UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Boehringer Ingelheim International GmbH and
Boehringer Ingelheim Pharmaceuticals, Inc.
Petitioner

v.

Genentech, Inc.
Patent Owner

CASE IPR2015-00417
Patent 7,976,838

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

TABLE OF CONTENTS

Page

Page

Page

Page

Cases

Statutes

I. INTRODUCTION

Rheumatoid arthritis ("RA") is a debilitating autoimmune disorder with no known cure and a dreadful prognosis. RA patients suffer a chronic course of disease that, even with therapy, often results in painful joint destruction, deformity, disability, and even premature death. Ex. 1001 at 4:3-7.

RA therapy has been "traditionally characterized by escalation." Ex. 1028 at 309. "The first step is non-steroidal anti-inflammatory drugs (NSAIDs), and then if necessary a sequence of progressively toxic second-line drugs (disease-modifying antirheumatic drugs [DMARDs]) is introduced." *Id.*

In the 1990s, targeted therapies called TNFα-inhibitors kindled new hope for RA patients. But for many patients, that hope proved fleeting. According to Petitioner, physicians quickly recognized that "[a]pproximately 40% of patients do not respond to TNFα-inhibitors." Pet. 36. Because "TNF-inhibitors were generally given after the patient had failed at least 2-3 conventional RA therapies, . . . patients who were eligible for treatment with TNF-inhibitors [in the first place] had already demonstrated that their disease was particularly hard to treat and drug-refractory." Ex. 1016 at ¶ 6. Patients needed an effective alternative treatment.

For years, RA patients who responded inadequately to TNFα-inhibitors had no other meaningful choices. Genentech, Inc. sought to change that—and succeeded. Genentech believed that rituximab (Rituxan®), a treatment initially developed and FDA approved for treating certain types of blood cancers, could be taken at a

different dose and dosing schedule to treat RA patients. And Genentech was correct. The results of clinical testing were remarkable. Nearly one third of RA patients demonstrated clinical improvement in a matter of months. For certain patients, rituximab actually halted erosive progression of RA. The FDA approved rituximab for the treatment of patients with moderate to severe RA who had experienced an inadequate response to a TNFα-inhibitor.

Genentech ultimately obtained U.S. Patent 7,976,838 (the '838 patent) for this novel treatment. Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (together "Boehringer") now request *inter partes* review of the patent. Because they have failed to demonstrate a reasonable likelihood of prevailing with respect to any claim, their request should be denied.

Every reference Boehringer relies on was fully considered by the Patent Office during examination, except for an abstract that the Office previously considered in the form of a full-length article. The Patent Office determined that none of these references renders the claims unpatentable. Boehringer has failed to identify any teachings in the references that support a contrary conclusion.

Because it cannot carry its burden, Boehringer instead attempts—in the guise of claim construction—to read out of the claims various limitations that it finds problematic. This includes one of the defining characteristics of the claimed methods: treating "a human patient who experiences an inadequate response to a TNFα-inhibitor." Boehringer argues that this description of the patient should be ignored

because it appears in the preambles of claims. Yet the patent specification makes clear that this targeted patient is a key characteristic of the inventions. Indeed, the description of the targeted patient in each preamble provides the antecedent basis for references to "the patient" in the bodies of the claims. Boehringer's attempt to read this key limitation (and others) out of the claims is contrary to law.

Although Boehringer asserts that the claims are anticipated, it does not even try to show that all of the claim elements and their limitations are expressly disclosed in a single prior art reference. Rather, Boehringer's anticipation position depends on its effort to read limitations out of the claims. Because that effort fails, so too does Boehringer's anticipation argument. Boehringer's fallback position—that the alleged prior art inherently discloses these limitations—also fails. There is no evidence that the limitations were necessarily present in prior art. Boehringer tries to rely on probabilities to establish inherent anticipation, even though the Federal Circuit has repeatedly held that probabilities are never sufficient to establish an inherent disclosure. Limitations must be necessarily present, not probably present.

As for its obviousness challenge, Boehringer never even tries to explain how any reference or combination of references allegedly renders obvious any claim of the patented invention. Boehringer never identifies differences between any claim and any reference, much less explains how the differences allegedly would have been bridged by modification or combination with other references. Nor does Boehringer articulate any reason for a skilled artisan to have modified or combined specific references, any

basis for concluding that its modifications or combinations would have been obvious to try, or any reasonable expectation of success in practicing the claimed inventions. Instead, Boehringer simply addresses claim limitations piecemeal, lists references and combinations in a table without explanation, and improperly tries to lay the burden on the Board to divine some theory of obviousness. The Board repeatedly has declined to institute trial under such circumstances.

Boehringer also fails to rebut the objective indicia of non-obviousness, including evidence of record that the claimed inventions satisfied a long-felt but unsolved need for treatment of RA in patients who did not respond to anti-TNFα therapy. And Boehringer fails to rebut the evidence of unexpected results, including no erosive progression of RA in more than half of such patients.

Boehringer's petition for *inter partes* review falls far short of demonstrating a reasonable likelihood of prevailing with respect to any claim of the '838 patent. The Board should therefore decline to institute trial.

II. BACKGROUND

A. Prosecution History

The prosecution of the '838 patent began with a provisional application filed on April 9, 2003. Ex. 1001. Boehringer acknowledges that the claims of '838 patent are entitled to at least that priority date. Pet. 5-6.

Every reference that Boehringer identifies in its "Prior Art and Proposed Combinations" (Pet. 55-57) was cited during prosecution of the '838 patent and

considered by the Patent Office, with one exception: Instead of the clinical study abstract that Boehringer refers to as "De Vita 2001" (Ex. 1006), a full-length article reporting on the very same study was cited and considered. Ex. 1001 (identifying in the "References Cited" De Vita *et al.*, "Efficacy of Selective B Cell Blockade in the Treatment of Rheumatoid Arthritis," Arthritis and Rheumatism 46(8): 2029-2033 (Aug. 2002)).

The Office rejected claims based on several of the cited references, including the full-length De Vita article and a clinical protocol for the study reported in the "Tuscano" abstract (Ex. 1008). Genentech distinguished these references and also presented compelling evidence of long-felt unmet need and unexpected results. E.g., Ex. 1036 at 11-12. The Office agreed that the cited references neither anticipated nor rendered obvious the claimed inventions. Ex. 2001 at 2.[1]

B. FDA Approval Of Rituximab To Treat Rheumatoid Arthritis

Rituximab is an antibody that binds to a cell-surface antigen called CD20. Ex. 1001 at 2:32-34. Genentech first obtained FDA approval for rituximab in 1997

[1] Boehringer asserts that "the European Patent Office revoked the foreign counterpart of the '838 patent because it lacked novelty," Pet. 10 n.4, but fails to mention that the Technical Board of Appeal later overturned the EPO's decision on novelty, finding that the subject matter was "novel and fulfils the requirements of Article 54 EPC." Ex. 1018 at 27.

for treatment of relapsed or refractory, low-grade or follicular non-Hodgkin's lymphomas. Ex. 1012. Genentech later worked with collaborators to study administration of two 1000-mg doses of rituximab—a different dosing regimen than that approved for treatment of the non-Hodgkin's lymphomas—in patients with active moderate to severe RA who had a prior inadequate response to at least one TNF inhibitor. Genentech's pivotal Phase III clinical trial was called "REFLEX."

To assess patient responses, the REFLEX investigators used a scale developed by the American College of Rheumatology to assign an "ACR" score to measure improvements. Ex. 2002 at 733-34. The score is expressed as a percentage, which refers to [a] the percent fewer tender joints, [b] the percent fewer swollen joints, and [c] the percent improvement in at least three of the following five additional areas: (i) the patient's overall (global) assessment of his or her own RA, (ii) the physician's global assessment of the patient's RA; (iii) the patient's assessment of his or her own pain; (iv) the patient's assessment of his or her own physical functioning; and (v) the results of an erythrocyte sedimentation rate test or a C-reactive protein blood test (both of which measure inflammation). *Id.* To score ACR70, for example, a patient must have at least 70% fewer tender joints, at least 70% fewer swollen joints, and at least 70% improvement in at least three of areas (i)-(v) above.

The limitations of the ACR scoring system are well known—particularly in open-label studies, where both the doctor and the patient know that active drug is being administered to the patient. "Of the 7 outcome measures [for the ACR scale],

3 are at least to some extent subjective on the part of the physician (tender joint count, swollen joint count, and Physician's global assessment of disease activity), and 3 are subjective on the part of the patient (patient's assessment of pain, patient's global assessment of disease activity, and patient's assessment of physical function)." Ex. 2003 at ¶ 9. Because of this subjectivity, "observer bias inevitably occurs due to the desire by both the patient and physician to see improvement in the disease outcomes due to treatment." *Id.*

Double-blind studies, where neither the doctors nor the patients know who is receiving the studied therapy, are preferred because they eliminate observer bias based on knowledge of the treatment. But even double-blind studies remain vulnerable to the "placebo effect"—when a patient who is administered an inactive substance nevertheless perceives, or actually experiences, some level of improvement. Placebo effects are especially problematic in RA studies because, as one leading RA expert explains: "it has been clearly demonstrated that ACR20 responses are seen in a sizeable proportion of patients given 'placebo' (inactive substance) treatment in the setting of a controlled trial (where other patients are receiving an active drug)." Ex. 1016 at ¶ 17. "Among such 'placebo'-treated patients, 20-30% may show an ACR20 response, which is believed to be due to the placebo effect or to the naturally occurring fluctuations of the disease." *Id.*; *see also* Ex. 2004 at 1935 (showing in Fig. 2 that about 20% of placebo patients exhibited an ACR20 response); Ex. 2005 at 2546 (showing in Fig. 2 that about 30% of placebo patients scored at ACR20 or higher

starting at month 3); Ex. 2006 at 1062 (reporting in the Abstract that 22% of placebo patients achieved ACR20 scores and 8% achieved ACR50 scores).

To reduce observer bias and distinguish placebo effects, REFLEX was conducted as a double-blind, placebo-controlled study. The results of the study showed marked improvement in TNFα inadequate responders who received two 1000 mg doses of rituximab plus methotrexate. Indeed, more than half of such patients achieved ACR20 scores (versus 18% for placebo plus methotrexate), 27% achieved ACR50 scores (versus 5% for placebo plus methotrexate), and 12% achieved ACR70 scores (versus 1% for placebo plus methotrexate) at 24 weeks. Ex. 2007 at 2793. Based on these remarkable results in this particularly hard-to-treat patient population, the FDA approved rituximab in combination with methotrexate for treatment of "patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies." Ex. 2011 at 18.

