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.
Biogen Idec, Inc.
Patent Owners

CASE IPR2015-00415
Patent 7,820,161

GENENTECH, INC.'S AND BIOGEN INC.'S PATENT OWNER PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107

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I. INTRODUCTION

Rheumatoid arthritis ("RA") is a crippling autoimmune disorder that inflicts severe joint swelling and pain that worsens into destruction of cartilage and bone, ultimately leading to substantially decreased mobility and other serious handicaps. Ex. 1014 at ¶ 5. The prognosis for patients is grim. Even today, there is no cure.

Traditional RA therapy used non-steroidal anti-inflammatory drugs (NSAIDs) and sequences of "progressively toxic second-line drugs" referred to as disease-modifying antirheumatic drugs ("DMARDs"). Ex. 1022 at 309. "[B]oth patients and physicians [had been] dissatisfied with the long-term results of traditional therapy." *Id.*

Collaborators Biogen Inc. and Genentech, Inc. departed from this traditional approach and developed a creative new therapy. They believed that an antibody called rituximab (Rituxan®)—initially developed and FDA approved for treating certain blood cancers—could be administered as more than one dose and in combination with methotrexate to provide an improved treatment regimen for RA. And they were right. The combination proved to have unexpected synergistic efficacy and became a commercial blockbuster. Both the FDA and its European counterpart approved treating RA with the combination of rituximab and methotrexate. Worldwide sales of rituximab for use in this approved regimen for RA have since totaled about $7 billion.

Biogen and Genentech obtained U.S. Patent No. 7,820,161 (the "'161 patent") for this novel treatment. Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively "Boehringer") now request *inter partes*

review of the '161 patent, alleging obviousness based on various combinations of references, but without meeting its burden to set forth with particularity the reasons that a skilled artisan allegedly would have combined any specific set of references and done so with an expectation of successfully achieving the claimed invention.

Setting aside the dearth of reasoning for any particular combination of references, all of the combinations fail at the outset. They all are based on one of two primary references (both considered by the Patent Office during examination), neither of which can plausibly support an obviousness challenge.

The first of these references, the "Gryn Letter" (Ex. 1026), is simply not a printed publication. It is a private letter. Boehringer completely ignores, and offers no evidence to meet, the Federal Circuit's "printed publication" standard—that the document in question was disseminated or otherwise made available before the priority date such that a skilled artisan, exercising reasonable diligence, could have located it. *See SRI Int'l, Inv. v. Internet Sec. Sys.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008). Instead, Boehringer argues that the Gryn Letter is a printed publication because it supposedly was sent to a commercial entity without any confidentiality or other restrictions on use. Although Boehringer offers no evidence showing that the Gryn Letter was actually sent without any expectation of confidentiality, it would make no difference if Boehringer had done so. The Federal Circuit has held that the absence of a legal obligation of confidentiality does not transform a document into a printed publication. *See Cordis Corp. v. Boston Scientific Corp.*, 561 F. 3d 1319, 1335 (Fed. Cir.

2009). Because Boehringer has failed to meet its burden to show that the Gryn Letter is a "printed publication," trial cannot be instituted based on combinations that include the letter.

The other primary reference on which Boehringer bases its combinations is "the Edwards 1998 Hypothesis" (Ex. 1025). The hypothesis proposed that it might be possible to cure RA (a disease that still has no known cure) by administering rituximab and/or another agent that targets and kills all B cells in a patient. All of the combinations based on the Edwards 1998 Hypothesis fail because, as detailed in Section IV.A.3.(b)(i)(a) below, this untested hypothesis turned upon three premises, each of which was inconsistent with scientific literature available to skilled artisans as of the priority date. Boehringer offers no evidence that skilled artisans would have accepted this hypothesis notwithstanding the infirmities in its foundations.

Moreover, Boehringer fails to show that, even if skilled artisans had accepted the hypothesis, they would have combined its teachings with those of Boehringer's secondary references and arrived at a treatment coupling rituximab and methotrexate. In fact, the opposite is true: they would have found no reason to administer rituximab with methotrexate. As Edwards himself has explained, it would be "completely illogical" to use rituximab with methotrexate "because the 2 treatments are unrelated, they're not doing the same thing." Ex. 2001 at 3. Boehringer articulates no reason that any skilled artisan who might have accepted the hypothesis would have believed that adding methotrexate to rituximab would have any therapeutic value. The hypothesis

was to kill all B cells as a means of curing RA—and none of Boehringer's references identifies methotrexate as an agent that kills B cells.

Boehringer also never establishes that skilled artisans would have had a reasonable expectation of success in arriving at the claimed inventions by combining the teachings of the hypothesis with other references, despite the infirmities in its underlying premises. The hypothesis itself conceded it was "uncertain" whether rituximab would succeed as an RA treatment. And as discussed above, a skilled artisan who accepted the hypothesis would have anticipated no therapeutic value from adding methotrexate to rituximab. Moreover, out of dozens of DMARDs in the prior art, Boehringer identifies only two as having been successfully combined with methotrexate—while ignoring that many DMARDs had proven ***unsuccessful*** in combination with methotrexate. Boehringer offers no theory under which skilled artisans would have had a reasonable expectation of success for combining a new, untested RA treatment with methotrexate despite this track record.

Simply put, skilled artisans would not have—and in the case of the Gryn Letter, could not have—relied on either of Boehringer's primary references as of the priority date. Nor would skilled artisans have had reason to combine them with any other cited references to result in a therapy of rituximab and methotrexate that those skilled artisans would have reasonably expected to be successful in treating RA. Boehringer therefore cannot establish a *prima facie* case of obviousness. Boehringer also fails to

rebut the objective indicia of non-obviousness, including commercial success and evidence of unexpected synergistic results of the inventions.

The petition suffers from other fatal flaws as well. Boehringer never bothers to state with particularity any specific grounds for challenging each claim, despite numerous Board decisions enforcing the requirement to do so. It never identifies differences between any claim and any reference, let alone how those differences allegedly would have been bridged by other references. It also does not articulate any reason for a skilled artisan to have combined specific references or to have expected success with any combination in achieving the claimed inventions. Instead, it addresses claim limitations piecemeal, argues against the claims in the abstract, lists references and combinations in a table without explanation, and improperly tries to lay the burden on the Board to surmise some theory of obviousness. The Board repeatedly has declined to institute trial in the face of such deficiencies.

Boehringer's petition for *inter partes* review does not establish a reasonable likelihood of prevailing with respect to any claim of the '161 patent. The Board should therefore decline to institute trial.

II. BACKGROUND

A. Rituximab With Methotrexate To Treat RA.

Rituximab is a genetically-engineered monoclonal antibody directed against the CD20 antigen, which is expressed on B-cells. Ex. 1001 at 2:29-31. The FDA first approved rituximab to treat low-grade non-Hodgkin's lymphoma ("NHL"), a type of

blood cancer. Ex. 1006 at 1. Rituximab co-developers Genentech and Biogen also tested rituximab for non-cancer uses, including RA. After clinical trials showed surprising synergistic efficacy using the combination of rituximab and methotrexate in patients with RA, as discussed below in Section IV.B.2, the FDA approved that combined use as a treatment for RA. Ex. 2002 at 18. The '161 patent encompasses this approved use.

B. Prosecution History

The '161 patent traces its lineage to a provisional application filed on May 7, 1999. Ex. 1001 at 1:6-8. Boehringer acknowledges that the claims of the '161 patent are entitled to at least this priority date. Pet. 6. Patent Owners rely upon the same date solely for purposes of this Preliminary Response.

During examination, both of the primary references that Boehringer relies on in this IPR—the Edwards 1998 Hypothesis (Ex. 1025) and the Gryn Letter (Ex. 1026)—were discussed at length. Patent Owners overcame all rejections based on these references. *See, e.g.*, Ex. 2003 at 4 (withdrawing obviousness rejections over combinations based on the Edwards 1998 Hypothesis); Ex. 2004 at 6 (withdrawing 102(b) rejection over the Gryn Letter). Similarly, Patent Owners overcame Boehringer's principal argument here—that it would have been obvious to combine rituximab with methotrexate because every new RA drug treatment supposedly would be combined with methotrexate. For example, Patent Owners distinguished various references that disclosed combining drugs other than rituximab with methotrexate.

See, e.g., Ex. 1032 at 4-23 (addressing WO98/04281 (Davis), WO95/09652 (Feldman), and O'Dell 1996 [Ex. 1004]). In allowing the issued claims, the Patent Office agreed that these references did not render obvious the claimed combination of rituximab with methotrexate. *See* Ex. 2003 at 4 (crediting Patent Owners' evidence and arguments). The secondary references that Boehringer relies on here—such as O'Dell 1997 (Ex. 1003), Pincus (Ex. 1008), and Kalden (Ex. 1020)—also describe combining methotrexate with drugs other than rituximab. In this respect, they are merely cumulative of the references overcome during examination.

III. CLAIM CONSTRUCTION

Instead of focusing on particular claim terms and proposing claim constructions (as required by 37 C.F.R. § 42.104(b)), Boehringer's petition briefly comments on the claims of the '161 patent and makes various assertions about what supposedly would be "included" within the broadest reasonable constructions of claims as a whole. Pet. 13-14. Yet Boehringer does not rely on any of these comments or assertions as a basis for arguing that its cited references teach the subject matter of any claim. Patent Owners agree that the Board need not construe any terms of the '161 patent in addressing the petition under 37 C.F.R. § 42.108, while reserving all rights with respect to any claim construction issues that might arise in the future.

Patent Owners do not, however, endorse Boehringer's comments and assertions regarding the claims. And given the lack of specificity in the "Claim Construction" section of the petition, Patent Owners do not attempt here to provide

an exhaustive list of all their disagreements with Boehringer's characterizations. Nevertheless, Patent Owners note, for example, that Boehringer's comments ignore—inadvertently or otherwise—the preambles of the claims, which specify that the claims are directed to methods "of treating rheumatoid arthritis in a human." Ex. 1001 at 29:42-30:44. These preambles provide the antecedent basis for references to "the human" in the bodies of the claims. It is well-established that such use of language in a preamble is limiting. *See, e.g., Eaton Corp. v. Rockwell Int'l*, 323 F.3d 1332, 1339 (Fed. Cir. 2003) (holding that 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"); *HBPSI v. SRAM*, IPR2013-00174, Paper 21 at 13 (Aug. 12, 2013).

