UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc. and Pfizer, Inc.
Petitioners,
v.

Biogen, Inc. and Genentech, Inc.
Patent Owners

Patent No. 7,820,161 B1

Title: TREATMENT OF AUTOIMMUNE DISEASES

Inter Partes Review No. IPR2016-01614[1]

PETITIONER'S REPLY TO PATENT OWNERS' RESPONSE

[1] Case IPR2017-01115 has been joined with this proceeding.

I. The Claimed Regimen of Rituximab and Methotrexate To Treat RA Is Obvious over the Prior Art.

The claims of the ’161 patent are drawn to methods of treating rheumatoid arthritis (“RA”) with rituximab and methotrexate. Petitioner’s challenge is based on the following indisputable facts:

(1) Prior to the introduction of biologic therapies, methotrexate was the dominant treatment for RA in the 1990s.

(2) Methotrexate was given to patients, even those who did not fully respond to it, because it was the best treatment available at the time.

(3) Methotrexate was often used as one agent in “combination therapy” and the FDA recommended its use as “background therapy” with all new agents.

(4) The prior art, including an article by Dr. Jonathan Edwards, recommended the use of rituximab to treat RA.

(5) Dr. Edwards, and not anyone associated with the named inventors of the ’161 patent or with Patent Owners, was the first physician to treat RA patients with rituximab, and he did so based on the reasoning in the prior art before the priority date of the ’161 patent.

This Reply is supported by the Expert Declaration of Dr. Boers. (“Boers2,” Ex. 1064.)

A. The Prior Art Taught the Use of Rituximab To Treat RA.

In 1998, Dr. Edwards recommended the use of rituximab to treat RA. (Ex. 1030.) His suggestion was based on the known connection between RA and B-cells, described in many publications. (*See*, *e.g.*, Ex. 1066, "Do Nonimmunological Mediated Pathways Play a Role in the Pathogenesis of Rheumatoid Arthritis?" (1993); Ex. 1067, "B Lymphocytes and Humoral Immune Responses in Rheumatoid Arthritis" (1995); Ex. 1069, "B cells in rheumatoid arthritis" (2000); Ex. 2033 (a collection of abstracts submitted by Patent Owner containing a section titled "B Cells in RA") (1999).) Indeed, even Ex. 2002, a reference submitted by Patent Owners specifically to stress that persons of ordinary skill in the art ("POSAs") in the 1990s thought that T cells and not B cells were the primary drivers of RA, compared the cellular components involved in RA to an orchestra, with the T cells as the conductor, and the B cells (i.e., the antigen presenting cells) as the actor who wrote the score. (Ex. 2002 at 729; *see also* Ex. 1063 ("Silverman Depo.," Transcript of Deposition of Patent Owners' Expert Dr. Silverman) at 129:17-21, agreeing that B cells are antigen presenting cells.) And Patent Owners' expert agreed that, during the 1990s, RA was viewed as an auto-immune disease with clear "involvement of B lineage cells." (*Id*. at 19:16-21:10.)

Patent Owners and their expert Dr. Silverman assert that the RA community had "discarded" the B-cell theory as of the 1990s. (Patent Owner Response

("POR") at 32; Ex. 2085 at ¶ 128.) Far from it, that community continued to research the connections between RA and all aspects of the immune system and the inflammatory process, including B cells. (*See* above; Boers2 at ¶¶ 8,9.) This research continues to this day, as the exact mechanism of RA, both at its inception and for the duration of this chronic disease, is still not fully elucidated. (*See, e.g.*, Ex. 1070 (an article published in 2016) at 2026 ("the pathogenetic events initiating and mediating chronicity of synovitis are not yet fully understood…"); Boers2 at ¶ 10.) Although Patent Owners criticize Dr. Edwards' theory as based on "faulty premises" (POR at 26), this criticism rings hollow as, even to this day, Dr. Edwards' theory "has neither been proven nor disproved." (Ex. 2043 at 217.) Moreover, it is undisputed that the rationale for treating RA patients with rituximab and the basis for the reasonable expectation that this treatment would be successful was based on the undisputed fact that B cells were known to play a role—even if not precisely defined—in the pathology of RA.