Importantly, an extension to the REFLEX study also showed that rituximab prevented erosive progression in 60% of patients evaluated—even after two years; that 87% of patients who had no erosive progression in the first year also had no erosive progression in the second year; and that patients treated with a different dose of rituximab did not achieve the same outcome. Ex. 2008 at 27-28.

III. CLAIM CONSTRUCTION

The Board gives a patent claim its "broadest reasonable interpretation consistent with the specification." *In re Bond*, 910 F.2d 831, 833 (Fed. Cir. 1990).

Boehringer's claim construction positions are unreasonable because, among other things, they expressly read out nearly half the words—or more—of each claim. In fact, Boehringer invites the Board to eviscerate entire claims through what it calls "construction." Indeed, under its proposals, multiple dependent claims would be reduced to nothing more than: "The method of claim [#]."

A. The Preamble Phrase "a human patient who experiences an inadequate response to a TNFα-inhibitor" Is Limiting.

A preamble is limiting if it "recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim." *NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1305 (Fed. Cir. 2005). The preamble phrase, "a human patient who experiences an inadequate response to a TNFα-inhibitor," does both. The target patient is the object of the claimed steps and provides the antecedent basis for references to "the patient" in the body of each claim. Moreover, the specification makes clear that this target patient is a critical characteristic of the claimed inventions. And Genentech relied on the description of the target patient to distinguish prior art during prosecution. The description of the target patient in the preambles is limiting.

1. "[A] human patient who experiences an inadequate response to a TNFα-inhibitor" Is Limiting Because It Provides The Antecedent Basis For "the patient" In The Body Of Each Claim.

Language in a claim preamble is limiting "[w]hen 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); *NTP,* 418 F.3d at 1306

(finding that reference to "the" destination processors in body of a claim referred to preamble antecedent "destination processors in the electronic mail system" and that "based on this antecedent relationship, a destination processor . . . must also be 'in an electronic mail system.'").

The Board regularly applies this rule to find a wide range of preamble language limiting. *See, e.g.*, *Ex Parte Lutz*, Appeal 2010-007127, 2013 WL 1309969 (P.T.A.B. Mar. 14, 2013) ("The body of the claim relies on the preamble for antecedent basis for the 'valve disk.' The preamble limits the disk to a particular type of structure used in the method—one that deforms to throttle a fluid."); *Phigenix, Inc. v. Genentech, Inc.*, IPR2014-00842, Paper 10 at 8 (Dec. 9, 2014) ("We consider the phrase 'method for the treatment of a tumor' in the preamble to be limiting, especially when read in combination with the 'whereby' clause reciting that 'said tumor' [has certain characteristics]" because "[t]hose limitations define a critical component of the challenged claims."); *Brinkman Corp. v. Coprecitec S.L.*, IPR2013-00435, Paper 6 at 8-9 (Oct. 29, 2013) (holding preamble term "a natural gas" limited controller described in body of claim as "specifically configured for the delivery of the natural gas").

The steps recited in the body of all '838 patent claims repeatedly refer to "the patient." Who is "the patient"? The answer is found in the preamble language that Boehringer would have the Board ignore. The claims use the indefinite article "***a***" in the preamble to introduce "a human patient who experiences an inadequate response to a TNFα-inhibitor" and then repeatedly use the definite article "***the***" in the bodies

of the claims to refer back to "the patient" defined in the preamble. Ex. 1001.[2] The preamble phrase therefore plainly defines and limits the scope of each claim.

Boehringer argues that deleting the preamble phrase "would not affect the structure or steps" of the inventions because "[t]he methods of treatment are the same regardless of who receives them." Pet. 12. That is incorrect. The claimed methods of treatment are ***expressly defined by*** who receives the treatment. The claims recite administering a CD20 antibody to "the patient," which the preamble defines as "a human patient who experiences an inadequate response to a TNFα-inhibitor." Deleting the preamble phrase would leave unspecified to whom the CD20 antibody is administered. A preamble is limiting where, as here, "the claim drafter [chose] to use both the preamble and the body to define the subject matter of the claimed invention." *Bell Commc'ns Research. v. Vitalink Commc'ns.*, 55 F.3d 615, 620 (Fed. Cir. 1995).

2. The Specification Makes Clear That "a human patient who experiences an inadequate response to a TNFα-inhibitor" Is An Important Characteristic Of The Claimed Invention.

In assessing whether preamble language is limiting, it is important to undertake a "review of the entirety of the patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim." *Corning Glass Works v.*

[2] The preamble of claim 11 varies slightly: "a human rheumatoid arthritis patient who experiences an inadequate response to a TNFα-inhibitor."

Sumitomo Electric USA, Inc., 868 F.2d 1251, 1257 (Fed. Cir. 1989). A specification "replete with references" to preamble language shows that the inventor considered such language "an important characteristic of the claimed invention" and that the preamble language is limiting. *Poly-Am., LP v. GSI Lining Tech., Inc.*, 383 F.3d 1303, 1309-10 (Fed. Cir. 2004); *Rotable Techs., LLC v. Motorola Mobility LLC*, 567 F. App'x 941, 943 (Fed. Cir. 2014) (finding preamble term "selectively rotating" limiting because "[t]he specification is replete with references to 'selectively rotating,' underscoring the importance of the feature to the claimed invention").

The administration of rituximab to "patients who experience an inadequate response to a TNFα-inhibitor" appears throughout the specification of the '838 patent—starting with the title: "Therapy of Autoimmune Disease In A Patient With An Inadequate Response To A TNFα Inhibitor." Ex. 1001. The discussion runs through the abstract, *id.*, the Field Of The Invention, *id.* at 1:15-18, the Summary Of The Invention, *id.* at 4:60-5:1, and the Detailed Description Of The Preferred Embodiments. *Id.* at 28:45-48; 31:8-10. The specification thus shows that the preamble's description of the target patient is a critical characteristic of the claimed invention, establishing another independent reason that this preamble language is limiting. *Rotable Techs.,* 567 F. App'x at 943 (finding preamble term "selectively rotating" limiting where "patent's title, abstract, background of the invention, summary of the invention, description of the drawings, detailed description, and all independent claims recite 'selectively rotating'").

3. Reliance On "a human patient who experiences an inadequate response to a TNFα-inhibitor" To Distinguish Prior Art During Prosecution Also Indicates That The Phrase is Limiting.

"[C]lear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com*, 289 F.3d 801, 808 (Fed. Cir. 2002); *Smith & Nephew, Inc. v. Bonutti Skeletal Innovations, LLC*, IPR2013-00605, Paper 9 (Feb. 26, 2014). In the *Smith & Nephew* IPR, the Board found preamble language limiting because it "was relied on during prosecution to distinguish the prior art." *Id.* at 8-9.

Here, Boehringer argues that "[t]here is no suggestion in the prosecution history that the patentee ***added*** this preamble phrase to distinguish the alleged invention from the prior art." Pet. 35 (emphasis added). Boehringer cites no authority for limiting the applicable rule of claim construction to amendments made during prosecution—and none exists. Boehringer simply ignores that Genentech expressly relied on the preamble language during prosecution to distinguish alleged prior art. For example, in a December 17, 2010 claim amendment, Genentech distinguished a Tuscano reference from pending claim 24 on the ground that the reference "does not disclose treating anti-TNF inadequate responders." Ex. 1036 at 8. This is yet a third independent reason why the description of the patient in the preambles is limiting.

4. "[A] human patient who experiences an inadequate response to a TNFα-inhibitor" Is Someone Who Has Actually Experienced An Inadequate Response To A TNFα-inhibitor.

Boehringer ultimately retreats to the position that, "[t]o the extent the preamble phrase is deemed to be a limitation," an inadequate response "may be experienced in patients ***who have never been treated with TNFα-inhibitors***." Pet. 13 (emphasis added). That argument runs contrary to core principles of claim construction. It is well-established that "[w]hen a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009). The '838 patent contains such a definition: "The term 'inadequate response to a TNFα-inhibitor' refers to an inadequate response ***to previous or current treatment*** with a TNFα-inhibitor because of toxicity and/or inadequate efficacy." Ex. 1001 at 5:25-28 (emphasis added). Accordingly, "a human patient who experiences an inadequate response to a TNFα-inhibitor" is, by definition, someone who experiences an inadequate response to previous or current treatment with a TNFα-inhibitor—i.e., someone who has been, or is being, so treated. The express definition is logical: a person cannot "experience" a response (inadequate or otherwise) to something to which he or she has never been exposed.

Boehringer asserts that "the specification of the '838 patent explains that an 'inadequate response' [to TNFα-inhibitors] can be experienced due to toxicity and/or lack of efficacy, even if the patient has never been treated with TNFα-inhibitors." Pet. 12. The specification says nothing of the sort. The passage cited by Boehringer

expressly juxtaposes a patient "who experiences an inadequate response to previous or current treatment with a TNFα-inhibitor" with a patient who "may be considered to be prone to experience a toxicity, e.g., cardiac toxicity, with a TNFα-inhibitor before therapy has begun" or who "may be determined to be one who is unlikely to respond to therapy with a TNFα-inhibitor." Ex. 1001 at 28:45-61. Nowhere does the patent describe individuals who are prone to experience toxicity or are unlikely to respond to therapy with a TNFα-inhibitor as having ***experienced*** an inadequate response to a TNFα-inhibitor. Boehringer's suggestion otherwise is nonsensical.

The '838 patent claims are limited to a patient "who experiences an inadequate response to a TNFα-inhibitor" and therefore require that the patient actually have received TNFα-inhibitor therapy (and responded inadequately). The Board should reject Boehringer's construction because it disregards the claim language.

B. "[T]wo intravenous doses of 1000 mg" In Claim 2 Cannot Be Construed To Be The Same As "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."

Boehringer appears to argue that "two intravenous doses of 1000 mg" should be equated with "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." Pet. 13. The Board should reject Boehringer's argument because it is factually and legally unsupportable.

Factually, Boehringer admits that two 1000-mg doses of a CD20 antibody such as rituximab will not produce any clinical response in some patients. *See, e.g.,* Pet. 47 ("This treatment will produce a clinical response in some ***but not all*** patients.") (emphasis added). Accordingly, it is not the case that "two intravenous doses of 1000 mg" will be "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" in every patient. The two phrases simply cannot be equated.