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

Boehringer relies on alleged obviousness as its sole basis for challenging the '161 patent. Yet Boehringer never attempts to articulate how any particular combination of references allegedly renders obvious any claim of the patent and fails to rebut the record evidence of objective indicia of non-obviousness.

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

The petition begins by discussing claim limitations in isolation. Pet. 31-42. It next includes a section entitled "Proposed Combinations of Prior Art" that is less than three pages long—including a page-long chart that simply lists, in bullet-point

format, various references and combinations of references without any explanation whatsoever. Pet. 42-45. The discussion following this bullet-point chart, amounting to less than two pages, does not specifically address any of the proposed combinations. The petition then goes on to repackage its earlier piecemeal discussion in the form of "Claim Charts" purporting to show "exemplary disclosure in prior art"—once again, without explaining how any of the alleged prior art references fit together. Pet. 45-57.

Boehringer nowhere articulates any reason or motivation for a skilled artisan to have combined specific references or why a skilled artisan allegedly would have had any reasonable expectation of success in practicing the claimed inventions. Nor does Boehringer anywhere address any individual claims or any differences between any claim and any reference it cites. Moreover, it selectively relies on alleged teachings from those references while ignoring their teachings as a whole, including statements that teach away from the claimed invention.

Boehringer's petition does not satisfy the requirement that a petitioner 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) (emphasis added). Nor does it comply with the 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 the 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)) (emphasis added).

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 v. EveryMD.com*, 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.").

The Board has repeatedly rejected Boehringer's strategy of simply identifying combinations without any corresponding explanations and hoping that the Board will institute trial anyway. 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 has made clear it 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 does not raise evidence that would support such an argument, in any event.

Boehringer's strategy also prejudices Genentech and Biogen. Because Boehringer fails to provide any explanation of how any particular combination of references allegedly renders any claim of the patent obvious, Patent Owners are unfairly left to guess as to the grounds for the challenge. The Board should deny the petition on this ground alone.

1. Boehringer Nowhere Articulates Any Reason For A Skilled Artisan To Have Combined Specific References And Arrived At Any Claimed Invention.

Boehringer devotes a substantial portion of the petition to a piecemeal discussion of where various claim limitations allegedly can be found in the relied-upon references. Pet. 31-42. That piecemeal discussion would be insufficient even if Boehringer showed that each limitation could be found in those references. 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 a skilled artisan would have combined any specific references based on the state of the art as of the effective filing

date. Instead, it ignores the perspective of skilled artisans at the time and tries to piece together information in the references using the patented inventions as a guide. This is classic hindsight, and it 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 come nowhere near to explaining why a skilled artisan allegedly would have combined any of the references, much less would have arrived at any of the claimed inventions as a result. Boehringer argues that "[t]he reason to combine the references is expressly provided in the prior art—namely, to improve treatments for RA patients via combination therapies involving rituximab, methotrexate, and other therapeutic agents, such as glucocorticosteroids." Pet. 43. But none of the references cited by Boehringer discloses a combination therapy involving even rituximab and methotrexate, let alone "rituximab, methotrexate, and other therapeutic agents, such as glucocorticosteroids." Moreover, Boehringer never explains how a desire "to improve treatments for RA patients" allegedly would have led skilled artisans to combine any of the identified references and arrive at the claimed inventions. It is hard to imagine a disease for

which there is not a desire "to improve treatment." But that generalized desire does not make all improved treatments obvious.

Without identifying any particular combination of references, Boehringer argues in the abstract that "[a] person of ordinary skill had compelling reasons to combine rituximab with methotrexate and other therapeutic agents to treat RA." Pet. 3. Yet Boehringer fails to establish even that abstract statement.

For example, Boehringer argues that "[b]y 1997, the use of combination therapies to treat RA had 'increased dramatically' and 'over 90% of rheumatologists used combinations' [of some sort] to treat RA." Pet. 44 (quoting from Ex. 1003). While the quoted passage says nothing about combining rituximab with methotrexate, Boehringer fails to mention that, according to this very passage, those rheumatologists used combinations of some sort in only a small minority of their patients. Ex. 1003 at 789 (estimating 17%). Boehringer also neglects to mention that the leading textbook in the field, Kelley's Textbook of Rheumatology, concluded in that same year that "double-blind, randomized control studies seldom suggest the efficacy or comparative safety of combination therapy." Ex. 2005 at 946. In any event, it would not follow, from the proposition that rheumatologists had prescribed one or more "combinations of DMARDs" generally, that skilled artisans would have been motivated to combine rituximab with methotrexate in particular—especially given that rituximab was not even established as a DMARD, and given that methotrexate was one of a great many available DMARDs. *See infra* Section IV.A.2.

Boehringer also asserts that "methotrexate should be the cornerstone of ***most*** combinations," Pet. 44 (quoting Ex. 1003) (emphasis added), and that "it may be advantageous from both a clinical and a business standpoint to develop ***most*** drugs in RA . . . for use in combination with methotrexate." Ex. 1008 at 593 (quoted in part at Pet. 44) (emphasis added). Even if accepted, however, these assertions still fail to establish that skilled artisans would have been motivated to combine rituximab with methotrexate. For example, neither Boehringer nor any cited reference ever explains ***how to identify which*** combinations "methotrexate should be the cornerstone of" or ***which*** drugs it "may be advantageous from both a clinical and a business standpoint to develop . . . for use in combination with methotrexate." The statements in these references are far too general—none of them has anything to do with rituximab or its potential use, alone or in combination in RA therapy—to lead skilled artisans to combine rituximab and methotrexate in particular.

Boehringer repeatedly asserts that "[t]he consensus among persons of ordinary skill was that the combination of biological agents with methotrexate was of 'special value' when treating RA." Pet. 3, 44. But this supposed "consensus among persons of ordinary skill" was actually just the opinion of Boehringer's proposed expert Dr. Kalden. *Id.* (citing Ex. 1020 at S-96). Moreover, Dr. Kalden was not referring to rituximab. He was referring to "biological agents ***such as anti-CD4 monoclonal antibodies*** or other anti-inflammatories," which he said "***might be*** of special value in combination with drugs such as MTX and other immunosuppressive compounds."

Ex. 1020 at S-96 (emphasis added). Rituximab, which targets B cells, is not a biologic such as anti-CD4 antibody, which targets T cells. Ex. 1018 at 206.

Dr. Kalden's reference to combining methotrexate with biologics such as anti-CD4 is understandable given that methotrexate can suppress undesired, biologic-induced immune responses experienced by many patients. These undesired immune responses, known as a Human Anti-Mouse Antibody (HAMA) response or a Human Anti-Chimeric Antibody (HACA) response, arise when the patient generates antibodies that attack the murine-derived portion of the biologic. Ex. 1015 at ¶ 16. For example, the biologic anti-TNFα antibody cA2 produced a HACA response in 53% of patients, which was reduced to no more than 15% with concomitant methotrexate treatment. Ex. 1021 at 1561.

But rituximab was known to be different. As the FDA label for Rituxan® shows, it was known that rituximab does not tend to provoke such responses. Ex. 1006 at 1 (stating that "HAMA[] was not detected in 67 patients evaluated" and "[l]ess than 1.0% (3/355) of patients evaluated for . . . HACA[] were positive"); Ex. 1015 at ¶ 11; Ex. 2017 at ¶¶ 9-10.

For this reason, Boehringer's suggestion that skilled artisans would have been motivated to combine rituximab with methotrexate to suppress a HAMA/HACA response is belied by Boehringer's own evidence—the FDA label. Pet. 37. Contrary to Boehringer's representations, the FDA label shows that HAMA/HACA responses were ***not*** "a specific concern associated with rituximab use." Pet. 37; Ex. 1006 at 1.

Boehringer also contends that "[c]ombination therapies involving methotrexate had demonstrated so much promise in the prior art that the FDA guidance told the drug development industry that 'it is inevitable that new agents [for RA] will be used in combination with methotrexate in clinical practice unless a contraindication exists.'" Pet. 44-45. But in fact, the FDA guidance nowhere suggests the existence of any such promise. Nor does it imply that all new agents for RA will be combined with methotrexate. It simply observes that there likely would be new RA agents used in combination with methotrexate "since methotrexate therapy is used to treat many RA patients" and "[s]tudies in RA patients, except in those with very mild disease, are carried out in the presence of concurrent active therapies." Ex. 1012 at 17-18.

Boehringer states that the FDA "required" data regarding use of an investigational agent in combination with methotrexate to evaluate the potential for immunosuppression from combination therapy. Pet. 45. If there existed a requirement for such safety data and it applied to all new RA agents, however, it was only because the FDA could not predict which particular agents, or types of agents, might end up having therapeutic value when combined with methotrexate. And even if researchers would have been encouraged to combine a particular new agent with methotrexate to generate such safety data for submission to the FDA, doing so would not have led them to the claimed inventions, which are methods of actually treating RA, not methods of testing for drug interactions. *See Unigene*, 655 F.3d at 1360 (explaining that obviousness requires a reason to combine that would "yield the claimed invention").

2. Boehringer Nowhere Articulates Why A Skilled Artisan Allegedly Would Have Had A Reasonable Expectation Of Success With Respect To Any Of The Proposed Combinations.

"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). A petition must show an expectation of success, in addition to a reason to combine references: "A party who petitions the Board for a determination of obviousness must show that 'a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.'" *3d-Matrix, Ltd, v. Menicon Co., LTD*, IPR2014-00398, Paper 11 at 15 (Aug. 1, 2014).