That the RA community did not abandon the B-cell theory is also supported by real-world evidence. Once Rituxan® gained FDA approval for treating lymphoma in 1997 (*see* Ex. 1052), many different researchers and physicians had the idea to use rituximab to treat RA, including at least Dr. Edwards (Ex. 1030), Dr. Goldberg (Ex. 1028), and Dr. Gryn (Ex. 1006). Prior to this approval, although researchers knew that both T-cells and B-cells played a part in RA, they did not

test any B-cell agents in RA simply because there were no B-cell targeted agents available. (Boers2 at ¶ 9.) Once a B-cell agent became available, however, various physicians, working independently in different parts of the world, all had the same idea: to use rituximab to treat RA.

Notably, at least Dr. Edwards and Dr. Gryn documented their ideas prior to the priority date of the '161 patent. As explained in the Declaration of Dr. Jonathan C.W. Edwards (Ex. 1075), submitted with this Reply, Patent Owners' "invention" of the use of rituximab to treat RA was actually Dr. Edwards's invention, disclosed to Patent Owners by Dr. Edwards as early as December 1996. (Ex. 1075 at ¶ 6.) Further, Patent Owners' current assertion that POSAs did not credit Dr. Edwards's idea to use rituximab (POR at 26-42) rings hollow: after Dr. Edwards first disclosed his idea to Roche, a partner of Patent Owner Genentech, Roche credited his idea sufficiently to file a patent application and swear that the claimed "invention" had utility.

This real-world evidence confirms that the prior art taught the use of rituximab to treat RA.

B. The Prior Art Motivated the Use of Rituximab with Methotrexate To Treat RA.

Methotrexate was the dominant treatment for RA, and its use in combination with other agents was "universally accepted." (*See* Ex. 1065 (O'Dell Abstract) ("Combination DMARD therapy use has increased and is utilized by 99% of

rheumatologists."); *see also* Ex. 1011 at 6 (1996 guidelines of the American College of Rheumatology ("ACR") recommending the use of combination therapy to treat RA, particularly with methotrexate as one component).) (Patent Owners' expert Dr. Silverman admitted that the ACR is a prominent organization of rheumatologists and that he did not consider the ACR Guidelines while drafting his expert declaration. (Ex. 1063 (Silverman Depo.) at 55:19-56:2; 58:11-22.) Dr. Silverman himself has limited experience treating RA patients, devoting most of his time to research. (*Id*. at 65:14-24.).)

Because rheumatologists accepted methotrexate as the most common agent used in combination therapy, it was understood that "Virtually all of the new treatment modalities are currently being tested with MTX in patients who have active disease despite an adequate weekly dose of the drug." (Ex. 1019 at 1548.) The FDA publicly acknowledged that RA was often treated with combination therapy, particularly with methotrexate as one component, and instructed that clinical studies should be designed to accommodate this practice.[2] (Ex. 1020 at

[2] Traditionally, new agents had been tested in a placebo-controlled study, *i.e.*, a study with placebo as one arm and the new agent as another arm, in order to demonstrate efficacy. (Ex. 1062 at 6.) However, once methotrexate was identified as baseline treatment for RA, FDA and private parties were concerned that placebo-controlled studies were no longer a viable study design because of the

21.) In other words, patients in clinical trials—generally those who had experienced only a partial response to methotrexate—would continue methotrexate as background therapy while other treatments components were varied. (Boers2 at ¶ 13.) Accordingly, early development studies with new RA agents were tested in combination with methotrexate. (*See, e.g.*, Ex. 1100 (testing agent CM-T412 with methotrexate); Ex. 1022 (testing infliximab with methotrexate); Ex. 1021 (testing etanercept with methotrexate); *see also* Exs. 1013, 1020, 1062.) Patent Owners and their expert have not disputed that clinical trials in the 1990s were done on a