Legally, Boehringer's argument is erroneous because it equates two different terms in the same claim. "In the absence of any evidence to the contrary, we must presume that the use of [] different terms in the claims connotes different meanings." *CAE Screenplates Inc. v. Heinrich Fiedler GmbH & Co. Kg*, 224 F.3d 1308, 1317 (Fed. Cir. 2000). Boehringer cites no such evidence to the contrary. Indeed, the evidence shows that the two terms cannot be equated as a factual matter, as explained above.

C. <u>The "wherein" Clauses Of Claims 10 And 12-14 Are Limiting.</u>

The "wherein" clauses of claims 10 and 12-14 relate back to and clarify the claimed "administering" steps and methotrexate limitations. They do not state a necessary result of other limitations in the claims, and construing them away would create absurd outcomes. Moreover, Genentech's reliance on limitations in the "wherein" clauses during prosecution to distinguish prior art further indicates that they are limiting. The Board should reject Boehringer's invitation to read these clauses out of the claims.

1. The "wherein" Clauses Relate Back To And Clarify The "administering" Steps And The Methotrexate Limitations.

"Wherein" clauses are given limiting effect where they "relate back to and clarify what is required by the [claim]." *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002). Claims 10 and 12-14 of the '838 patent recite methods comprising "administering to the patient rituximab, and methotrexate," wherein certain clinical responses are achieved (e.g., "wherein the patient has no erosive progression at weeks 24 and beyond" in claim 10). While the earlier portions of these claims state the amount of rituximab to be administered (two 1000 mg doses), they do not specify an amount of methotrexate to be administered. The later "wherein" clauses relate back to the "administering" steps and clarify how much methotrexate is to be administered with the rituximab—namely, a quantity sufficient to produce the claimed clinical response as a result of the treatment. Accordingly, the "wherein" clauses of claims 10 and 12-14 are limiting.

2. The "wherein" Clauses Do Not State Necessary Results Of Other Limitations In The Claims.

Boehringer relies on *Texas Instruments v. ITC* to argue that "'[a] "***whereby***" clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim.'" Pet. 14 (emphasis added). Boehringer's argument fails because a "***wherein***" clause—as found in claims 10 and 12-14—is not the same as a "whereby" clause. *See, e.g., Griffin*, 285 F.3d at 1034 ("Griffin cites other cases in which the court determined that 'whereby' clauses were nonlimiting. Aside

from the fact that 'wherein' is an adverb and 'whereby' is a conjunction, those cases are all fact-specific . . . ."); *Integraph Hardware Techs. Co. v. Toshiba Corp.*, 508 F. Supp. 2d 752, 768-69 (N.D. Cal. 2007) (emphasizing distinction between "whereby" and "wherein," noting that "no case where a 'wherein' clause was held not to impose a limitation" had been cited, and finding the "wherein" clause at issue limiting).

Even if the test for "whereby" clauses were applied to "wherein" clauses, the "wherein" clauses here cannot be disregarded because they do not merely state necessary results of other claim limitations. Rather, they describe certain clinical responses that may or may not result from practicing the rest of the claim. As Boehringer admits, the claimed treatment will not produce a clinical response in some patients. Pet. 47. Thus, unlike the "whereby" clause in *Texas Instruments*, which "merely describe[d] the result of arranging the components of the claims in the manner recited," the "wherein" clauses here specify additional requirements that are not the necessary results of other limitations of the claims. 988 F.2d 1165, 1172 (Fed. Cir. 1993). The *Texas Instruments* case is inapposite.

Boehringer's reliance on *Ex Parte Berzofsky* is similarly unavailing. There, the claim described a "method of inhibiting recurrence of a tumor in a subject" comprising "administering a therapeutically effective amount of a [particular] monoclonal antibody" and also included language in a "wherein" clause about "inhibiting recurrence of the tumor in the subject." Appeal No. 2010-011270, 2011 WL 891756, at *1. The Board concluded that "the wherein clauses do not inform the

mechanics of how the 'administering' or 'contacting' steps are performed; rather, the wherein clauses merely characterize the result of that step." *Id.* at *5. As discussed above, that is simply not the case here. For example, the wherein clauses here specify that the amount of methotrexate to be administered must be sufficient to achieve certain clinical responses not otherwise required.

3. Construing The "wherein" Clauses Of Claims 12-14 As Nonlimiting Would Create Absurd Outcomes.

Claims 12-14 depend from claim 11, which recites a method of achieving a clinical response selected from a group consisting of three responses. Each dependent claim further limits that method by selecting one of those three responses, using the format: "The method of claim 11 wherein the clinical response is [one of the three responses of claim 11]." Thus, construing the "wherein" clauses of claims 12-14 as non-limiting would reduce each of those claims to simply: "The method of claim 11." That outcome is both absurd and contrary to law. "It is a well-settled canon of claim construction that claims should be interpreted such that each word is given meaning." *Ex Parte Behzad*, Appeal 2011-007124, 2014 WL 1311619, at *2 (P.T.A.B. Mar. 28, 2014); *Funai Elec. Co. v. Daewoo Elecs. Corp.*, 616 F.3d 1357, 1372 (Fed. Cir. 2010) ("We must give meaning to all the words in the claims.").

4. Reliance During Prosecution On Limitations In The Disputed "wherein" Clauses To Distinguish References Further Indicates That Those Clauses Are Limiting.

During prosecution, Genentech distinguished cited references by relying on subject matter in the "wherein" clauses at issue. For example, in a December 17, 2010 amendment, Genentech distinguished a Tuscano reference on the ground that it "nowhere mentions 'an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond." Ex. 1036 at 9. Genentech also argued that a De Vita reference failed to disclose ACR50 or ACR70 responses in anti-TNF inadequate responders. *Id.* at 6. Because Genentech used the limitations of the wherein clauses to distinguish references during prosecution, the subject matter of the wherein clauses is limiting. *Cf. Catalina,* 289 F.3d at 808 (finding that "clear reliance" on claim language "during prosecution to distinguish the claimed invention from the prior art . . . indicates use of the [language] to define, in part, the claimed invention"); *Tempo Lighting, Inc. v. Tivoli, LLC*, 742 F.3d 973 (Fed. Cir. 2014) (holding prosecution history "serves as intrinsic evidence . . . in construing patent claims before the PTO").

D. <u>The Phrase "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" Is Limiting.</u>

1. The "achieving a clinical response" Phrase In The Preambles Of Claims 12-14 Is Limiting Because The Bodies of The Claims Depend On And Derive Antecedent Basis From The Phrase.

As discussed in Section III.A.1 above, preamble language is limiting "[w]hen limitations in the body of the claim rely upon and derive antecedent basis from the

preamble." *Eaton*, 323 F.3d at 1339. Dependent claims 12-14 all refer to "***the*** clinical response," which derives antecedent basis from the preamble phrase in independent claim 11, "***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." Accordingly, the preamble phrase is limiting.

Boehringer's reliance on *Pitney Bowes* and *Rowe* is misplaced because the courts in both case found the preamble language at issue limiting. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305-06 (Fed. Cir. 1999); *Rowe v. Dror*, 112 F.3d 473, 478-79 (Fed. Cir. 1997). Like the bodies of the claims in those two cases, the bodies of claims 11-14 do not "'fully and intrinsically set[] forth the complete invention, including all of its limitations'" or "'define[] a structurally complete invention,'" contrary to Boehringer's suggestions. Pet. 16-17 (quoting both cases). Rather, the bodies of claims 12-14 rely on the preamble of claim 11 as the antecedent basis for their recitations of "the clinical response," as discussed above. The preamble is therefore limiting because the patentee chose "to use both the preamble and the body to define the subject matter of the claimed invention." *Bell*, 55 F.3d at 620.

2. Reliance On The Claimed Responses To Distinguish References During Prosecution Further Indicates That The Same Phrase In The Preamble Of Claim 11 Is Limiting.

When a patentee distinguishes prior art based on certain claim language, the patentee's use of the same language in the preamble of a new claim indicates that the language is being used to define the claimed invention and therefore is limiting. *Smith*

& Nephew, 2014 WL 1253096, at *5 (finding a preamble term limiting because the patentee distinguished prior art based on the same term nearly a year before adding the claim).[3] Here, Genentech distinguished a Tuscano reference during prosecution on the ground that it "nowhere mentions 'an ACR50 response at week 24, ACR70 response at week 24, or no erosive progression at weeks 24 and beyond.'" At the same time, it added this precise language to the preamble of claim 11, from which claims 12-14 depend. Ex. 1036 at 9. This confirms that the language in the preamble defines the claimed inventions.

IV. BOEHRINGER FAILS TO DEMONSTRATE ANY REASONABLE LIKELIHOOD OF PREVAILING ON ANTICIPATION.

"Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference." *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009) (reversing finding of anticipation under broadest reasonable interpretation standard). Unable to meet this exacting standard, Boehringer tries to read limitations out of the claims to manufacture an anticipation argument. It then tries to fall back on inherency arguments that are contrary to law. Boehringer's anticipation arguments fail.

[3] In *Smith & Nephew*, the patentee distinguished the term in a May 8, 2008 Response in Application 11/170,969, and added the claim on March 20, 2009.

A. Boehringer Erroneously Reads Limitations Out Of The Claims To Make Its Anticipation Arguments.

Boehringer asserts that Edwards 2002 (Ex. 1003) and the Genentech Press Release (Ex. 1004) anticipate claims 1-5 and 7-14. All of these claims include, among other limitations, treatment of rheumatoid arthritis "in a human patient who experiences an inadequate response to a TNFα-inhibitor." Ex. 1001. Claims 10 and 14 also include, for example, limitations requiring a clinical response of "no erosive progression at weeks 24 and beyond." *Id.* But neither Edwards 2002 nor the Genentech Press Release describes any study participant as a TNFα-inadequate responder, and neither reference describes a clinical response of no erosive progression, let alone at weeks 24 and beyond.

Boehringer does not contend otherwise. Rather, Boehringer argues that the claims should be construed so that the terms "in a human patient who experiences an inadequate response to a TNFα-inhibitor" and "no erosive progression at weeks 24 and beyond" are non-limiting. Boehringer's position is wrong as a matter of law, as explained in Section III above. Because these claim limitations cannot be construed away, Boehringer's anticipation arguments fail.

B. Boehringer's Fallback Position That The Alleged Prior Art Inherently Discloses The Limitations Sought To Be Read Out Of The Claims Also Fails As A Matter Of Law.