Boehringer mentions this requirement but two times, and in neither instance does it offer anything other than a naked conclusion. First, Boehringer vaguely asserts that "[t]he available clinical and experimental data associated with combination therapies provided a person of ordinary skill with a reasonable expectation of success when combining rituximab and methotrexate." Pet. 3. Boehringer never identifies the "clinical and experimental data" to which it refers. Nor does it explain how this unidentified data supposedly provided the skilled artisan with a reasonable expectation of success. None of the Boehringer's cited references describes any combination treatment involving rituximab—and Boehringer fails to offer any reason that data

regarding combinations that exclude rituximab would allegedly show an expectation of success for combinations that include rituximab.

Second, Boehringer simply restates the reasonable-expectation-of-success requirement in the form of a conclusion, unaccompanied by any support: "A person of ordinary skill in the art would have been motivated and able to combine the teachings of the above references with predictable results and a reasonable expectation of success." Pet. 43. A petitioner cannot satisfy the expectation-of-success requirement by recasting the requirement in the form of a conclusion.

Citing two paragraphs from the declaration of Dr. Kalden, Boehringer also asserts that skilled artisans would have expected "a synergistic therapeutic result from combining an antibody like rituximab with methotrexate to treat RA." Pet. 37. But neither of those paragraphs even mentions rituximab.

One paragraph generally asserts that "it was expected that combination therapies involving methotrexate and other DMARDs, particularly biologics such as antibodies, would yield a synergistic effect, at least in part by suppressing any anti-drug antibodies being produced by the immune system." Ex. 1002 at ¶ 67. Suppressing anti-drug antibodies was not a concern with rituximab, however, as discussed in Section IV.A.1 above.

The other paragraph refers to a paper positing a synergistic effect from combinations that do not even involve methotrexate—summarized as "'[c]ombination therapies with different cytokine-blocking agents or combinations of anti-T cell and

anti-proinflammatory cytokine treatment modalities.'" Ex. 1002 at ¶ 82 (quoting Ex. 1018 at 210-11). Moreover, the paper states that these combinations—not any combinations involving methotrexate, let alone rituximab—"'seem the most promising.'" *Id.* Boehringer offers no theory as to how combinations that involved neither rituximab nor methotrexate could possibly have given a skilled artisan a reasonable expectation of success in combining those two agents to treat RA.

In addition, the record rebuts any suggestion that skilled artisans would reasonably have expected that combining methotrexate with any and every new RA therapy would be successful. As of the earliest effective filing date, there existed numerous DMARDs for the treatment of RA, including anti-CD4 antibodies, anti-sICAM-1 antibodies, anti-TNF-α antibodies, aminopterin, azathioprine, CAMPATH-1H, chlorambucil, cyclophosphamide, cyclosporine, diphtheria-IL-2 fusion toxin, D-penicillamine, FK506, gold salts (e.g., auranofin, aurothiomalate, aurothioglucose), hydroxychloroquine, hydroxyurea, IL-l receptor antagonist, IL-10, intravenous immunoglobulin, sulfasalazine, tetracyclines (e.g., minocycline), TNF-α receptor fusion protein (e.g., p55 and p75), type II collagen, and Vβ17 T-cell receptor peptide. *See, e.g.*, Ex. 2005 at 939-47, Ex. 1018 at 207-10, Ex. 1020 at Table 1. Out of all these DMARDs, Boehringer identifies ***only two*** as having been successfully combined with methotrexate. *See* Pet. 23 (identifying sulfasalazine plus hydroxychoroquine plus methotrexate); Ex. 1002 at ¶ 62 (identifying an anti-TNFα antibody in combination with methotrexate).

In contrast, many agents had proven ***unsuccessful*** in combination with methotrexate to treat RA. Ex. 2006 at abstract ("Except for fewer withdrawals because of lack of response, combination therapy [of auranofin plus methotrexate] did not demonstrate any advantage in efficacy over single-drug treatment within the time frame of the study."); Ex. 2007 at abstract ("This study establishes that the combination of MTX and AZA in the dosages utilized is not associated with more toxicity than treatment with single agents; however, enhanced efficacy is also not seen."); Ex. 2008 at abstract ("Treatment with cM-T412 in this cohort of RA patients who were also taking methotrexate was not associated with clinical efficacy or enhanced toxicity from infectious complications, despite significant peripheral CD4+ T cell depletion."); Ex. 2009 at summary ("In conclusion, there were no significant differences in efficacy between combination [of sulphasalazine and methotrexate] and single therapy . . ."). Boehringer articulates no theory as to how, given this track record, a skilled artisan could reasonably have expected that every new RA therapy would be successful in combination with methotrexate.

Because Boehringer nowhere articulates any reasonable expectation of success in arriving at the claimed inventions by making any proposed combinations, Boehringer cannot prevail with respect to obviousness. *See Institut Pasteur v. Focarino,* 738 F.3d 1337, 1346 (Fed. Cir. 2013) (reversing a finding of obviousness based on the absence of a reasonable expectation of success); *Norman Int'l, Inc., v. Hunter Douglas, Inc.*, IPR2014-01173, Paper 7 at 14 (Feb. 10, 2015) (denying institution of an IPR

where the petitioner offered only a "broad-brush statement" about the collective teachings of the 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").

3. Boehringer Selectively Cites From References While Ignoring Their Teachings As A Whole, Including Teachings Away.

An obviousness challenge must be analyzed on a claim-by-claim basis. Not only does Boehringer fail to specifically analyze any particular combinations of references, it fails to specifically analyze any particular claims. Setting aside these failures (which themselves are sufficient grounds to reject the petition), all of Boehringer's "Prior Art Combinations" fail at the outset. Half of them fail because they rely on the Gryn Letter, which is not a printed publication. The other half fail because they are based on the Edwards 1998 Hypothesis, and Boehringer never explains how the gaps between that reference and the claims allegedly would have been bridged by any combination of references.

a) *Half Of Boehringer's "Prior Art Combinations" Fail At The Outset Because They Rely On The Gryn Letter (Ex. 1026), Which Is Not A Printed Publication.*

Half of Boehringer's "Prior Art Combinations" rely on a private letter addressed to a Ms. Beth Parker at 3030 Callahan Rd in San Diego, CA. Boehringer suggests that this letter was sent to "IDEC Pharmaceuticals," which it understands to

be "a predecessor to [Patent Owner] Biogen Idec." Ex. 1002 at 23 & n.2. The letter is attached to the Petition as Exhibit 1026 (the "Gryn Letter"). All of Boehringer's obviousness challenges based on the Gryn Letter fail because Boehringer cannot establish that the Gryn Letter is a printed publication.

A patent claim can be challenged in *inter partes* review "only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b); *see also Cisco Sys., Inc. v. Constellation Techs. LLC*, IPR2014-01085, Paper 11 at 9 (Jan. 9, 2015) ("Petitioner has not made a sufficient showing that Rosenberg qualifies as a printed publication under 35 U.S.C. § 102(b) and, thus, falls within the proper scope of an *inter partes* review.").

"'Public accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. § 102(b)." *SRI Int'l*, 511 F.3d at 1194 (quoting *In re Hall*, 781 F.2d 897, 898-99 (Fed. Cir. 1986)). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it." *Id.*; *Actavis, Inc. v. Research Corp. Techs., Inc.*, IPR2014-01126, Paper 22 at 10-12 (Jan. 9, 2015) ("Petitioner asserts that the LeGall thesis is available through University of Houston's library but provides no competent evidence to show that the library allows public access to the thesis.").

The Gryn Letter does not qualify as a "printed publication" because Boehringer has not shown that it was publicly accessible before the priority date of the '161 patent. Boehringer does not contend that the Gryn Letter was widely distributed or otherwise made available to skilled artisans. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 936-37 (Fed. Cir. 1990) (finding documents housed in a library at a commercial corporation were not printed publications); *In re Bayer*, 568 F.2d 1357, 1358-59 (C.C.P.A. 1978) (finding that thesis housed, but uncatalogued and unshelved, in university library was not a printed publication). Boehringer has the burden to establish that its cited references constitute printed publications and has thus failed to carry that burden for the Gryn Letter.

Boehringer's sole argument is that "[t]he letter is a 'printed publication' by virtue of the fact that it was sent to a commercial entity (*i.e.*, IDEC Pharmaceuticals) without any confidentiality or other restrictions on use." Pet. 20. Boehringer offers no evidence to support this conclusion. But even assuming the letter was not subject to a legal obligation of confidentiality, that still would not make it a printed publication. In *Cordis Corp. v. Boston Scientific Corp.*, for example, the Federal Circuit rejected the argument that a document sent to two commercial entities with "no legal obligation of confidentiality" necessarily qualified as a printed publication. 561 F. 3d at 1319, 1335 (Fed. Cir. 2009). The Court noted the absence of any showing that, among other things, the commercial entities "would make the existence of such documents known

and would honor requests for public access." *Id.* at 1335. No such showing has been made here either.

Boehringer cites *Garrett Corp. v. United States*, 422 F.2d 874 (Ct. Cl. 1970), in support of its argument. But *Garrett* did not hold that a document becomes a printed publication if sent to one commercial entity without any confidentiality or other restrictions on use. In *Garrett*, "[a]bout 80 copies" of a report "were distributed in Great Britain prior to 1955 to various British Government agencies, American Government personnel in Great Britain, and 6 commercial companies." *Id.* at 878. "[A]fter 1950, the report was made available for dissemination in the United States through the Defense Department to government contractors who were advised of its availability and could obtain copies upon request at no cost." *Id.* The Court of Claims concluded that "[c]oupled with distribution in Great Britain, evidence of availability in the United States to an interested segment of the public shows intent to make the contents of the report freely accessible" and therefore, the report "was a 'publication' within the meaning of 35 U.S.C. § 102(b)." *Id.* Here, by contrast, Boehringer alleges only that a single, private letter was sent to a single, commercial entity.

Even assuming that the Gryn Letter was non-confidential, it still would not be a printed publication because Boehringer does not establish that it was "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, [could] locate it." *SRI Int'l*, 511 F.3d at 1194. The absence of confidentiality may be necessary to qualify a

document as a printed publication, but it is by no means sufficient. Non-confidentiality is not the same as public accessibility. Here, Boehringer does not even contend that the Gryn Letter was sent to any company other than Biogen. The Federal Circuit has found that mailing a document to a single recipient does not transform the document into a printed publication even if multiple copies were sent "with a view to their being used to get some financial backing." *Preemption Devices, Inc. v. Minnesota Mining.*, 732 F.2d 903, 906 (Fed. Cir. 1984) ("There is no evidence to show further dissemination by the [recipient] before the critical date.").