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ethical and practical problems associated with treating patients with placebo for a progressive and irreversible disease for the duration of the trial, and because of the expected "flare" when treatment with methotrexate is stopped. (*Id.*; Ex. 1100 at 78 ("With the initial trials evaluating an agent never previously used as a therapy for RA, it was felt that treatment with cM-T412 for 6 months as the only therapeutic agent would not be appropriate. Therefore, the decision was made by the sponsoring pharmaceutical company and the US Food and Drug Administration to have the first study with cM-T412 in a cohort of patients with RA who were taking stable doses of MTX. The advantages of this approach were the following: homogeneous patient population, single baseline DMARD, easier patient accrual, and lack of a disease flare with DMARD washout.").)

background of methotrexate, and their expert admitted that he has practically no experience designing clinical trials. (Ex. 1063 (Silverman Depo.) at 24:24-26:7; 96:2-7.)

In this context, a POSA, who would have understood that the prior art taught the use of rituximab to treat RA, would have been motivated to use it in combination with methotrexate.[3] This motivation holds true regardless of

[3] Patent Owners argue that this combination is "completely illogical, because the 2 treatments are unrelated, they're not doing the same thing." (POR at 51-52, quoting Ex. 2015.) Patent Owners' citation of Dr. Edwards's alleged statement in a 2004 interview, however, does not bear on what a POSA would have understood in the 1990s. Further, obviousness is judged from the perspective of a POSA and not from the perspective of a particular individual. *See Bristol-Myers Squibb*, 752 F.3d at 978 (explaining that the skill or knowledge on any one person, including the inventor, is irrelevant to the obviousness inquiry).

In any event, as Dr. Edwards explains in his declaration, it was his opinion that although it may have been *scientifically* illogical to combine the two agents, he understood that as a *practical* matter, the two agents would be combined to treat RA. (Ex. 1075 at ¶ 9.) He has specifically acknowledged the potential of a combination of rituximab and methotrexate to treat RA in a 2002 article, published before 2003, when Patent Owners added the methotrexate limitation to the claims

methotrexate's mechanism of action: a POSA would have followed standard practice at the time and used a new agent such as rituximab in combination with methotrexate as background therapy to treat RA.

C. A POSA Would Have Had a Reasonable Expectation of Success in Treating RA with Rituximab and Methotrexate

The prior art, which provided a clear connection between RA and B cells, would have not only motivated a POSA to treat RA with rituximab, but would also have provided a reasonable expectation of success. In fact, the prior art motivated no less than three individual physicians (Dr. Edwards, Dr. Gryn, and Dr. Goldberg) to use rituximab to treat RA.

With respect to the combination of rituximab and methotrexate, Patent Owners incorrectly contend that reasonable expectation of success requires "additive" results. This argument is undercut by the claims themselves, which include no particular level of efficacy. Moreover, because patients who were treated with new agents most often were those who had exhibited only a partial response to methotrexate, "success" was realized when the trial arm with the test

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of the pending application that eventually led to the '161 patent: "The possibility that useful remission in mild to moderate cases can be achieved with rituximab alone, perhaps at a higher dose, or in combination with an agent such as methotrexate, is by no means excluded." (Ex. 1068 at 887.)

agent plus methotrexate performed better than the trial arm with methotrexate plus placebo. (Boers2 at ¶¶ 14-15; Ex. 2085 at 80.) In this type of trial, the addition of the test agent to methotrexate would not have been expected to increase efficacy over and above the efficacy of methotrexate in patients who have a full response to methotrexate (and those patients would not have been included in this type of trial). Instead, success was achieved if there was increased efficacy for patients who did not fully respond to methotrexate. (Boers2 at ¶¶ 14-15.) In short, some increased efficacy was expected based on the prior art teaching the B cell connection to RA. (*Id.*)

In an effort to support their incorrect "additive" requirement, Patent Owners focus their arguments on Dr. Boers's published 1998 study, Exhibit 2008, which collected research on combination therapy to determine whether there was rigorous evidence that combinations work better than treatment with a single agent. Dr. Boers's studies, however, investigated the efficacy of combinations in both patients who had not previously been treated with methotrexate (called "parallel" in the study) and those who had previously been treated with methotrexate (called "step-up" in the study). (Boers2 at ¶ 12; Ex. 2008 at ¶ 12.) These studies taken as a whole therefore, do not directly translate to any expectation regarding only patients receiving step-up therapy, i.e., those who had already tried and partially failed methotrexate, and were then started on a second treatment on top of

methotrexate. (Boers2 at ¶ 15.) When the step-up studies with methotrexate as background therapy are looked at alone, the results show an increase in efficacy when the second agent was added. (*Id.*; Ex. 2008 at 614-15.)