Boehringer argues that if the term "in a human patient who experiences an inadequate response to a TNFα-inhibitor" is limiting, it is "inherently and necessarily

disclosed in the prior art" because "[a]pproximately 40% of patients do not respond to TNFα-inhibitors." Pet. 36. Boehringer's reliance on percentages as proof of inherency is misplaced for at least two separate reasons.

First, Boehringer uses what it asserts to be the overall percentage of RA patients who ***would*** experience an inadequate response ***if*** they took TNFα-inhibitors. This is based on Boehringer's tortured claim construction position that an inadequate response to a TNFα-inhibitor can be experienced by a patient even if the patient has never been treated with a TNFα-inhibitor. But that claim construction position is untenable, as discussed in Section III.A.4. Under the correct construction, "a human patient who experiences an inadequate response to a TNFα-inhibitor" is someone who ***has*** actually taken a TNFα-inhibitor and ***has*** actually experienced an inadequate response to it. *Id.* Boehringer offers no corresponding percentage of all RA patients, let alone of the population from which the Edwards 2002 study drew its participants. And Edwards 2002 does not indicate that ***any*** of the participants had in fact even taken a TNFα inhibitor. Ex. 1003.

Second, even if the percentage used by Boehringer were appropriate, it would not support a finding of inherent anticipation. Prior art cannot "inherently" anticipate a claimed feature unless the feature "is ***necessarily*** present" in the prior art. *Allergan, Inc. v. Apotex, Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014) (emphasis added); *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006) (reversing inherency finding "[b]ecause anticipation by inherent disclosure is appropriate only when the reference

discloses prior art that must necessarily include the unstated limitation"); *Lone Star Distrib., Inc. v. Thermolife Int'l, LLC*, IPR2014-01201, Paper 12 at 25 (Feb. 2, 2015) ("Petitioner does not establish sufficiently that the methods . . . necessarily occurred").

Consequently, "[i]nherency may not be established by probabilities or possibilities." *Allergan*, 754 F.3d at 960 (finding no inherency where an event that would have satisfied a claim limitation "only *may*" have occurred in the prior art) (emphasis in original); *Ex Parte Peltz*, Appeal 2012-011729, 2015 WL 430562, at *2 (P.T.A.B. Jan. 13, 2015) ("Absent inevitability, inherency does not follow even from a very high likelihood that a prior art method will result in the claimed invention."); *Ex Parte May*, Appeal No. 1999-0941, 1999 WL 33224337, at *2 (B.P.A.I. Jan. 1, 2009) ("[A] showing of likely or probable inherency is not sufficient to support a rejection under 35 U.S.C. § 102 or 103 under the theory of inherency.").

Even an extremely high probability that the prior art included a claimed feature is insufficient to establish inherent anticipation. *See, e.g., Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, No. IP 02-0512-C-B/S, 2004 WL 1724632, at *27 (S.D. Ind. July 29, 2004), *aff'd on other grounds,* No. 05-0144, 2005 WL 1635262 (Fed. Cir. Sept. 8, 2005) (rejecting inherency theory where evidence suggested a "greater than 99.9999 percent" chance that the prior art included a claimed feature); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 676 F. Supp. 2d 352, 365 (D.N.J. 2009) (finding no inherent use of drug with ADHD suffers even though "[i]t is likely that at least one patient" in clinical trials suffered from ADHD).

Boehringer argues that, "[g]iven the high percentage of non-responders, it would only take a few RA patients to participate in a clinical study before a non-responder to TNFα-inhibitors would necessarily be present." Pet. 36. But even if the percentage of non-responders in the population were "high," as Boehringer asserts, it simply would not follow that any particular sample of the population would "necessarily" include a non-responder. It remains an issue of probabilities, and a long string of Federal Circuit and PTAB authorities hold that probabilities are insufficient to establish inherent anticipation. *See, e.g.*, *Allergan*, 754 F.3d at 960; *Peltz*, 2015 WL 430562, at *2.

V. BOEHRINGER FAILS TO DEMONSTRATE ANY REASONABLE LIKELIHOOD OF PREVAILING ON OBVIOUSNESS.

Boehringer does not even attempt to articulate how any reference or combination of references allegedly renders obvious any claim of the patented invention. Moreover, Boehringer fails to rebut the record evidence of objective indicia of non-obviousness. Boehringer's obviousness challenge should therefore be rejected.

A. Boehringer Never Attempts To Explain How Any Reference Or Combination Of References Allegedly Renders Obvious Any Claim Of The Patented Invention.

The section of Boehringer's petition entitled "All Challenged Claims Are Rendered Obvious by the Prior Art" is less than three pages long. It includes a two-page table of "Prior Art and Proposed Combinations" that simply lists, in bullet-point format, various references and combinations of references without any explanation

whatsoever. Pet. 55-57. Boehringer never identifies any differences between any claim and any reference, much less explains how those differences allegedly would have been bridged by modification or combination with other references. Nowhere does Boehringer articulate any reason to have modified or combined specific references, any basis for concluding that modifications or combinations would have been obvious to try, or any reasonable expectation of success in practicing the claimed inventions. Boehringer also fails to address any claims individually, and cherry-picks from the references it cites, ignoring their teachings as a whole, including teachings away. Boehringer has failed to carry it burden of showing a reasonable likelihood that it will prevail on its obviousness challenge.

Boehringer's petition for *inter partes* review does not satisfy the requirement that a petitioner must identify "with ***particularity***, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the ground for the challenge to each claim." 35 U.S.C. § 312(a)(3). Nor does it comply with this Board's rules, which place the burden on the petitioner to show "[h]ow the construed claim is unpatentable," 37 C.F.R. § 42.104(b), and which require each petition to include "a ***full statement*** of the reasons for the relief requested, including a ***detailed explanation*** of the significance of the evidence including material facts, the governing law, rules, and precedent." *Tasco, Inc. v. Pagnani*, IPR2013-00103, Paper 6 at 10 (May 23, 2013) (citing 37 C.F.R. § 42.22(a)(2)).

A failure to satisfy these requirements is fatal to a request for *inter partes* review. *See, e.g., Naughty Dog, Inc. v. McRO, Inc.*, IPR2014-00197, Paper 11 at 22 (May 28, 2014) ("Petitioner has failed to resolve any differences between the claimed invention and the cited references, identify any specific proposed modifications to the references, or explain persuasively why one skilled in the art would have made any specific modifications to the references relied on in the challenges . . . ."); *Tasco,* IPR2013-00103, Paper 6 at 11 ("These conclusory allegations are insufficient to meet Petitioner's burden."); *Google, Inc. v. EveryMD.com LLC*, IPR2014-00347, Paper 9 at 26 (May 22, 2014) (declining to institute trial where, as here, "Petitioners' assertion does not provide an articulated reasoning with rational underpinning to support the conclusion that the claimed invention would have been obvious.").

Boehringer's strategy of simply identifying references and combinations and hoping that the Board will somehow institute trial has repeatedly been rejected by the Board. Petitioners cannot, as Boehringer has done here, "place the burden on [the Board] to sift through the information presented by Petitioners . . . and identify any differences between the claimed subject matter and the teachings of [the references]." *Google*, Paper 9 at 25. The Board will not "attempt to fit evidence together into a coherent explanation that supports an argument that demonstrates a reasonable likelihood that Petitioner would prevail." *TRW Auto. U.S. LLC, v. Magna Elecs., Inc.*, IPR2014-00293, Paper 21 at 5 (Aug. 28, 2014). Boehringer's petition fails to identify

evidence that would support such an argument. But even if it did, the petition would have to be denied because no such argument is made.

Boehringer's strategy also should be rejected because it unfairly prejudices Genentech. Because Boehringer has articulated no argument whatsoever regarding how the references allegedly render any claim of the patent obvious, Genentech is left to guess as to the grounds for the challenge.

1. Nowhere Does Boehringer Articulate Any Reason To Have Modified Or Combined Specific References.

Boehringer devotes nearly a third of its petition to a piecemeal discussion of where various claim limitations allegedly are found in its references. Pet. 35-54. That piecemeal discussion would be insufficient even if Boehringer showed that each limitation could be so found. It is well settled that "[o]bviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). "Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.* Nowhere does Boehringer articulate any reason for a skilled artisan to have modified or combined any specific references. In short, Boehringer relies on hindsight instead of addressing the state of the art from the perspective of a skilled artisan as of the effective filing date. This is impermissible.

Obviousness "cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013); *Unigene*, 655 F.3d at 1361 (affirming summary judgment of nonobviousness).

Instead of addressing any specific combinations, Boehringer lumps all of the references together and makes sweeping generalizations that do not come close to explaining why a skilled artisan supposedly would have combined any of the identified references, much less arrived at any of the claimed inventions as a result. The sum total of Boehringer's discussion in this regard is a scant, five-sentence paragraph. In that paragraph, Boehringer offers the conclusory statements that "[a] person of ordinary skill would have reason to combine the teachings of the above references" because "[e]ach of the references is directed to the treatment of RA with rituximab," "[p]ersons of ordinary skill in the art had a clear incentive to improve treatments by optimizing dosing levels and regimens to reduce RA symptoms in refractory patients," and "[t]here was a clear reason to combine known elements to improve treatment for all RA patients, including those who did not experience an adequate response to TNFα inhibitors." Pet. 57.

These generic assertions are nowhere near sufficient to carry Boehringer's burden. It is hard to imagine a disease for which there is not a desire "to improve treatment for all" patients. But that does not make all improved treatments obvious. An obviousness showing cannot be made by merely offering sweeping aspirational

statements and empty assertions of the ultimate conclusion that "a person of ordinary skill would have had reason to combine the teachings of the" prior art. Nor is it enough to cite a cluster of references that are all directed to the disease addressed by the patent. Here, the various references describe different target patients, different numbers of doses, and different dose amounts, for example. Boehringer never explains why a skilled artisan allegedly would have chosen any parameter from one reference over that from any other reference in the group. This complete failure to provide any reason to combine one particular reference with another is fatal to Boehringer's petition.

Boehringer's other generalizations fare no better. Even if skilled artisans had clear incentives to improve treatments by optimizing dosing levels and regimens, Boehringer never explains how or why those skilled artisans allegedly would have arrived at the dosing levels and regimens of the claims. Similarly, even if all elements of the claims were known, and even if and there were a clear reason to combine those known elements to improve treatment for all RA patients, including those who have experienced an inadequate response to TNFα-inhibitors, Boehringer never explains how or why a skilled artisan supposedly would have chosen to combine the particular known elements necessary to arrive at the invention of any given claim. Thus, Boehringer's sweeping generalizations do not come close to establishing the required reason for any of its combinations.