Because Boehringer has failed to meet its burden to show that the Gryn Letter is a "printed publication," trial cannot be instituted based on any combination that includes it. *See, e.g.*, *Cisco Sys. v. Constellation Techs.*, IPR2014-00871, Paper 12 at 9 (Dec. 19, 2014) ("Petitioner's lack of evidence supporting its contention that Rosenberg was accessible publicly to those interested in the art is fatal to its Petition."); *A.R.M., Inc. v. Cottingham Agencies*, IPR2014-00671, Paper 10 at 7-8 (Oct. 3, 2014) (declining to institute trial based on a document because "Petitioner offers no evidence of a date certain for when [the document] was a publication, and no evidence that [the document] was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, could have located it.").[1]

[1] Boehringer's reliance on MPEP § 2128.02 for guidance regarding "'[a]

b) *The Other Half Of Boehringer's "Prior Art Combinations" Also Fail Because They Rely On The Edwards 1998 Hypothesis.*

The other half of Boehringer's "Prior Art Combinations" rely on a "Hypothesis" by Jonathan Edwards, Ex. 1025, that offers a controversial, untested theory about the cause of RA and speculates that "perhaps for the first time there is a strategy that would logically lead to disease cure." Ex. 1025 at 129. The Edwards 1998 Hypothesis does not suggest the claimed inventions, and Boehringer fails to show that the claimed inventions would have been rendered obvious by it in combination with any other references.

(i) Skilled Artisans Would Not Have Combined The Edwards 1998 Hypothesis With Other References And Arrived At Any Of The Claimed Inventions.

The Edwards hypothesis was based on three premises. The first premise, summarized in a series of "propos[als]" listed at the beginning of the document, was that RA is mediated by certain antibodies called "autoantibodies" that bind to antigens that are also antibodies. Ex. 1025 at 126. These autoantibodies—generated by B cells and daughter plasma cells—are called "rheumatoid factors" (RFs) and they bind to antibodies of a type called "immunoglobulin G" (abbreviated "IgG"). *Id.* The Edwards hypothesis focused on RFs that are themselves of the IgG type ("IgG RF") and therefore bind to each other to form dimeric complexes. *Id.* The hypothesis

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publication disseminated by mail,"' Pet. 20 (emphasis added), is misplaced because the Gryn Letter is by no stretch a publication.

posited that such complexes are small enough to avoid detection by the immune system and to pass through blood-vessel walls to reach surrounding tissue. *Id.* There, so the hypothesis went, the complexes stimulate macrophages (a type of white blood cell) to produce a protein called TNF-α. *Id.* According to the hypothesis, TNF-α causes the inflammation that is characteristic of RA and induces changes in certain cells (fibroblasts), which facilitate "generation of high local levels of RF and the formation of larger immune complex aggregates which induce further inflammatory events." *Id.*; Ex. 1014 at ¶ 19(a) (summarizing that the first element of the Edwards 1998 Hypothesis was "that RA was crucially mediated by autoantibody—specifically rheumatoid factor (RF), which is an anti-IgG (auto)antibody").

The second premise was that the B cells that generate IgG RF and corresponding daughter plasma cells "develop by chance mutations." Ex. 1025 at 128; Ex. 1014 at ¶ 19(b) (explaining that the second element of the Edwards 1998 Hypothesis was "that IgG-RF arise from a chance somatic mutation"). The hypothesis proposed that "if B cells of pathogenic RF specificity are destroyed, the chance of them reappearing may be no greater than that of *de novo* appearance on the same genetic background." Ex. 1025 at 128.

The third premise was that killing all "B cells of pathogenic RF specificity" could cure RA because the chance of such cells re-emerging after destruction would be low. *Id.*; Ex. 1014 at ¶ 19(c) (explaining that the third element of the Edwards 1998 Hypothesis was "that if the entire active B-cell population could be eliminated . . . a

new B-cell population would emerge that would not produce IgG-RF—its production would be permanently interrupted—and that therefore the disease RA should now be cured"). Implicit was the assumption that the existing daughter plasma cells—which produce RF in bulk—are short-lived, such that killing only B cells would be sufficient. Recognizing that "[s]elective destruction" of such pathogenic B-cells "poses major problems," the hypothesis proposed "to kill ***all*** B cells." *Id.* at 128-29 (emphasis added). According to the hypothesis, this would allow healthy B cells, "but not pathogenic IgG RF-producing clones, to re-emerge." *Id.* at 129. The Edwards 1998 Hypothesis states that "[r]ecent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects." Ex. 1025 at 129.

(a) Skilled Artisans Would Not Have Accepted The Edwards Hypothesis Because Its Underlying Premises Were Inconsistent With Scientific Literature As Of The Priority Date.

The Edwards 1998 Hypothesis states that "[s]everal detailed aspects of the hypothesis ***need to be tested***." Ex. 1025 at 129 (emphasis added). But in fact, all three premises of the hypothesis were inconsistent with scientific literature available to skilled artisans as of the priority date. Although evidence of these defects in the Edwards hypothesis was submitted during prosecution, *see* Ex. 1014 at ¶¶19-27, Boehringer ignores this evidence of record and offers no reason that a skilled artisan would have accepted a hypothesis grounded in these scientific infirmities.

The First Premise Of The Edwards Hypothesis Was Inconsistent With The Literature

The theory that RF plays a central role in mediating RA, per the first premise of the Edwards hypothesis, was inconsistent with the scientific literature in several respects. For example, it was already known that "some patients with RA do not exhibit RFs, while on the other hand, RFs are found in many people who do not have RA." Ex. 1014 at ¶ 21. As a leading textbook at the time explained, although elevated levels of RF may be found in RA patients, "its absence in patients with seronegative rheumatoid arthritis argues against its being a causative factor in joint disease." Ex. 2005 at 243.

Moreover, it was known from a study conducted in the 1980s that even in chronic RA patients in which RFs could be found, removing the RFs from the blood (using a process called "plasmapheresis") did not provide a clinical benefit. Ex. 2010 at abstract ("Significant reductions in the . . . rheumatoid factor titer . . . . does not have clinical benefit in chronic rheumatoid arthritis."). And conversely, it also was known from a 1950s study (of dubious ethical status) that injecting RFs into healthy patients did not cause them to develop RA. Ex. 2011 at abstract ("There was no indication in these studies that transfusion of the rheumatoid factor complex has had ability to produce disease in the recipients."); Ex. 1014 at ¶ 21.

The Second Premise Of The Edwards Hypothesis Was Soon Disqualified

By April 1999, scientific literature had refuted the second premise of the Edwards hypothesis: "that pathogenic autoantibodies such as IgG RF develop by chance mutations . . . during responses to unrelated antigens"—at least as to IgG RF specifically. Ex. 1025 at 128. For example, one contemporaneous study showed that instead of being generated by mutations, the genes that encode RFs are already present in the hereditary DNA of most people. Ex. 2012 at 5 ("The results of our investigations have shown that genes encoding rheumatoid factor autoantibodies are present in the germ line of most people.").

"In fact, several groups of investigators had presented data pointing towards an exogenous stimulus," as opposed to chance mutation, causing RA. Ex. 1014 at ¶ 23. For example, a May 1998 report presented data associating RA in certain people with exposure to cats and the microbes they harbor, not with random mutations. Ex. 2013 at 734 ("Taken together, the findings suggest an interaction between an environmental agent harboured by cats and certain RA susceptibility conferring DR genotypes.").

The Third Premise Of The Edwards Hypothesis Also Was Inconsistent With The Literature

The third premise of the Edwards hypothesis contained "a largely erroneous assumption, *i.e.* that plasma cells are short-lived and dissipate rapidly." Ex. 2014 at 825. As Edwards himself later acknowledged, "[e]vidence that this was not so was already available from lymphoma subjects treated with rituximab, in whom total

immunoglobulin levels changed little, despite the absence of circulating B-lymphocytes for many months." *Id.*

Moreover, a March 1998 article examining "the issue of plasma cell longevity" based on studies in mice reported that "a substantial fraction of plasma cells can survive and continue to secrete antibody for extended period of time (>1 year) in the absence of any detectable memory B cells." Ex. 2015 at 363. Long-lived plasma cells have a "half-life that extends for multiple years." Ex. 1014 at ¶ 25 (explaining that "[t]his long lifespan is essential to their role in the immune system").

The lifespan of plasma cells was critical to the Edwards hypothesis because RFs—which the hypothesis theorized to be disease-inducing—are "produced in bulk by daughter plasma cells." Ex. 2014 at 825. And unlike B cells, those plasma cells do not display the CD20 marker to which rituximab binds. Ex. 1014 at ¶ 25. "Therefore, merely eliminating CD20 cells would not obviously eliminate the production of RF" by the RF-producing daughter plasma cells. *Id.* If such plasma cells are long-lived, contrary to the third premise of the Edwards hypothesis, then killing all B cells would not eliminate production of RF and would not cure RA.

* * *

The Edwards 1998 Hypothesis addresses a conceptual theory and speculates that it might eventually "lead to disease cure." Ex. 1025 at 129. Nowhere does it teach administering "more than one intravenous dose of a therapeutically effective amount

of rituximab," as claimed, and nowhere does it even mention a combination with methotrexate, as also claimed. Boehringer does not contend otherwise.

Boehringer asserts that claims 1-12 of the '161 patent are obvious based on the Edwards 1998 Hypothesis in combination with various other references. Each of Boehringer's proposed combinations based on this reference fails as a threshold matter because Boehringer does not establish that as of the earliest effective filing date, skilled artisans would have accepted the hypothesis despite its infirm foundations (described above) and would have pursued any sort of treatment in reliance on it. Even Boehringer's own proposed expert, Dr. Kalden, apparently did not believe that rituximab could be used for RA before—and even after—that time. For example, he failed to include any mention of rituximab in his 1997 or 1998 reviews of biologic agents for RA (Exs. 1020 and 1018), or even his 2000 review published well after the 1998 Edwards Hypothesis. Ex. 2019.