In any event, even Dr. Boers' published analysis of the studies taken as a whole did not conclude that combinations offered no benefit over treatment with a single agent as Patent Owners argue. After searching 611 articles in the prior art, Dr. Boers found that only 20 of these articles reported on studies that met his exacting standards for rigorous scientific proof, and analyzed the results of those 20 articles. Dr. Boers concluded that the remaining 591 studies were not individually rigorous enough to provide hard evidence one way or the other regarding the efficacy of treatments and thus disregarded them for his 1998 paper because of their study design, and for no other reason. (Ex. 2008 at 612-13.)

Of the 20 studies that Dr. Boers reviewed, 10 combinations were graded as either "substantially more effective," "more effective," or "positive trend," for the combination as compared with a single agent therapy, while 10 showed "no difference" in efficacy. (Ex. 2008 at 614.) Thus, half of the studies reported a benefit with the combination. Regarding the 591 studies that Dr. Boers did not review, while their data, individually, did not meet Dr. Boers's rigorous standards for reliability, they, collectively and along with the 20 reviewed studies, motivated 99% of physicians to treat patients with combination therapy, most often with

methotrexate as a component of that combination. (Ex. 1065.) Thus, Patent Owners' mischaracterization of Dr. Boers' review of combination therapy is not the complete story regarding a POSA's belief about combination therapy.

The complete story, of course, is that the vast majority of practicing physicians used methotrexate in combination with both new and old agents to treat RA; the FDA recognized the use of methotrexate in combination and accommodated this use in developing clinical trials designs; the ACR recommended the use of combination therapy with methotrexate; and many individual clinicians and researchers predicted and planned the use of methotrexate with all new agents, including biologics. In the face of all of this evidence, Patent Owners' arguments that a POSA would not have had a reasonable expectation of success that a combination of methotrexate and a new biologic agent would effectively treat RA is simply unsupported by the record.

Patent Owners also argue that prior failures with biologic treatments for RA would have diminished the expectation that treatment with rituximab and methotrexate would be effective. (POR at 42-44.) To the contrary, far from dissuading further studies, these prior experiments helped to elucidate disease mechanisms and discover other treatments. Indeed, in the articles that Patent Owners cite, as prior treatment failures are described as "the foundation" for effective treatments: "Despite the failure in developing most of these agents, they

have provided substantial insight into study design, immunobiology, pharmacodynamics, and safety issues related to biologic therapy. These agents provide the foundation on which more efficacious therapies will be generated." (Ex. 2048 at 257.)

In particular, Patent Owners point to a study with "CAMPATH-1H," which, as explained by Patent Owners, "targeted the CD52 antigen found on the surfaces of mature B cells and T cells." (POR at 43, citing Ex. 2032.) According to Patent Owners, after studies showed that CAMPATH-1H did not successfully treat RA, POSAs would have abandoned hope that an agent directed at B cells would be able to treat RA. (POR at 43.) Patent Owners, however, do not explain why the study of CAMPATH-1H, which, as admitted, targeted both B cells and T cells, would not have dissuaded a POSA from pursuing further therapies directed at *T cells*. Patent Owners' arguments should not be credited: as of the critical date, there had been many more studies of agents directed to T cells (none of which resulted in a successful product) than of agents directed to B cells, so much so that at least one researcher concluded that "the role of T cells in established RA may be of minimal clinical importance." (Ex. 1061 at 1586.) Yet, POSAs continued to pursue T cell based treatments, as admitted by Patent Owner. (POR at 32.) This fact demonstrates that prior studies not resulting in commercially viable products did not dissuade POSAs from pursuing either T cell or B cell treatments.