Elsewhere, Boehringer argues that "it would have also been obvious to a person of ordinary skill to treat RA patients who do not respond to TNFα-inhibitors with alternative therapies." Pet. 37. But the claimed inventions are not directed to the general concept of treating TNFα non-responders with alternative therapies of any kind. Rather, they are directed to particular alternative therapies for TNFα non-responders. Even if it would have been obvious to use an alternative therapy of one kind or another, it would not follow that the particular alternative therapies of the '838 patent would have been obvious.

Citing a 1999 article, Boehringer goes on to assert that "a person of ordinary skill would have tried other known RA therapies using drugs with different modes of action, as well as combination therapies, until the patient exhibited an improvement in signs and symptoms." Pet. 37. Even if true, this would not suggest that the ***particular therapies recited in the claims*** would have been obvious. *See, e.g., Medichem, SA v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("[O]ne must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.") (internal quotation marks omitted). Moreover, several authors of the 1999 article that Boehringer relies upon separately suggested that same year that, instead of drugs with different modes of action, "sequential use of TNF blocking agents will [be] considered" because "it is anticipated

that TNF blocking agents will have slightly different mechanisms of action (for example, differing affinity constants, differing pharmacokinetics)." Ex. 1034 at 726. And such sequential use of TNF blocking agents is precisely what investigators reported around the time of the earliest effective filing date. *See, e.g.,* Ex. 2009. Like Boehringer's other generalizations, this generalization fails to provide the necessary reason to modify or combine.

2. Boehringer Fails To Establish That Any Of Its Modifications Or Combinations Were Obvious To Try.

Boehringer argues that "[a]t minimum, it would have been obvious to try alternative RA therapies when dealing with patients who did not adequately respond to TNFα-inhibitors." Pet. 38. But even if that were true, it would not follow that the ***particular*** therapies of the claims would have been obvious to try. The claims are directed to ***specific*** alternative therapies for TNFα non-responders, not the general concept of treating TNFα non-responders with alternative RA therapies of any kind.

Moreover, there did not exist here "a finite (and small in the context of the art) number of options easily traversed" by skilled artisans. *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); *see also* MPEP § 2143(I)(E), Example 5. Boehringer's own proposed expert Dr. Kalden asserts that, at the time of the invention, there existed "***numerous*** methods of treating RA patients who did not respond to TNF alpha-inhibitors" and "***many*** effective treatment protocols," Ex. 1002 at ¶¶ 71, 39 (emphasis added), not a finite number of options easily traversed.

Here the options were legion. In addition to TNF blockers such as etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®), Pet. 28, treatments for rheumatoid arthritis as of the effective filing date included abatacept (e.g., Orencia®), anakinra (e.g., Kineret®), auronofin, azathioprine (e.g., Imuran®), bucillamine, chlorambucil (e.g., Leukeran®), cyclophosphamide (e.g., Cytoxan®), cyclosporine (e.g., Sandimmune®), cyclophosphamide, dapsone, D-penicillamine (e.g., Depen®, Cuprimine®), folate, gold salts, gold infusions, hydroxychloroquine (e.g., Plaquenil®), intravenous immunoglobulin (IVIG), leflunomide (e.g., Arava®), non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate, methylprednisolone, sulfasalazine (e.g., Asulfidine®), minocycline (e.g., Dynacin®, Minocin®), staphylococcal protein A immunoadsorption, not to mention combinations such as gold salts plus bucillamine and sulphasalazine plus methotrexate, to name just a few. *See, e.g.,* Ex. 1001 at 30:6-14; Ex. 1005 at 25:9-16; Ex. 1032 (Table 1).

Consequently, Boehringer's "obvious-to-try" argument fails as a matter of law based on Boehringer's own evidence. *See, e.g., Ortho-McNeil*, 520 F.3d at 1364. It also fails because Boehringer does not articulate any reasonable expectation of success in practicing the claimed inventions, as discussed in Section V.A.3 below.

3. Nowhere Does Boehringer Establish Any Reasonable Expectation Of Success In Practicing The Claimed Inventions.

"An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the

prior art." *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009); *Hoffman-La Roche Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1340 (Fed. Cir. 2014) ("For an invention to be obvious to try, there must be a finite number of known choices in the prior art, and a reasonable expectation of success for the choice that is tried.").

Boehringer pays lip service to the "expectation of success" requirement, but never actually articulates why a skilled artisan allegedly would have perceived a reasonable expectation of success in making the claimed inventions in light of prior art. The closest Boehringer gets is simply restating the requirement itself as a naked, general conclusion. *See* Pet. 3 ("In light of the known RA therapies available as of the earliest priority date of the '838 patent, a person of ordinary skill would have had a reasonable expectation of success using the claimed methods of treating RA.").

Boehringer also asserts that skilled artisans "would have had a reasonable expectation of success" practicing methods ***other than those claimed***. Boehringer discusses simply administering "two IV doses of 1000 mg" of rituximab without regard to whether the recipient had experienced an inadequate response to a TNFα inhibitor, Pet. 43, "treating RA patients with rituximab" generally, *id.* at 49-50 (discussing claims 10-14), and abstractly "treating non-responders to TNFα-inhibitors with [unspecified] alternative therapies involving different modes of action." *Id.* at 39. Boehringer does not establish a reasonable expectation of success even for those methods. For example, even if there had existed "only a finite number" of treatments, it would not have followed that there was a reasonable expectation of success that one

of them would work. *Id.* Boehringer's other arguments based on these methods rely on unidentified "data available at the time of the invention," *id.* at 49-50, and try to redefine "success" to mean simply "increas[ing] patient compliance," instead of treating the RA as claimed. *Id.* at 43. In any event, all Boehringer's arguments in this regard are inapposite because they do not address the claimed inventions.

Because Boehringer nowhere establishes any reasonable expectation of success in practicing the claimed inventions, Boehringer cannot prevail with respect to obviousness. *Institut Pasteur v. Focarino,* 738 F.3d 1337, 1346 (Fed. Cir. 2013) (reversing finding of obviousness based on absence of reasonable expectation of success); *Norman Int'l, Inc., v. Hunter Douglas, Inc.*, IPR2014-01173, Paper 7 at 14 (Feb. 10, 2015) (denying institution where petitioner offered only "broad-brush statement" about collective teachings of prior art instead of "sufficient articulated reasoning with rational underpinning as to why an ordinary artisan, at the time of the invention, would have had a reason to combine the prior art elements in the manner required by [the] claims . . ., or how one would have done so with a reasonable expectation of success").

4. Boehringer Fails To Address Any Individual Claims And Cherry-picks From The References It Cites, Ignoring Their Teachings As A Whole, Including Teachings Away.

Alleged obviousness must be analyzed on a claim-by-claim basis. Not only does Boehringer fail to address any particular combinations of references, it fails to address any particular claims. Boehringer's challenge must be rejected.

a) Boehringer Never Explains How Gaps Between Claim 1 And The Relied-Upon References Allegedly Would Have Been Bridged By Modification Or Combination.

Claim 1 is "[a] method of treating rheumatoid arthritis in a human patient who experiences an inadequate response to a TNFα-inhibitor, comprising administering to the patient an antibody that binds to CD20, wherein the antibody is administered as two intravenous doses of 1000 mg." Ex. 1001.

(i) Edwards 2002 (Ex. 1003) Alone

Boehringer's table of "Prior Art and Proposed Combinations" lists Edwards 2002 (Ex. 1003) by itself in the entry for claims 1-5, 7-14. Edwards 2002 is an abstract that describes a study of rituximab in patients who "were receiving methotrexate." Ex. 1003. Nowhere does Edwards 2002 disclose using rituximab to treat rheumatoid arthritis "in a human patient who experiences an inadequate response to a TNFα-inhibitor," as recited by claim 1.

Boehringer never explains how this gap between Edwards 2002 and claim 1 allegedly would have been bridged by modifying Edwards 2002, much less articulates any reason to have made modifications or any reasonable expectation of success, as discussed above in Sections V.A.1-3. For example, Boehringer does not articulate any reason why a skilled artisan allegedly would have moved away from the target population in Edwards 2002—methotrexate users—to a brand-new target population of patients who had experienced inadequate responses to TNFα-inhibitors. Nor does

Boehringer explain why the skilled artisan allegedly would have changed the target population and yet arrived at the claimed dosing for that population.

Boehringer also does not show that skilled artisans would have had any reasonable expectation that administering rituximab to patients who had experienced inadequate responses to TNFα-inhibitors would be successful. In fact, the alleged prior art suggested the opposite. For example, De Vita 2002 (Ex. 1007) described a study of five patients who had previously failed treatment with methotrexate plus cyclosporine-A, including two patients who also happened not to have responded to anti-TNF alpha therapy. The investigators administered rituximab to all five patients in "4 weekly intravenous infusions of 375 mg/m^2." Ex. 1007 at 2030. The results demonstrated that while other patients showed major improvement with ACR70 and ACR50 responses, the two patients who had not responded to anti-TNF alpha therapy exhibited little or no improvement. *Id.* at 2030, 2032. One of the two patients "exhibited no improvement," and the other exhibited no greater than a typical placebo-level response—and only "from month 3 to month 5," with subsequent relapse. *Id.* at 2032; *see supra* Section II.B. Significantly, both of the patients experienced an ***increase*** in the number of eroded joints. *Id.* As a leading expert on rheumatoid arthritis has explained, De Vita 2002 "steers the reader away from choosing anti-TNF inadequate responders for further study given the poor results in those patients." Ex. 1016 ¶ 27 (discussing references listed in Ex. 2010).

(ii) Edwards 2002 (Ex. 1003) in view of De Vita 2001 (Ex. 1006)

Boehringer fails to explain how De Vita 2001 allegedly fills the holes in Edwards 2002, and as discussed above in Sections V.A.1-3, fails to identify any reason to have combined the references or any reasonable expectation of success.