Even apart from the flawed premises of the hypothesis, the state of the art pointed away from the hypothesis's focus on B cells and RF in the pathogenesis of the disease. Indeed, "[a]t the time this [Edwards] hypothesis ran counter to the prevailing view that T cells and innate immunity were the keys to RA." Ex. 2016 at 83. "A pathogenic role for immune complexes, and those formed by RF of the IgG class in particular, seemed likely in the 1970s," but had by the time of the Edwards hypothesis "become less fashionable, being championed only by a few." Ex. 1025 at

126. Boehringer fails to show that skilled artisans would have looked to the Edwards 1998 Hypothesis to develop treatments for RA notwithstanding this state of the art.

(b) The Edwards Hypothesis Would Have Discouraged Skilled Artisans From Combining Any Of The References And Arriving At The Claimed Inventions.

Even assuming that skilled artisans would have accepted the Edwards hypothesis, Boehringer fails to articulate any reason they allegedly would have combined it with any reference and arrived at the claimed inventions—all of which require administration of rituximab and methotrexate.

In fact, based on the Edwards hypothesis, skilled artisans would have had no reason to administer a CD20 antibody like rituximab with methotrexate. The hypothesis was that RA can be cured by "kill[ing] all B cells," and according to the hypothesis, "[r]ecent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody." Ex. 1025 at 129. If skilled artisans would have believed that such an antibody kills all mature B cells, then they would have believed that administration of the antibody alone would cure RA according to the Edwards hypothesis—and no other agent would need to be administered in combination with it. On the other hand, if they believed that the antibody alone would not kill all mature B cells, then the Edwards hypothesis would dictate using something else that can do so, or perhaps using rituximab in combination with another agent that targets and kills B cells to finish the job. Methotrexate would not qualify as such an agent because none of the cited references indicates that it kills

B cells. As Edwards himself has explained, it would be "completely illogical" to use rituximab with methotrexate "because the 2 treatments are unrelated, they're not doing the same thing." Ex. 2001 at 2-3.

Moreover, a physician guided by the Edwards hypothesis would have been motivated ***not*** to administer methotrexate along with rituximab because it was well known that methotrexate increases the size of rheumatoid nodules, *see, e.g.,* Ex. 1003 at 787, which—according to the hypothesis—play a central role in the pathogenesis of RA. Ex. 1025 at 127. The hypothesis explains that "[t]he rheumatoid nodule may be seen as the hallmark connective tissue lesion of RA" and states that "[t]he architecture of the nodule, with a ring of macrophages surrounding an area of necrosis, is consistent with a self-propagating response to a constant supply of extravascular immune complexes," *e.g.*, IgG RF dimers. *Id.* Because these IgG RF dimer complexes stimulate the macrophages in rheumatoid nodules to produce inflammation-producing TNF-α according to the hypothesis, Ex. 1025 at 126, increasing the size of the nodules would worsen the disease per the hypothesis. Ex. 2017 at ¶ 20. Thus, the hypothesis taught against administering a nodule-increasing agent like methotrexate.

Apparently, even Boehringer's proposed expert Dr. Kalden did not expect that rituximab would be used in combination with methotrexate—or anything else—to treat RA. He never once mentions rituximab in his 1997, 1998, and 2000 articles addressing treatment of RA using biological agents in combination therapies, including combinations involving methotrexate. Exs. 1020, 2018, 2019.

If skilled artisans pursuing the Edwards hypothesis would have looked for other agents to administer with rituximab, their focus would not have been on methotrexate, but rather on agents that target and kill B cells like rituximab. Indeed, when the authors of the Edwards 1998 Hypothesis began to test elements of their theory, their very first study addressed administration of rituximab with cyclophosphamide, not methotrexate, to reach the "threshold of B-lymphocyte depletion." Ex. 2020 at 206. The Edwards 1998 Hypothesis specifically calls out high-dose cyclophosphamide to achieve substantial depletion of B cells. Ex. 1025 at 129 (referring to the hypothesized effect of "destroy[ing] all mature B cells" and stating "[t]his may well be what happens when subjects with RA treated with high-dose cyclophosphamide prior to bone marrow transplantation go into long-term remission").

(c) Based On The Edwards Hypothesis, Skilled Artisans Would Not Have Had A Reasonable Expectation Of Success In Combining Any Of The References And Arriving At The Claimed Inventions.

Boehringer also fails to establish that skilled artisans would have had a reasonable expectation of success in combining the Edwards 1998 Hypothesis with any other references and arriving at a method of treating RA. Indeed, Boehringer fails even to address it. This omission is all the more glaring, given that each premise of the hypothesis had been disqualified by the scientific literature known to skilled artisans as of the priority date (as discussed above). Even on its face, the Edwards 1998 Hypothesis would have failed to inspire a reasonable expectation of success because it

concedes that the prospect of successfully eliminating RF-producing B cells to cure RA "is uncertain." Ex. 1025 at 129.

* * *

Even if Boehringer had established that the Edwards hypothesis would have been accepted and pursued by a person having ordinary skill in the art, it still fails to show that the differences between the Edwards 1998 Hypothesis and the claims would have been bridged by combination with any other references.

(ii) Boehringer Fails To Establish That The Differences Between Claim 1 And The Edwards 1998 Hypothesis Would Have Been Bridged By Combination With Any Other References.

(a) Edwards 1998 Hypothesis In View Of O'Dell (Ex. 1003)

Boehringer never explains how O'Dell (Ex. 1003) allegedly bridges the gaps between claim 1 and the teachings of the Edwards 1998 Hypothesis and, as discussed above in Sections IV.A.1-3, fails to identify any reason to have combined the Edwards 1998 Hypothesis and O'Dell, or any reasonable expectation of success in doing so.

O'Dell is an article entitled "Methotrexate Use In Rheumatoid Arthritis." Ex. 1003. Although it reports that methotrexate has been popular, it acknowledges that some studies "have failed to show an advantage of methotrexate," and that the "Bad News" was that methotrexate "rarely induces remissions of RA." *Id.* at 782. "In fact," O'Dell points out, "even if standards are lowered considerably and 50% improvement accepted (by the Paulus criteria), only approximately one third of RA patients treated with methotrexate achieve this modest goal at 2 or 4 years." *Id.* The

article also describes various toxicities and side effects associated with administration of methotrexate. *Id.* at 784-86.

Despite this, Boehringer asserts that "[a]ccording to O'Dell 1997, methotrexate 'should be the foundation of most combination therapies.'" Pet. 25. But O'Dell nowhere explains how to identify ***which*** combinations methotrexate supposedly "should be the foundation of."

O'Dell contains no mention of CD20 antibodies generally or rituximab in particular, much less administration of either for treatment of RA. In fact, O'Dell expresses skepticism about using biologics even for RA monotherapy. For example, O'Dell reports that although "much publicity about biologic agents and their application to the treatment of RA has appeared, . . . the results of these interventions, when studied in controlled trials (with the possible exception of therapies directed against tumor necrosis factor alpha), have been ***singularly unimpressive***." Ex. 1003 at 792 (emphasis added). And far from suggesting even generally that biologics should be administered with methotrexate, O'Dell cautions that "[c]ontinued research on combinations of DMARDs, as well as combinations that include biologic agents and methotrexate and possibly other DMARDs, is necessary." *Id.*

Boehringer does not articulate any reason why a skilled artisan allegedly would have combined the Edwards 1998 Hypothesis with O'Dell and arrived at the invention of claim 1. Nor could it. O'Dell does not address any aspect of the hypothesis, including any way to achieve destruction of mature B cells. Nowhere, for

example, does O'Dell suggest that methotrexate kills B cells. O'Dell also does not provide results for parts of the Edwards 1998 Hypothesis that still "need to be tested." Ex. 1025 at 129.

Boehringer also does not articulate any basis for skilled artisans to have had a reasonable expectation of success in achieving the claimed inventions by combining the Edwards 1998 Hypothesis with O'Dell. And no such basis existed, given the known flaws in the hypothesis.

(b) Edwards 1998 Hypothesis In View Of Pincus (Ex. 1008)

Boehringer fails to articulate how Pincus (Ex. 1008) supposedly bridges the gaps between the Edwards 1998 Hypothesis and claim 1 and fails to identify any reason to have combined these references or any reasonable expectation of success in doing so, as discussed above in Sections IV.A.1-3.

The Pincus editorial does not refer to CD20 antibodies generally or rituximab in particular. It does not even mention biologics, much less assert that they should be used either alone or in combination with anything else, including methotrexate, to treat RA. In fact, even with respect to non-biologics, Pincus warns: "More evidence is needed concerning the effectiveness of methotrexate as an initial drug or in 'combination' with other DMARDs in early RA." Ex. 1008 at 592.

Boehringer fails to identify any reason why a skilled artisan supposedly would have disregarded the warning in Pincus and somehow arrived at the invention of claim 1 by combining the Edwards 1998 Hypothesis with Pincus. Like O'Dell, Pincus

does not address any aspect of the Edwards 1998 Hypothesis, including any way to achieve destruction of mature B cells, and does not suggest that methotrexate kills B cells. And like O'Dell, Pincus does not provide results for any parts of the Edwards 1998 Hypothesis that still "need to be tested." Ex. 1025 at 129.

Boehringer acknowledges Pincus's statement that "'the use of drugs in combination is not a traditional strategy in pharmaceutical development,'" Pet. 26 (quoting Ex. 1008). But Boehringer contends that "Pincus et al. identified an ***economic incentive*** to combine methotrexate with other RA drugs during pharmaceutical development" because it stated that "'the fact that more than 50% of patients with RA under the care of rheumatologists in the U.S. take methotrexate ***suggests*** that it ***may*** be advantageous from both a clinical and a business standpoint to develop ***most*** drugs in RA at this time for use in combination with methotrexate.'" *Id.* (emphasis added). Even taking this equivocal statement at face value, Pincus still fails to establish that there was any reason to combine methotrexate with rituximab. It provides no guidance, for example, on how to identify ***which*** drugs for RA it may be "advantageous from both a clinical and a business standpoint to develop . . . for use in combination with methotrexate." Pet. 44. Nor does it explain why skilled artisans allegedly would have treated a unique drug like rituximab like "most drugs in RA." Pincus also fails to articulate how such development "may be advantageous from both a clinical and a business standpoint."

