited art, Petitioner asserts that the claimed clinical responses are the "inevitable result" of administering the claimed dosing regimen. Pet. at 50. Petitioner then reasons that because the dosing regimen would be obvious, the claimed clinical responses, too, are obvious. *Id*. Petitioner's argument is without merit. For the reasons discussed *supra* § VIII(A), Petitioner has failed to establish the cited art taught or suggested the claimed dosing regimen. And even if it did, Petitioner has failed to establish that the claimed clinical outcomes are the necessary consequence, or inherent result, of the treatment described in the other claimed steps, particularly for hard-to-treat TNFIRs.

Because Petitioner has failed to show that the cited art teaches or suggests the claimed clinical responses in TNFIRs, Petitioner's claim 2–7 and 10–14 arguments fail and institution should be denied for this additional reason.

IX. Conclusion

Petitioner has failed to show that there is a reasonable likelihood that it will prevail in proving any Challenged Claim unpatentable, and the Petition should be denied in its entirety.[21]

Respectfully submitted by: Dated: January 5, 2018

/J. Steven Baughman /
J. Steven Baughman (Reg. No. 47,414)
Paul, Weiss, Rifkind, Wharton &
Garrison LLP
2001 K Street, NW
Washington, DC 20006-1047
P: 202-223-7340/F: 202-403-3740
sbaughman@paulweiss.com

Megan Raymond (Reg. No. 72,997)
Paul, Weiss, Rifkind, Wharton &
Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com

Attorneys For Patent Owner

[21] Patent Owner reserves the right to make additional arguments based on the Supreme Court's decision in *Oil States* (No. 16-712, now pending).

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107 complies with the type-volume limitation in 37 C.F.R. § 42.24(b)(1). According to the word-processing system's word count, the brief contains 13,975 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a)(1).

Dated: January 5, 2018

Respectfully Submitted,

By: /s/ Megan Raymond

Megan Raymond (Reg. No. 72,997)
Paul, Weiss, Rifkind, Wharton & Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

Petitioner's Counsel of Record:

Siegmund Gutman (Reg. No. 46,304)
Colin Cabral (Reg. No. 73,952)
Graham Cole (Reg. No. 72,626)
Christopher Lynch (Reg. No. 68,915)
Proskauer Rose LLP
2049 Century Park East
Los Angeles, CA 90067
Telephone: (310) 284-4533
Facsimile: (310) 557-2193
sgutmanptabmatters@proskauer.com
ccabral@proskauer.com
gcole@proskauer.com
clynch@proskauer.com

Dated: January 5, 2018

Respectfully Submitted,

By: /s/ Crystal Lohmann Parker

Crystal Lohmann Parker
Paul, Weiss, Rifkind, Wharton & Garrison LLP
1285 Avenue of the Americas
New York, NY 10019
Tel: (212) 373-3069
Fax: (212) 492-0069
cparker@paulweiss.com