De Vita 2001 reports preliminary results from the same study that is the subject of De Vita 2002 (Ex. 1007). Those preliminary results describe four RA patients who had not responded to "a combination therapy with methotrexate and cyclosporine-A." Ex. 1006. Unlike the method of claim 1, which requires dosing an antibody that binds to CD20 at 1000 mg per infusion, the dose of rituximab in De Vita 2001 was 375 mg/m^2 (based on surface area) per infusion. *Id.* And unlike claim 1, which requires only two infusions, the study reported in De Vita 2001 required four. *Id.*

De Vita 2001 notes that in addition to failing combination therapy with methotrexate and cyclosporine-A, "patients 3 and 4 had not responded to anti-TNF alpha therapy" too. *Id.* De Vita 2001 does not attribute study results to patient 3, and reports internally contradictory results for patient 4, stating both that "[p]atient 4 achieved an ACR20 response" (a typical placebo response) in one of several months observed and that "patient 4 did not respond to the treatment."[4] *Id.* In contrast, De

[4] Even were it assumed that one of these references to patient 4 should have been a reference to patient 3, nothing better than a typical placebo response—which does not provide a reason to combine or expectation of success—was observed.

Vita 2001 reports that the two patients who had ***not*** experienced an inadequate response to a TNFα-inhibitor (patients 1 and 2) showed "marked clinical improvement" with ACR 70 and ACR 50 responses. *Id.* Accordingly, De Vita 2001 taught against administering rituximab to the claimed population: "a human patient who experiences an inadequate response to TNFα-inhibitor."

Even if Boehringer could establish that there existed a reason to have combined Edwards 2002 and De Vita 2001, actually combining the two references would not have led to the invention of claim 1. Neither Edwards 2002 nor De Vita 2001 on its own singled out or otherwise targeted patients who did not respond to TNFα-inhibitor treatment. Rather, De Vita 2001 targeted "patients [who] did not respond to a combination therapy with methotrexate and cyclosporine-A" while Edwards 2002 targeted patients "receiving methotrexate," as discussed above. Boehringer does not articulate any reason why a skilled artisan allegedly would have combined Edwards 2002 and De Vita 2001 but then abandoned the targets of both studies and somehow identified as a new target patients who had experienced inadequate responses to TNFα-inhibitors.

Nor does Boehringer articulate any reason why a skilled artisan allegedly would have then elected not to use the relative 4 x 375 mg/m^2 dose of De Vita 2001 and would instead supposedly have chosen the fixed, lower overall dose of Edwards 2002 (2 x 1000 mg) for this new, hard-to-treat patient population. In fact, De Vita 2001 would have discouraged such a choice because even its higher dose at best produced

nothing better than a typical placebo response in any member of the target patient population. Also, a "trend towards higher DMARD doses in April 2003" would have discouraged such a choice. Ex. 1016 at ¶ 31; *id.* at ¶ 4 (describing the focus on "using higher doses of DMARDs," citing Ex. 2012). "If anything," as one leading RA expert explains, "a rheumatologist would have been inclined to administer the maximum available dose (4 doses 1 week apart), rather than just 2 doses." Ex. 2003 at ¶ 3.

Boehringer also fails to explain why the skilled artisan allegedly would have had a reasonable expectation of success notwithstanding the disclosure of De Vita 2001, which suggests that administering rituximab to patients who experienced an inadequate response to a TNFα-inhibitor is likely to be unsuccessful.

(iii) Edwards 2002 (Ex. 1003) in view of Tuscano (Ex. 1008)

Boehringer never articulates how Tuscano allegedly bridges the gap between claim 1 and Edwards 2002, and never identifies any reason to have combined the references or any reasonable expectation of success in doing so, as discussed above in Sections V.A.1-3.

Tuscano is an abstract reporting on a study that used rituximab to treat rheumatoid arthritis in patients who had "previously failed multiple DMARDs." Ex 1008. For an undisclosed subset of the patients, one of those DMARDs was infliximab. *Id.* Unlike the method of claim 1, which requires two infusions of 1000 mg each, the dose reported in Tuscano was "100 mg on wk #1, followed by 375 mg/m^2 on wk #2, and 500 mg/m^2 on wks 3 and 4." *Id.*

Tuscano reports that out of the 9 patients enrolled, 7 patients were evaluable. Ex. 1008. Tuscano does not disclose whether any of those 7 patients was from the subset of enrollees that had previously failed infliximab. But even assuming that all 7 of the evaluable patients were infliximab-refractory (which the reference does not say), Tuscano would not encourage administering rituximab to infliximab-refractory patients because those 7 patients showed little or no improvement after treatment with rituximab. Indeed, of those 7 evaluable patients, only "3 met criteria for an ACR 20" response, consistent with a typical placebo effect, as discussed above in Section II.B. Ex. 1008. "Since this was comparable to the ACR20 responses seen with placebo in randomized clinical trials . . ., this did not provide evidence that the drug was effective (i.e. that the apparent improvement was due to the drug rather than chance or placebo effect) . . . ." Ex. 1016 at ¶ 28 (referring to references listed in Ex. 2010).

In fact, skilled artisans would have viewed the "results" of Tuscano with significant skepticism because Tuscano was "a small open label study." Ex. 1016 at ¶ 28 (discussing Ex. 2010 references). In an open-label study, "both the doctor and the patient know what drug the patient is being treated with, which increases the risk for a greater 'placebo [e]ffect' (i.e. the measurable, observable, or felt improvement in health or behavior not attributable to a medication that has been administered) than in a blinded trial." *Id.* This effect is exacerbated by the fact that ACR scoring depends in large part on subjective measures by the physician and the patient, as discussed in Section II.B. above. Ex. 2003 at ¶ 9. During scoring, "observer bias inevitably occurs

due to the desire by both the patient and physician to see improvement in the disease outcomes due to treatment." *Id.* Open label studies are therefore "significantly less reliable than double-blinded trials" and are "viewed with skepticism by clinicians." Ex. 2003 at ¶¶ 8-9. "Many such studies are reported or even published but the treatments reported in them quite frequently fail to demonstrate efficacy when tested more rigorously." *Id.* at ¶ 8. Consequently, "[p]ractitioners in the field are generally and rightly skeptical about the many small scale open-label studies [like Tuscano] that are frequently reported at conferences and in the literature." *Id.* at ¶ 10.

Combining Edwards 2002 with Tuscano would not have led to the invention of claim 1 for the same reasons combining Edwards 2002 and De Vita 2001 would not have done so. *See supra* Section V.A.4.a)(ii). Neither Edwards 2002 nor Tuscano targeted particular human patients who experienced inadequate responses to TNFα-inhibitors. Edwards 2002 targeted patients "receiving methotrexate" and Tuscano generally targeted patients who had "previously failed multiple DMARDs." Ex. 1008. Boehringer does not offer any reason why a skilled artisan allegedly would have combined Edwards 2002 and Tuscano and then abandoned the targets they taught in favor of the claimed target of patients who had experienced inadequate responses to TNFα-inhibitors.

Boehringer also fails to articulate any reason why a skilled artisan allegedly would then have decided not to use Tuscano's graduated doses of "100 mg on wk #1, followed by 375 mg/m^2 on wk #2, and 500 mg/m^2 on wks 3 and 4" and purportedly

would have instead selected the ***lower*** and ***fewer*** overall doses of 1000 mg x 2 dose of Edwards 2002 for this new target population. Such a selection would have been discouraged by the fact that Tuscano at best reported no better than placebo-level responses at its higher overall dose, and by the trend towards using higher doses of DMARDs, Ex. 1016 at ¶ 31, as discussed above in Section V.A.4.a)(ii). Boehringer also fails to explain why the skilled artisan allegedly would have had a reasonable expectation of success despite such responses.

(iv) Genentech Press Release (Ex. 1004) alone and in view of De Vita 2001 (Ex. 1006) or Tuscano (Ex. 1008)

Boehringer's table of "Prior Art and Proposed Combinations" identifies a Genentech Press Release by itself and in combination with each of De Vita 2001 and Tuscano. The press release simply reports on the results described in the Edwards 2002 abstract, and like Edwards 2002, does not disclose using rituximab to treat rheumatoid arthritis "in a human patient who experiences an inadequate response to TNFα-inhibitor," as required by claim 1. Because the Genentech Press Release and Edwards 2002 provide substantively the same disclosure, Boehringer fails to establish a reasonable likelihood of prevailing on obviousness based on the Genentech Press Release for all the same reasons it fails to establish such a likelihood based on Edwards 2002, as discussed above in Section V.A.4.a)(i)-(iii).

(v) Curd PCT Publication (Ex. 1005)

Boehringer's table of "Prior Art and Proposed Combinations" lists the Curd PCT Publication (Ex. 1005) by itself in the entry for claims 1-5, 7-14. The Curd PCT Publication is a patent application filed by Genentech and a collaborator concerning "treatment of autoimmune diseases with antagonists which bind to B cell surface markers, such as CD19 or CD20." Ex. 1005 at 1.

The Curd PCT Publication does not disclose or suggest using rituximab to treat rheumatoid arthritis "in a human patient who experiences an inadequate response to TNFα-inhibitor," as required by claim 1. Boehringer does not contend otherwise.

The Curd PCT Publication also does not recite dosing rituximab with two 1000 mg infusions, as required by claim 1. Ex. 1005. Citing two Federal Circuit cases, Boehringer argues that "[t]he Curd PCT Publication disclosed multiple IV doses of rituximab in a range that includes 1000 mg" and therefore "[t]he Curd PCT Publication creates a presumption of obviousness." Pet. 42. Boehringer's argument is factually and legally inaccurate.

Factually, the passage that Boehringer cites as support from the Curd PCT Publication does not, in fact, disclose multiple IV doses of rituximab in a range that includes 1000 mg. Pet. 42 (citing Ex. 1005 at 23:23-27). Rather, it discloses two doses, stating that an "initial dose may be in the range from about 20 mg/m^2 to about 250 mg/m^2 (*e.g.*, from about 50 mg/m^2 to about 200 mg/m^2) and the subsequent dose may be in the range from about 250 mg/m^2 to about 1000 mg/m^2." Ex. 1005 at

23:25-27. "[A]ssuming an average body surface area of 1.6 m^2," as Boehringer does, Pet. 42, the absolute range for the first dose is about 32 mg to about 400 mg, and the range for the second dose is 400 mg to 1600 mg. Because 1000 mg is outside the range of the first dose, the cited passage does not disclose multiple doses of rituximab in a range that includes 1000 mg as Boehringer represents. To the contrary, it teaches a first dose in a range that ***excludes*** 1000 mg.