Boehringer also fails to articulate any basis for a skilled artisan to have had a reasonable expectation of success in arriving at the claimed inventions by combining the Edwards 1998 Hypothesis with Pincus. And no such basis existed because of the flawed underpinnings of the Edwards hypothesis.

(c) Edwards 1998 Hypothesis In View Of Kalden (Ex. 1020)

Boehringer never explains how Kalden (Ex. 1020) allegedly supplies the teachings missing from the Edwards 1998 Hypothesis and, as discussed in Sections IV.A.1-3 above, fails to identify any reason to have combined these references or any reasonable expectation of success.

Kalden contains no mention of rituximab in particular or even anti-CD20 antibodies generally, much less administration of any such antibodies for treatment of RA—either alone or in combination with methotrexate. In fact, Kalden mentions administration of methotrexate only three times, in connection with two specific RA drugs. It concludes that one of those drugs demonstrated a "lack of clinical efficacy, as shown in double-blind placebo controlled trials," Ex. 1020 at S-94, and equivocally states that "[c]ombining methotrexate and the repeated administration of anti-TNF-α Mab CA2, Kavanaugh *et al.* (41) demonstrated that combination therapy ***might be*** an important therapeutic approach for RA patients whose disease is not completely controlled by MTX alone." Ex. 1020 at S-96 (emphasis added).

Boehringer does not articulate any reason why a skilled artisan allegedly would have combined the Edwards 1998 Hypothesis with Kalden and arrived at the

invention of claim 1. Kalden does not address any aspect of the Edwards 1998 Hypothesis, including any way of achieving destruction of mature B cells, and does not suggest that methotrexate kills B cells. Nor does it provide results for any parts of the Edwards 1998 Hypothesis that still "need to be tested." Ex. 1025 at 129.

Boehringer fails to articulate any basis for skilled artisans to have had a reasonable expectation of success in achieving the claimed inventions by combining the Edwards 1998 Hypothesis with Kalden, and no such basis existed, given the known flaws in the hypothesis.

(d) Edwards 1998 Hypothesis In View Of (O'Dell or Pincus or Kalden) and The Rituxan® Label (Ex. 1006)

In addition to listing the Edwards 1998 Hypothesis in combination with each of O'Dell, Pincus, and Kalden, Boehringer's table of "Prior Art Combinations" includes each of those pairs in further combination with the Rituxan® Label (Ex. 1006).

Boehringer fails to articulate how the Rituxan® Label supposedly bridges the gaps between claim 1 and the combination of the Edwards 1998 Hypothesis in view of either O'Dell, Pincus, or Kalden, as discussed in Sections IV.A.3.b)(i)(a)-(c). Nor does Boehringer identify any reason to have made such combinations or any reasonable expectation of success, as discussed above in Sections IV.A.1-3.

Like O'Dell, Pincus, and Kalden, the Rituxan® Label does not suggest using rituximab, either alone or in combination with any other agent, to treat RA. As

Boehringer acknowledges, the label addresses "use of rituximab for treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-Hodgkin's lymphoma[s]," which are types of blood cancers. Pet. 15. The Rituxan® Label nowhere even mentions methotrexate, much less suggests that it kills B cells.

Boehringer offers no theory how the Rituxan® Label—which suffers from the same kind of deficiencies as O'Dell, Pincus, and Kalden—allegedly would, in combination with any of those very same references, somehow have rendered claim 1 obvious based on the Edwards 1998 Hypothesis.

(e) Edwards 1998 Hypothesis In View Of (O'Dell or Pincus or Kalden) and Maloney (Ex. 1023)

Boehringer's table of "Prior Art Combinations" includes the Edwards 1998 Hypothesis in combination with each of O'Dell, Pincus, and Kalden, in further combination with Maloney (Ex. 1023). As with the similar combinations using the Rituxan® Label, Boehringer never articulates how Maloney allegedly supplies the teachings missing from the other references in each triplet. *See supra* Sections IV.A.3.b)(i)(a)-(c). Moreover, Boehringer fails to articulate any reason to have made such combinations or any reasonable expectation of success in doing so, as discussed in Sections IV.A.1-3.

Maloney—like O'Dell, Pincus, and Kalden—does not teach using rituximab, either alone or in combination with any other agent, to treat RA. Maloney does not even address RA. Rather, Maloney reports results from a ***cancer*** study of a "recurrent

B-cell lymphoma." Pet. 17. As Boehringer concedes, that study involved a "'single-dose infusion with chimeric anti-CD20 antibody,'" Pet. 17, not administering "more than one intravenous dose" of such an antibody, as required by claim 1. Ex. 1001.

Maloney also does not suggest administering methotrexate to patients, as also required by claim 1. Ex. 1001. And like O'Dell, Pincus, and Kalden, it nowhere suggest that methotrexate kills B cells.

Simply put, Boehringer does not even try to explain how a reference like Maloney, which suffers from the same kind of deficiencies as O'Dell, Pincus, and Kalden, allegedly would have rendered claim 1 obvious based on the Edwards 1998 Hypothesis in combination with any of those very same references.

(iii) Boehringer Fails To Establish That The Differences Between Claim 2 And The Edwards 1998 Hypothesis Would Have Been Bridged By Combination With Any References.

Claim 2 depends from claim 1 and adds the requirement that "each administration of rituximab is a dose in the range from about 250 mg/m^2 to about 1000 mg/m^2." Ex. 1001 at 30:1-3. Boehringer challenges claim 2 based on all of the same combinations that it identifies for claim 1. Pet. 42-43. Because dependent claim 2 incorporates all of the limitations of claim 1, Boehringer's challenge to claim 2 fails for at least all of the same reasons that its challenge to claim 1 fails. *See supra* Section IV.A.3.b)(i)-(ii).

Boehringer's challenge to claim 2 also fails because none of the references Boehringer relies on (the Edwards 1998 Hypothesis, O'Dell, Pincus, Kalden, the

Rituxan® Label, or Maloney) teaches the claimed doses to treat RA. The Edwards 1998 Hypothesis does not teach any dose for rituximab or anti-CD20 antibodies, Ex. 1025, and none of O'Dell, Pincus, and Kalden even mentions such agents, much less describe any dosing for them. Exs. 1003, 1008, and 1020. The Rituxan® Label discloses four 375 mg/m^2 doses of rituximab to treat non-Hodgkin's lymphomas—not RA—and Maloney teaches administering ***single*** doses for the same purpose. Boehringer fails to articulate any reason why skilled artisans allegedly would have adopted any dosing for NHL to treat patients with RA, a completely different disease.

In addition, Boehringer fails to identify any reason to combine the references so as to arrive at the claimed invention, and fails to articulate any reasonable expectation of success in doing so, as discussed above in Sections VI.A.1-3.

(iv) Boehringer Fails To Establish That The Differences Between Claim 3 And The Edwards 1998 Hypothesis Would Have Been Bridged By Combination With Any References

Claim 3 depends from claim 1 and adds the step of "administering to the human a glucocorticosteroid." Ex. 1001 at 30:4-5. Boehringer's table of "Prior Art Combinations" lists three combinations based on the Edwards 1998 Hypothesis in the entry for claim 3. Pet. 43. Boehringer does not contend that any of these combinations also renders obvious independent claim 1. *See* Pet. 42-43. And if a combination cannot render obvious independent claim 1, then neither can it render obvious dependent claim 3. *Cf. Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1344

(Fed. Cir. 2009) ("A broader independent claim cannot be nonobvious where a dependent claim stemming from that independent claim is invalid for obviousness").

Boehringer argues generally that "[g]lucocorticosteroids had been used in treating RA patients for many years prior to the filing date of the '161 patent." Pet. 40. Even if true, this would of course be insufficient to prove that the ***three-drug*** regimen of rituximab, methotrexate, and glucocorticosteroids was obvious.

Moreover, Boehringer ignores statements in its own reference that teach against using glucocorticosteroids with rituximab in particular. Indeed, a transcript of an FDA hearing that took place on July 25, 1997—submitted by Boehringer in related proceeding IPR2015-00418—teaches that steroids could interfere with rituximab's ability to destroy B cells. Ex. 2021. According to the transcript, after Patent Owner Biogen (then IDEC Pharmaceuticals) presented study data regarding use of rituximab to treat non-Hodgkin's lymphomas, it reported its concern that "there might be an interference by steroids with the mechanism of action of the [rituximab] antibody," explaining that for that reason, it "did make that an exclusion criterion and . . . did not permit the administration of steroids in this study." *Id.* at 75.

In addition, it was known by January 1998 that steroids might prevent the recruitment of immune effector functions to mediate B-cell lysis, e.g., antibody-dependent cellular cytotoxicity (ADCC). In particular, it was known that rituximab destroys B cells through ADCC, among other mechanisms, *see* Ex. 1006 at 1, and that steroids could interfere with this mechanism of action. *See, e.g.,* Ex. 2022 at 89

("Glucocorticoids inhibit NK-cell-mediated cytotoxicity and antibody-dependent cell cytotoxicity (ADCC)"). Boehringer ignores these facts.

Citing only the opinion of its proposed expert Dr. Kalden, Boehringer argues that claim 3 is obvious because it supposedly "was well known that the injection of glucocorticosteroids prior to or concurrent with the infusion of immunoglobulins (*i.e.*, antibodies such as rituximab) will prevent possible adverse side effects." Pet. 41. Dr. Kalden's opinion, in turn, fails to cite any evidence and simply repeats Boehringer's petition. *See* Ex. 1002 ¶ 89. The Board should not credit such conclusory assertions. *See* 37 C.F.R. § 42.65(a); *Atoptech, Inc. v. Synopsys, Inc.*, IPR2014-01150, Paper 11 at 17-18 (Jan. 21, 2015) (disregarding expert declaration that "lacks any evidence to support the Petition's conclusions, and indeed, simply repeats verbatim the Petition's conclusions in each instance."). If prophylactic steroid use to prevent side effects were so "well known," then Boehringer presumably would have been able to identify references describing such use.