Legally, neither case cited by Boehringer would support its argument even if it were correct about the facts. As Boehringer's own parentheticals for the cases expressly state, a presumption of obviousness arises when "'***the claimed invention***" itself falls within a range disclosed in the prior art, not when only ***one limitation*** of the claimed invention—e.g., the 1000 mg limitation in claim 1—happens to fall within such a range. Pet. 42-43 (emphasis added). Even if the ranges for both doses in the cited passage encompassed 1000 mg, a presumption of obviousness still would not arise because the Curd PCT Publication nowhere discloses the other limitations of "the claimed invention," including administering such doses to a human patient who experiences an inadequate response to a TNFα-inhibitor.

Boehringer never explains how the gaps between the Curd PCT Publication and claim 1 allegedly would have been bridged by modifications, much less articulates any reason to have made such modifications or any reasonable expectation of success in doing so, as discussed above in Sections V.A.1-3.

(vi) Curd PCT Publication (Ex. 1005) in view of De Vita 2001 (Ex. 1006) or Edwards 2001 (Ex. 1022) or Tuscano (Ex. 1008) or De Vita 2001 with Edwards 2001.

Boehringer fails to articulate how any of De Vita 2001 (Ex. 1006), Edwards 2001 (Ex. 1022), Tuscano (Ex. 1008), or De Vita 2001 with Edwards 2001 allegedly bridges the gaps between claim 1 and the Curd PCT Publication, and fails to identify any reason to have made these various combinations or any reasonable expectation of success in doing so, as discussed above in Sections V.A.1-3.

Neither De Vita 2001 nor Tuscano bridges the "experiences an inadequate response to a TNFα-inhibitor" gap between claim 1 and the Curd PCT Publication for all the same reasons that each one fails to bridge that same gap between claim 1 and Edwards 2002, as discussed in Sections V.A.4.a)(ii)-(iii). Each also fails to fill the 2 x 1000 mg hole in the Curd PCT publication because neither reference discloses such doses. *See* Ex. 1006 (disclosing a dose "consisting of 4 intravenous infusions per week of 375 mg/m^{2}"); Ex. 1008 (disclosing a graduated dose of "100 mg on wk #1, followed by 375 mg/m^2 on wk #2, and 500 mg/m^2 on wks 3 and 4"). Nor does either reference overcome the Curd PCT Publication's teaching against such doses.

Edwards 2001 also fails to fill the "experiences an inadequate response to a TNFa-inhibitor" and 2 x 1000 mg dosing holes in the Curd PCT Publication because it suffers from the very same holes itself. Edwards 2001 describes an open-label study of five patients who had each previously failed treatment for RA with at least gold, azathioprine, sulphasalazine, and methotrexate. Ex. 1022 at 206 (Table 1 and note b).

None of the patients is identified as having experienced an inadequate response to a TNFα-inhibitor, as required by claim 1. *Id.* Nor were any of the patients administered two 1000-mg doses of rituximab, as required by claim 1. Rather, each patient in the study was administered "four i.v. infusions (over 3h) on days 2, 8, 15 and 22, of 300, 600, 600, and 600 mg respectively." Ex. 1022 at 206.

De Vita 2001 and Edwards 2001 together fail to fill the holes in the Curd PCT Publication for the same reasons they separately fail to fill those holes. Boehringer does not offer any theory to the contrary.

(vii) De Vita 2001 (Ex. 1006) In Combination with the Curd PCT Publication (Ex. 1005) alone and also with Edwards 2001 (Ex. 1022) or Tuscano (Ex. 1008).

Boehringer never articulates how the Curd PCT Publication (Ex. 1005) alone or with either Edwards 2001 (Ex. 1022) or Tuscano (Ex. 1008) allegedly bridges the gaps between claim 1 and De Vita 2001, much less identifies any reason to have made such combinations or any reasonable expectation of success in doing so, as discussed above in Sections V.A.1-3.

The first two of these combinations based on De Vita 2001 are identical to combinations Boehringer bases on the Curd PCT Publication, but with the references listed in a different order. Because Boehringer never discusses any of the obviousness combinations, there is no way for Genentech to know how (or whether) Boehringer believes that these differently ordered combinations differ substantively. In any event, the duo of De Vita 2001 and the Curd PCT Publication and the triplet of De Vita

2001 and the Curd PCT Publication and Edwards 2001 both fail for the same reasons that the identical, but differently ordered, combinations based on the Curd PCT Publication fail, as discussed above in Section V.A.4.a)(vi).

The third combination based on De Vita 2001 simply substitutes Tuscano for Edwards 2001 in the above-mentioned triplet. Tuscano does not fill the holes left by the De Vita 2001 or the Curd PCT Publication, as discussed above in Section V.A.4.a)(iii).

b) Boehringer Likewise Never Explains How The Gaps Between Each Of Claims 2-14 And The Relied-Upon References Allegedly Would Have Been Bridged By Modification Or Combination With Other References.

Like claim 1, each of claims 2-14 contains a limitation that requires administering an antibody that binds to CD20 to a patient who experiences an inadequate response to a TNFα-inhibitor, and a limitation that requires the dose of the antibody to be two 1000 mg infusions. These same two limitations distinguish claim 1 from the corresponding references and combinations of references listed in Boehringer's table of "Prior Art and Proposed Combinations." Because Boehringer lists the very same references and combinations for claims 2-5 and 7-14, Boehringer's challenges to those claims fail for at least the same reasons its challenge to claim 1 fails, as discussed above in Section V.A.4.a).

As for claim 6, all but the first two combinations that Boehringer lists in the table for that claim are identical to the references and combinations that Boehringer

lists for claim 1. Thus, Boehringer's challenge to claim 6 based on those references and combinations fails for at least the same reasons its challenge to claim 1 fails on those bases. *See supra* Sections V.A.4.a)(v)-(vi). The two combinations that are not identical to combinations Boehringer lists for claim 1 are Edwards 2002 or the Genentech Press Release in view of the Curd PCT Publication. But none of the references in those combinations teaches the limitation requiring administration to a patient who experiences an inadequate response to a TNFα-inhibitor. And Boehringer fails to articulate any theory under which such references in combination could be considered to teach what none of them discloses individually. Boehringer also never articulates any reason to have combined the references, or any reasonable expectation of success, as discussed above in Sections V.A.1-3.

Boehringer fails to establish a reasonable likelihood of prevailing with respect to claims 2-14 for additional, independent reasons as well. None of Boehringer's references teaches: (i) "no erosive progression," as claims 10 and 14 require; (ii) at least an ACR50 or ACR 70 response in a patient who experiences an inadequate response to a TNFα-inhibitor, as required by claims 2-7 and 11-13; or (iii) also administering methylprednisolone and prednisone, as claim 6 requires.

(i) None of Boehringer's References Teaches "No Erosive Progression," As Required By Claims 10 and 14.

Claims 10 and 14 both require that the patient achieve a clinical response of "no erosive progression at weeks 24 and beyond." Ex. 1001. This is an important

clinical benefit of the patented invention. Ex. 2008 at 27-28. Achieving an ACR score by treating an RA patient's symptoms is enormously helpful, but actually slowing or stopping erosive disease progression can allow a patient to avoid long-term disability. Ex. 1016 at ¶ 18. None of Boehringer's references teaches achieving, or even trying to achieve, no erosive progression as claimed. Unable to contend otherwise, Boehringer attempts to read the "no erosive progression" limitations out of the claims. But that attempt fails, as discussed above in Section III.C.

Boehringer would be unable to establish a reasonable likelihood of prevailing with respect to claims 10 and 14 even if its references disclosed achieving no erosive progression at weeks 24 and beyond because Boehringer fails to identify any reason to have modified or combined, and fails to articulate any reasonable expectation of success, as discussed above in Sections V.A.1-3. In fact, alleged prior art cited by Boehringer suggested to skilled artisans that administering rituximab to patients who had not responded to TNFα-inhibitors would ***not*** be expected to result in no erosive progression. For example, in De Vita 2002, both patients who happened to have failed prior anti-TNF alpha therapy experienced an ***increase*** in the number of eroded joints at 24 weeks after treatment with rituximab. Ex. 1007 at 2032 ("The number of eroded joints as seen on hand and foot radiographs increased . . . from 14(baseline) to 15 (month 6) in patient 4, and from 20 (baseline) to 23 (month 6) in patient 3.").

(ii) Boehringer's References Fail To Teach Achieving At Least An ACR50 Or ACR70 Response In TNFα-Inadequate Responders, As Required By Claims 2-7 and 11-13.

Claims 2-7 and 11-13 all require at least an ACR50 or ACR70 response (or no erosive progression) at week 24, but none of the prior art identified by Boehringer teaches any such results from a patient who experiences an inadequate response to a TNFα-inhibitor. At very most, De Vita 2001 and Tuscano report nothing higher than ACR20 responses (typical of placebo) for certain members of this hard-to-treat patient population, with some members showing no improvement at all, while non-members achieved much higher scores. *See supra* Sections V.A.4.a)(ii)-(iii). Boehringer tries to read the clinical responses out of the claims, contrary to law. *See supra* Section III.C. And Boehringer fails to articulate any reason to combine or any reasonable expectation of success that at least an ACR50 or ACR70 response could be achieved in these drug refractory RA patients.

(iii) None Of Boehringer's References Teaches Administering Methylprednisolone And Prednisone, As Required By Claim 6.

Claim 6 requires that the patient be further treated with concomitant methotrexate and a corticosteroid regimen that "consists of methylprednisolone and prednisone." Ex. 1001. Boehringer fails to identify any teaching in the art of administering both methylprednisolone and prednisone to a patient, much less administering such a regimen along with rituximab and methotrexate, for example, or to a patient who experiences an inadequate response to a TNFα-inhibitor.

Neither Edwards 2002 nor the Genentech Press Release mentions methylprednisolone and prednisone. Ex. 1003; Ex. 1004. Boehringer quotes part of a passage from the Curd PCT Publication stating that a patient treated with rituximab may "optionally further [be] treated with any one or more agents for treating RA" in a list of more than half a dozen categories and sixteen specific examples of such agents, including corticosteroids. Pet. 52 (quoting Ex. 1005 at 25:10-16). Nowhere, however, does the Curd PCT Publication single out corticosteroids from this list, much less corticosteroids plus methotrexate. More importantly, the Curd PCT Publication does not identify either methylprednisolone or prednisone in particular—much less both methylprednisolone and prednisone—as the corticosteroids to be administered to the patient if corticosteroids are selected from the list. In fact, the Curd PCT Publication expressly teaches away from administering anything else with rituximab when it states that "[p]referably however, the patient is ***only*** treated with RITUXAN®." Ex. 1005 at 25 (emphasis added). None of the other references in Boehringer's table of "Prior Art and Proposed Combinations" for claim 6 disclose or suggest using both methylprednisolone and prednisone.