Dr. Kalden's opinion is not only unsupported, it is also contrary to Boehringer's own references, including the FDA Transcript discussed above. Ex. 2021 at 35, 81(explaining that "[t]he use of steroids prophylactically or during infusion was specifically prohibited" in rituximab clinical trials for NHL). Moreover, Boehringer acknowledges that Maloney showed that patients using rituximab experienced "minimal infusional-related toxicity," making prophylactic administration of steroids unnecessary. Pet. 17 (*citing* Ex. 1023 at 2460).

Thus, Boehringer's general arguments do not withstand scrutiny. Nor do its "Prior Art Combinations" for claim 3.

(a) Edwards 1998 Hypothesis In View Of Verhoeven (Ex. 1016)

Boehringer never explains how Verhoeven (Ex. 1016) allegedly bridges the differences between the Edwards 1998 Hypothesis and claim 3, including the absence of any teaching of administering "more than one intravenous dose of a therapeutically effective amount of rituximab," or of administering methotrexate. And as discussed in Sections IV.A.1-3 above, Boehringer fails to identify any reason to have combined these references or any reasonable expectation of success.

Verhoeven is a review article that does not even mention anti-CD20 antibodies, much less treating RA by administering such antibodies alone or in combination with other agents. In fact, Verhoeven mentions only one biologic (anti-CD4 [T-cell] antibody), and the combination of methotrexate with that biologic failed to show superiority over methotrexate monotherapy. Ex. 1016 at 613, 615.

Boehringer does not identify any reason why skilled artisans allegedly would have combined the Edwards 1998 Hypothesis and Verhoeven and arrived at the invention of claim 3. And, in fact, no such combination would have been made. Verhoeven does not address destruction of mature B cells or any other aspect of the Edwards hypothesis. Nowhere does Verhoeven suggest that methotrexate kills B cells.

Boehringer also does not explain why skilled artisans allegedly would have had a reasonable expectation of success combining the Edwards 1998 Hypothesis with

Verhoeven and arriving at the claimed inventions. In fact, Verhoeven stands as a powerful reminder of why a skilled artisan would ***not*** reasonably expect that RA drugs could be randomly mixed and matched for two- or three-drug combination therapy with success. Verhoeven provides examples of some RA drugs that work in combination with some agents but not others. For example, Verhoeven reports that combining cyclosporine with one drug increased efficacy (Tugwell [8]) but combining it with another drug did not (Bendix [9]). Ex. 1016 at 614 (Table 1). It reports the same thing for hydroxychloroquine (compare Scott [12] to Faarvang [13]), methylprednisolone (compare Corkill [24] to Ciconelli [25]), and methotrexate (compare Trnavsky [16] to Williams [19]). *Id.* Thus, skilled artisans would not assume that combining any new RA drug with methotrexate would be successful.

Boehringer cites Verhoeven for the proposition that "'step-down bridge therapy that includes corticosteroid leads to much enhanced efficacy at acceptable or low toxicity.'" Pet. 40. But even if skilled artisans would have taken from such a statement that a corticosteroid should be combined with every RA drug, including rituximab—contrary to the teachings from the FDA hearing transcript discussed above—they still would not have arrived at the invention of claim 3, which also requires administration of methotrexate. Boehringer states that "[t]he same paper also referred to one study where 'prednisolone [a glucocorticosteroid] was added together with methotrexate." *Id.* (citing the Boers reference, further addressed below in Section IV.A.3.b)(iv)(c)). But Boehringer ignores Verhoeven's conclusion that there

appears to be no trend for an overall beneficial effect of methotrexate in a combination. Ex. 1016 at 617 (studying methotrexate and numerous other drugs in combinations and concluding that "[e]xcept for corticosteroids, there appears to be no trend for an overall beneficial effect of a particular drug in a combination"). Thus, Verhoeven would not have encouraged skilled artisans to make the claimed combination.

(b) Edwards 1998 Hypothesis In View Of Kavanaugh (Ex. 1019)

Boehringer does not explain how Kavanaugh (Ex. 1019) allegedly fills the gaps between the Edwards 1998 Hypothesis and claim 3 and does not identify any reason to have combined these references or to have had any reasonable expectation of success, as discussed in Sections IV.A.1-3 above.

Kavanaugh is an abstract reporting on a study in RA patients whose disease was "incompletely controlled" with methotrexate. These patients were given "adjunctive therapy with an anti-TNFα mAb." Ex. 1019. Kavanaugh concludes that "adjunctive therapy with an anti-TNF-α mAb may be an important therapeutic approach for RA patients whose disease is incompletely controlled by MTX." *Id.* Kavanaugh does not mention any anti-CD20 antibodies, let alone administering such antibodies alone or in combination with methotrexate or any other agents to treat RA.

Boehringer does not articulate any reason why skilled artisans allegedly would have combined the Edwards 1998 Hypothesis and Kavanaugh and arrived at the invention of claim 3. But even assuming such a reason existed, given that Kavanaugh

teaches adjunct therapy with an anti-TNFα mAb, combining the Edwards 1998 Hypothesis with Kavanaugh would have led to the administration of anti-TNFα mAb as an adjunct to rituximab, not the claimed combination of methotrexate, rituximab and a corticosteroid. Kavanaugh does not address any aspect of the Edwards hypothesis and does not suggest that methotrexate kills B cells.

Kavanaugh reports that patients in the study "were ***allowed*** stable doses of NSAIDs and prednisone," *id.* (emphasis added), but does not differentiate its results based on whether patients ended up requesting and receiving NSAIDs, prednisone, or both or neither. Kavanaugh, therefore, does not provide a reason for using a three-drug combination of rituximab plus methotrexate plus a corticosteroid, nor a reasonable expectation of success for such a combination.

(c) Edwards 1998 Hypothesis In View Of Boers (Ex. 1022)

Boehringer never explains how Boers (Ex. 1022) allegedly bridges the differences between the Edwards 1998 Hypothesis and claim 3. And Boehringer fails to identify any reason to have combined these references or any reasonable expectation of success, as discussed in Sections IV.A.1-3 above.

Boers describes study results comparing treatment with sulphasalazine monotherapy to step-down treatment with a combination of sulphasalazine, prednisolone, and methotrexate, where prednisolone was withdrawn gradually, followed by withdrawal of methotrexate. Ex. 1022 at 310.

Nowhere does Boers contain any mention of rituximab or any anti-CD20 antibodies, much less administration of the same in combination with methotrexate and glucocorticosteroids or any other agents. In fact, Boers questions the benefit of combination therapy in RA. Boers acknowledges that "[t]he value of intensive combination therapy in early rheumatoid arthritis is unproven." Ex. 1022 at 309. "To date," Boers explains, "most drug combination trials have not shown addition or synergy (i.e., benefits equal or better than the sum of benefits attributed to the single drugs)." *Id.* at 317. Boers concludes that "more study on the merits of combination therapy is necessary." *Id.* at 318.

Boehringer identifies no reason why skilled artisans supposedly would have combined the Edwards 1998 Hypothesis with Boers and arrived at the invention of claim 3. Boers does not address any facet of the Edwards hypothesis, and it does not suggest that methotrexate kills B cells. Moreover, the results of Boers would not have encouraged skilled artisans to include methotrexate in their combinations. Boers reports that "[t]he difference in clinical efficacy between the treatment groups [the combination versus sulphasalazine alone] decreased and was no longer significant after the withdrawal of prednisolone, and there were ***no further changes when methotrexate was withdrawn*** (figure 2)." Ex. 1022 at 313 (emphasis added). Indeed, Boers acknowledges that "[t]he value of the combination of methotrexate and sulphasalazine is uncertain." *Id.* at 317.

Boehringer also fails to establish that skilled artisans would have had any expectation of success in arriving at the claimed inventions by combining these references. Notably, Boers used well-established DMARDs in combination, *see id.* at 309; not an untested drug only hypothesized to be effective in RA, like rituximab. Even if the results of Boers could be abstracted and generalized, Boehringer offers no reason for extending such results beyond well-established DMARDs.

(v) Boehringer Fails To Establish That The Differences Between Claim 4 And The Edwards 1998 Hypothesis Would Have Been Bridged By Combination With Any References.

Claim 4 depends from claim 1 and additionally requires "an initial dose of the rituximab followed by a subsequent dose, where the mg/m^2 dose of the rituximab in the subsequent dose exceeds the mg/m^2 dose of the rituximab in the initial dose."

(a) Edwards 1998 Hypothesis In View Of (O'Dell or Pincus or Kalden) And The Rituxan® Label (Ex. 1006)

Boehringer lists the Edwards 1998 Hypothesis with each of O'Dell, Pincus, and Kalden, plus the Rituxan Label (Ex. 1006) as combinations against claim 4. Boehringer cites these same combinations against claim 1. Because claim 4 contains all the same limitations as claim 1, Boehringer's challenge to claim 4 based on these combinations fails for at least the same reasons its challenge to claim 1 fails on those bases.

Moreover, contrary to Boehringer's representations, the Rituxan® Label does not disclose a subsequent dose of rituximab that "exceeds the initial dose." Pet. 41.

Rather, it discloses escalating dose ***rates*** (mg/hr). Ex. 1006 at 2. An escalating rate is not the same as an escalating dose. Claim 4 expressly requires an escalating dose. Under 37 C.F.R. § 42.65(a) and decisions such as *Atoptech*, IPR2014-01150, Paper 11 at 17-18, the Board should not give weight to the conclusory testimony of Boehringer's proposed expert that "increasing the second dose of rituximab would be obvious." *See* Pet. 42.

(b) Edwards 1998 Hypothesis In View Of (O'Dell or Pincus or Kalden) and Tobinai (Ex. 1013)

Boehringer lists the Edwards 1998 Hypothesis with each of O'Dell, Pincus, and Kalden, plus Tobinai (Ex. 1013) as combinations against claim 4. Boehringer's challenge based on the subcombinations of the Edwards hypothesis with each of O'Dell, Pincus, and Kalden fail for the reasons discussed above in Section IV.A.3.(b)(ii)(a)-(c), and Boehringer never articulates how Tobinai allegedly fills the gaps left by these subcombinations. Like the Rituxan® Label, Tobinai addresses NHL, not RA. It does not teach using rituximab to treat RA, and it contains no mention of methotrexate.

Contrary to Boehringer's representations, Tobinai does not disclose "escalating dose levels" of rituximab in a patient. Boehringer quotes Tobinai as referring to "'dose-escalation in two steps'" with the starting dosage "'set at 250 mg/m^2/infusion'" and a later dosage "'escalated to 375 mg/m^2/infusion.'" *See* Pet. 41. But Boehringer fails to disclose that this refers to different doses in different patients,

not escalating doses in a single patient. Tobinai in fact expressly states: "No intrapatient dose escalation was allowed." Ex. 1013 at 528. Boehringer does not articulate any reason why a skilled artisan purportedly would have combined these references, or would have had any reasonable expectation of success in doing so, as discussed above in Sections IV.A.1-3.

(vi) Boehringer's "Prior Art Combinations" For Claims 5-12 Fail For At Least The Same Reasons They Fail For Claims 1-4.

Boehringer asserts that independent claims 5 and 9 are the same as independent claim 1, and lumps all three claims together in the petition. *See* Pet. 6-7. Likewise, Boehringer asserts that claims 2, 6, and 10 are identical, that claims 3, 7, and 11 are identical, and that claims 4, 8, and 12 are identical. *See* Pet. 7-9. Boehringer then cites all of the same art against each triplet of claims, without differentiation. Accordingly, Boehringer's challenges to claims 5-12 fail for at least the same reasons as its challenges to claims 1-4 fail.

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). "[O]bjective indicia of nonobviousness are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Such

objective indicia include long-felt but unsolved need, unexpected results, and commercial success. *Apple, Inc.*, 725 F.3d at 1375. Here, these objective indicia are evidenced by the record from prosecution—and that record stands unrebutted.

1. The Claimed Treatment Addresses A Long-Felt Need For A New Way To Treat RA, And Enjoys Significant Commercial Success.

During prosecution, in a section of an amendment entitled "The Claimed Treatment Methods Address a Long-Felt Need for a new Way to Treat RA, and Enjoys Significant Commercial Success," the Patent Owners explained that the claimed FDA-approved method of using rituximab in combination with methotrexate "represents an important new advance in the treatment of patients suffering from the debilitating disease of rheumatoid arthritis." Ex. 1032 at 27; *see also* Ex. 1015 at ¶ 5. The Patent Owners also informed the Patent Office that "[w]orldwide sales of rituximab for use in combination with methotrexate to treat RA have been significant since its approval in 2006." Ex. 1032 at 27. Boehringer does not dispute any of this.

Sales of rituximab for RA since patent examination demonstrate even greater commercial success. In fact, worldwide sales of rituximab for RA since the FDA and its European counterpart approved, Ex. 2031 at 1, the combination of rituximab and methotrexate for such use now total more than $7 billion. *See, e.g.*, Exs. 2023 at 47, 2024 at 7, 2025 at 7, 2026 at 8, 2027 at 11, 2028 at 12, 2029 at 13-14, 2030 at 12-13.[2]

[2] Roche Reports use Swiss francs as currency; the conversion rate to U.S. dollars is approximately one-to-one. Sales of rituximab for immunology after 2011

2. The Claimed Treatment Produces Unexpected Results.

During prosecution, Patent Owners presented evidence of unexpected synergistic results from a study sponsored by a collaborator (Roche). Ex. 1032 at 24-26. The study, referred to as "Edwards et al. 2004," showed that the claimed combination of rituximab with methotrexate provided greater therapeutic effects than rituximab alone in patients who "had active rheumatoid arthritis despite [prior] treatment with methotrexate." Ex. 1033 at abstract, Fig. 2; Ex. 1014 at ¶¶ 28-31. Boehringer argues that synergy was not unexpected because "by the earliest priority date, a person of ordinary skill would have been aware, at minimum, of a synergistic therapeutic result from combining an antibody like rituximab with methotrexate to treat RA." Pet. 37. According to Boehringer, "[b]y suppressing the immune response, methotrexate contributes to a synergistic effect that improves the ability of rituximab and similar biologics to treat RA in patients." *Id.* Boehringer fails to show that synergistic results between rituximab and methotrexate would have been expected.

Citing only the declaration of its proposed expert Dr. Kalden, Boehringer asserts that "the 'extended therapeutic response' [synergy] of a biologic agent (such as rituximab), when combined with methotrexate to treat RA, had been observed and was well-known before the earliest priority date of the '161 patent." Pet. 58-59. But

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also reflect then-approved indications for two rare disorders—Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA)—in addition to RA.

Dr. Kalden fails to identify any prior observation of synergy involving rituximab or a biologic agent similar to rituximab. His declaration identifies only one biologic agent that purportedly demonstrates synergy when combined with methotrexate, and that is the anti-TNFα antibody cA2, also known as infliximab. *See* Ex. 1002 at ¶ 99 (citing Ex. 1021, which studied cA2, and Ex. 1018, which is a review article reporting a successful combination with methotrexate only for cA2). The Board should decline Boehringer's invitation to arbitrarily conclude that skilled artisans would have formed an expectation about synergy between methotrexate and rituximab—a B cell-depleting agent—based on synergy between methotrexate and cA2, which is a TNFα inhibitor. Such an expectation would have been particularly unlikely given that the field of biotechnology is unpredictable. *Elan Pharm., Inc. v. Mayo Found.*, 346 F.3d 1051, 1055 (Fed. Cir. 2003).

Moreover, the record indicates that skilled artisans would not have expected the combination of methotrexate and rituximab to be synergistic based on the synergy observed for methotrexate and cA2. As of the priority date, skilled artisans knew that cA2 was synergistic with methotrexate because methotrexate decreased the incidence of a HACA response to cA2. *See* Ex. 1021 at 1561 (noting a decrease in HACA incidence from 53% to 15% with concomitant methotrexate and explaining that "the apparent synergy of the action of cA2 plus MTX is based in part on the decreased immunogenicity of cA2 given simultaneously with MTX"). Such synergy would not have been expected with rituximab because skilled artisans also knew, as of the

priority date, that HAMA/HACA responses were not a problem with rituximab. For example, the FDA-approved rituximab prescribing information reports that there was no HAMA response and the incidence of HACA was less than one percent. Ex. 1006 at 1 ("Human anti-murine antibody (HAMA) was not detected in 67 patients evaluated. Less than 1.0% (3/355) of patients evaluated for human anti chimeric antibody (HACA) were positive.").

It is simply indefensible for Boehringer to suggest that synergy between rituximab and methotrexate would have been expected because of "methotrexate's ability to suppress a patient's immune response to the biological agent—the so-called anti-drug antibody response (or HAMA/HACA response)." Pet. 59. Skilled artisans chose to combine methotrexate with cA2 to address an immune-reaction problem with cA2 that simply does not exist with rituximab. Ex. 1021 at 1553. They would not have expected a methotrexate-rituximab combination to be synergistic based on synergy observed for the methotrexate-cA2 combination.

Boehringer also argues that "it is clear from the conditions of the [Edwards et al. 2004] study that the 'extended therapeutic response' cannot be extended across the full scope of the claims because: (i) unexpected results were only seen 'after 24 weeks,' whereas the challenged claims require only one dose of methotrexate and more than one dose of rituximab; and (ii) the clinical study applied only to a small subset of the patient population covered by the challenged claims." Pet. 59. Boehringer cites no authority for its suggestion that evidence of unexpected results—admittedly within

the scope of the claims—should be disregarded unless the evidence addresses the broadest possible embodiments of the claims. In fact, that suggestion is contrary to well-established Federal Circuit and CCPA case law. The Federal Circuit has held that evidence of objective indicia, including unexpected results, need only be "reasonably commensurate with the scope of the claims" and has explained that "[t]his does not mean that an applicant is required to test every embodiment within the scope of his or her claims." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). "Often, one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof." *In re Kollman*, 595 F.2d 48, 56-57 (C.C.P.A. 1979).

Here, the authors of Edwards et al. 2004 concluded that their results extended broadly to "patients with active rheumatoid arthritis" and not only "a small subset of the patient population," as Boehringer argues. *See* Ex. 1033 at 2580 ("[T]his study provides clear evidence that a single short course of rituximab provides significant, clinically meaningful benefits to patients with active rheumatoid arthritis."). This is consistent with the FDA's Guidance that studies in subpopulations of RA patients "may, of course, imply something about efficacy in other groups." Ex. 1012 at 18.

Boehringer's attempt to discount the "unexpected results [as] only ***seen*** 'after 24 weeks,'" Pet. 59, confuses when a phenomenon is observed with when the phenomenon began. Nowhere does the Edwards et al. 2004 study suggest that the rituximab-methotrexate combination was unexpectedly synergistic only after 24 weeks

of treatment. The study's primary clinical endpoint was efficacy at 24 weeks; the article reports on efficacy at 24 weeks for that reason. It would be illogical for skilled artisans to infer that synergy evident at 24 weeks was nonexistent before that time.

Critically, the FDA did not limit its approval of rituximab-methotrexate combination therapy to any length of prescribed therapy. *See* Ex. 2002. Thus, the results of Edwards 2004 are reasonably commensurate with the scope of the claims in view of the conclusion of the Edwards 2004 authors themselves, the FDA Guidance documents, and the FDA's approval of rituximab and methotrexate for treating RA.

V. CONCLUSION

For the reasons set forth above Patent Owners respectfully submit that the Board should deny Boehringer's petition for *inter partes* review in its entirety.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on April 27, 2015, a copy of the foregoing document **GENENTECH, INC.'S AND BIOGEN INC.'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:

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