B. Boehringer Fails To Rebut The Record Evidence Of Objective Indicia Of Non-Obviousness.

The Federal Circuit has "repeatedly held that . . . objective evidence of secondary considerations . . . must be considered before determining whether the claimed invention would have been obvious." *Apple, Inc. v. ITC*, 725 F.3d 1356, 1365

(Fed. Cir. 2013). Such objective indicia include long-felt but unsolved need, unexpected results, and commercial success. *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013). Boehringer acknowledges the record of long-felt need and unexpected results, but is unable to rebut it.

1. The Claimed Inventions Satisfied A Long-Felt But Unsolved Need For Treatment Of Rheumatoid Arthritis In Patients Who Did Not Respond To Anti-TNFα Therapy.

According to Boehringer, it was recognized in the art at least as far back as 1998 that approximately 40% of patients did not respond to TNFα-inhibitors and therefore needed an effective alternative treatment. Pet. 36 (citing 1998 article attached as Ex. 1029 to Petition as "reporting a response rate to TNFα-inhibitors of approximately 60%"). TNFα-inhibitors "were generally given after the patient had failed at least 2-3 conventional RA therapies," and therefore "patients who were eligible for treatment with TNF-inhibitors had already demonstrated that their disease was particularly hard to treat and drug-refractory." Ex. 1016 at ¶ 6.

The need for an effective alternative treatment for anti-TNFα nonresponders persisted for years. In 2002, reports indicated that "[a] fraction of RA patients remain nonresponders" to aggressive combination therapy and TNF-alpha blockade treatments "due to still-undefined mechanisms of resistance," and acknowledged that "[b]ecause of the high prevalence of RA, the clinical impact of this subgroup is important." Ex. 1007 at 1. The group of patients who did not respond to anti-TNFα

therapies "represented a significant unmet medical need" and as of the earliest effective filing date "[i]n April 2003, they represented the most therapy resistant, and therefore difficult to treat, RA patients." Ex. 1016 at ¶ 7. As a leading RA physician has explained, "[i]t was extremely important to me and other clinicians in April 2003 to find a safe and effective treatment option for these treatment-resistant anti-TNF inadequate responders." *Id.* at ¶ 8.

Clinicians finally found that treatment in the methods claimed in the challenged patent. In 2006, the FDA approved rituximab in combination with methotrexate in "patients with moderately-to-severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies." Ex. 2011 at 18.

Boehringer argues that the "invention did not meet a long-felt need" because "according to the '838 patent, the standard dosing regimen (375 mg/m^2 i.v. weekly x 4) was 'therapeutically effective' for treating RA in non-responders to TNFα inhibitors." Pet. 59. But Boehringer ignores the fact that before the invention, doctors were not using the standard dosing regimen to target non-responders to TNFα inhibitors. And to the extent the standard dosing regimen happened to be administered to such non-responders at the time, the results suggested that such a dose was in fact ***not*** "therapeutically effective." Ex. 1007 (De Vita 2002) (reporting that the number of eroded joints increased after anti-CD20 treatment for both such patients in the study, with one exhibiting no improvement and the other exhibiting a

response no greater than that typically observed after administration of a placebo—and even then, only for a short window of time, followed by relapse).

Boehringer's proposed expert Dr. Kalden argues that "[e]ven assuming a need existed for an effective alternative treatment for non-responders to anti-TNF drugs at the time of the invention in 2003, it would not have been 'long-felt'" because "TNF-inhibitors were only approved for use in humans 'from 2000 onwards.'" Ex. 1002 at ¶ 108. Dr. Kalden is wrong about the first approval date. As he acknowledges elsewhere, TNFα-inhibitors were approved in the U.S. by 1998. Ex. 1002 at ¶ 44. In any event, Dr. Kalden's focus on approval dates is a red herring given that studies are conducted prior to approval and in view of Boehringer's own position that the need for an effective alternative treatment was known in the art at least as far back as 1998, as discussed above. If "[p]ersons of ordinary skill in the art had a clear incentive to improve treatments by optimizing dosing levels and regimens to reduce RA symptoms in refractory patients" as Boehringer asserts, Pet. 57, then the fact that years passed without those persons using the claimed methods to alleviate the intense suffering of such patients is a powerful indication that the methods were not obvious.

Dr. Kalden also argues that "[t]o the extent a long-felt need existed in the medical community for an effective treatment regimen for anti-TNF non-responders, it would have been met by the work of Dr. Edwards and not by the claimed invention of the '838 patent." Ex. 1002 at ¶ 109. But that is simply a restatement of Boehringer's

position that Edwards 2002 anticipates '838 patent claims. And that anticipation argument does not withstand scrutiny, as discussed above in Section IV.

2. The Claimed Inventions Produced Unexpected Results.

As of the earliest effective filing date, a skilled artisan would have understood from studies such as De Vita 2002 (Ex. 1007) and Tuscano (Ex. 1008) "that it was going to be harder to treat anti-TNF inadequate responders than patients with less drug-refractory disease." Ex. 1016 at ¶ 30 (discussing references listed in Ex. 2010). Such studies showed little or no response to rituximab in patients who happened to have failed anti-TNFα therapy while reporting outstanding results in other patients, as discussed above in Sections V.A.4.a)(i) & (iii). To the extent the studies assessed joint destruction radiographically, they reported that the number of eroded joints ***increased*** in such patients. *See* Ex. 1007 at 2032. Based on what such references disclosed, "[i]t would ***not*** have been expected that much better clinical benefits, AC[R]50, ACR70, and ***certainly not*** preventing joint progression in anti-TNF inadequate responders, could be achieved" using rituximab. *Id.* (emphasis added).

But those are precisely the results that the treatment regimen claimed in the '838 patent produced. For example, the rituximab prescribing information reports such results from a randomized, double-blind, placebo-controlled study of adult patients with moderately to severely active RA who had a prior inadequate response to at least one TNF inhibitor. Ex. 2008 at 24. More than 25% of patients who received "Rituxan 2 x 1000 mg + MTX," consistent with all the claims of the '838

patent, achieved ACR50 (versus 5% for placebo + MTX), and nearly 15 percent achieved ACR70 (versus 1% for placebo + MTX) at 24 weeks. *Id.* (Section 14.6, Table 8); Ex. 2007 at 2793.

Even more remarkably, when researchers followed up with the patients who had received rituximab, almost 60% of those evaluated showed no erosive progression of joint destruction after two years; and 87% of patients who had no erosive progression in the first year also had no erosive progression in the second year. Ex. 2008 at 27-28; Ex. 1016 at ¶¶ 14-15, 19-20 (explaining that ACR50, ACR70 and prevention of radiographic joint damage were all achieved with same treatment regimen claimed in '838 patent).

Dr. Kalden argues that ACR50 and ACR70 scores "were reported in October 2002, about six months before the Cutoff Date, when Dr. Edwards and Genentech both presented on the promising initial results of a clinical study using the same exact dosing regimen required by the claims of the '838 patent." Ex. 1002 at ¶ 111. But that study was not directed to patients who experienced an inadequate response to anti-TNFα therapy, and none of the patients is identified as an anti-TNFα non-responder. The same is true of the Edwards 2001 study reported at Ex. 1022. In any event, neither Edwards 2002 nor the Genentech Press Release report no erosive progression.

3. The Claimed Inventions Have Enjoyed Great Commercial Success

The FDA authorized Genentech to start marketing rituximab for treating RA in 2006. The only approved RA indication was use, as claimed in the '838 patent, "in

combination with methotrexate . . . in adult patients with moderately- to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies" at doses of "two-1000 mg IV infusions separated by 2 weeks." Ex. 2011 at 18, 42. Rituximab was an instant success. As reported in Genentech's SEC filings for the first two full years following approval, net U.S. sales of rituximab totaled $4.872 billion, and of that amount, it was estimated that sales for the claimed RA indication totaled approximately ***half a billion dollars***. *See, e.g.,* Ex. 2013 at 47 (Page 54 of 141 in printout) (reporting $2.285 billion in U.S. sales of Rituxan® for 2007, with approximately 8% to 10% estimated to be sales in the immunology setting, and $2.587 billion in U.S. sales of Rituxan® for 2008, with approximately 11% to 13% estimated to be immunology sales). This commercial success confirms that the '838 patent claims are not obvious.

VI. CONCLUSION

Boehringer seeks *inter partes* review of the '838 patent by, among other things, trying to read out of the claims limitations it finds problematic and ignoring basic legal requirements designed to prevent obviousness attacks based on impermissible hindsight. Unable to mount a real challenge to patentability, Boehringer's strategy is to throw references at the Board in the hope that the Board will somehow conclude that there is some basis to institute trial. There is no such basis. And Boehringer's strategy has repeatedly been rejected by the Board. Genentech respectfully submits that the Board should deny Boehringer's request for *inter partes* review in its entirety.

Dated: April 15, 2015

Respectfully submitted,

/ Jeffrey P. Kushan /

Jeffrey P. Kushan, Reg. No. 43,401 (Lead)
James A. High, Reg. No. 55,266
Sidley Austin LLP
1501 K Street, N.W.
Washington, DC 20005
Telephone: (202) 736-8914

Gary N. Frischling, Reg. No. 35,515
Keith A. Orso, Reg. No. 52,084
Irell & Manella LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, CA 90067
Telephone: (310) 277-1010

Attorneys for Patent Owner
Genentech, Inc.

Of Counsel
David I. Gindler
Irell & Manella LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, CA 90067
Telephone: (310) 277-1010
Pro Hac Vice Pending

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on April 15, 2015, a copy of the foregoing document **GENENTECH'S PATENT OWNER PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107** has been served in its entirety via e-mail on counsel of record for petitioners at the following address:

BI-USPTO-Comm@proskauer.com

and will be transmitted via Federal Express to counsel of record for petitioners at the following address:

Siegmund Y. Gutman
Proskauer Rose LLP
2049 Century Park East, Suite 3200
Los Angeles, CA 90067-3206

Dated: April 15, 2015

Respectfully submitted,

/Jeffrey P. Kushan/
Jeffrey P. Kushan
Reg. No. 43,401
Attorney for Patent Owner