II. Claims 3, 7, and 11 Are Obvious.

Patent Owners argue that Petitioner has not established a reasonable expectation of success for the method claimed in claims 3, 7, and 11, which adds the limitation "administering to the human a glucocorticosteroid." (POR at 24.)

As explained in the Petition, a POSA would have been motivated to treat RA patients with a glucocorticosteroid for one of two reasons, and, for each reason, a POSA would have had a reasonable expectation of success. First, the glucocorticosteroid would treat any expected hypersensitivity resulting from the use of rituximab. It was well established as of 1999 that glucocorticosteroids successfully treat hypersensitivity reactions, and that is reason that the prior art Rituxan® label instructed that these drugs "should be available for immediate use in the event of a reaction." (Petition at 31-32; Ex. 1037 at 1; Ex. 1055 at 3; Boers2 at ¶¶ 23-24.)

Second, the glucocorticosteroid would be administered as another agent to treat RA. A POSA would have had a reasonable expectation of success that the addition of a glucocorticosteroid would further the goals of RA treatment: The 1996 ACR Guidelines provides three scenarios in which glucocorticosteroids are used to treat RA: (1) minimizing disease activity while awaiting DMARD response; (2) decreasing disease activity for a limited time period; and (3) control of active disease despite NSAID and DMARD treatment. All three of these

reasons are applicable during combination therapy with other drugs. (Ex. 1011 at 6; Boers2 at ¶¶ 23-24.)

III. Patent Owners' Evidence of Secondary Considerations Fail To Overcome the *Prima Facie* Showing of Obviousness.

A. The Alleged Secondary Considerations Lack a Nexus to the Claimed Method.

Secondary considerations of non-obviousness are only relevant to the extent that they bear some nexus to the allegedly new and novel aspects of the claims. *Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016). In this case, the only potentially new and novel aspect of the method in the claims is the addition of methotrexate to the treatment with rituximab (and even this is neither new nor novel, as explained). Indeed, during prosecution, Patent Owners were unable to patent claims directed to treatment with rituximab alone, and only succeeded in having their claims allowed after the addition of the methotrexate limitation. (Ex. 1060 ('161 Patent File History) at 712, 732.) In this case, any secondary considerations, including unexpected results, the satisfaction of a long-felt need, and commercial success, to the extent that they are present, are due to the use of rituximab to treat RA, which "was known in the prior art," and are therefore "not pertinent." *Ethicon*, 812 F.3d at 1034.

Patent Owners cannot support their contention that their claimed commercial success is due to the claimed combination. First, as Dr. Boers explained in his

opening declaration (¶ 93; *see also* Petition at 46), a large number of patients are treated with rituximab and not with a combination of rituximab and methotrexate.

Second, rituximab is frequently prescribed to treat conditions for which it is not approved. (*See*, e.g., Ex. 1073 at 821-22.) Any such uses are not within the scope of the '161 patent claims, and the sales of rituximab for such uses do not constitute evidence of commercial success of the '161 patent.

Third, in its Patent Owner Preliminary Response in IPR2015-00417, Patent Owner alleged that the claimed method of U.S. Patent 7,967,838 ("the '838 patent"), *i.e.*, treating patients who have an inadequate response to a TNFα-inhibitor with two doses of 1000 mg of rituximab, was the reason that rituximab has been a commercial success of the same magnitude claimed here. (Ex. 1024 at 55.) This method, however, is not claimed in the '161 patent; if any alleged commercial success is due to the regimen claimed in the '838 patent—which does not include the concomitant treatment with methotrexate—as Patent Owners asserted, then success cannot also be due to the regimen claimed in the '161 patent, which requires, as its allegedly inventive concept, the concomitant treatment with methotrexate.

Fourth, any commercial success that Patent Owners enjoyed due to sales of rituximab to treat RA is success that, absent barriers to sale of rituximab by entities other than Patent Owners, would have been enjoyed by others who had the idea to

use rituximab to treat RA before Patent Owners. For example, both Dr. Gryn and Dr. Edwards approached Patent Owners asking for help with trials to use rituximab to treat RA; neither of these individuals had access to supplies of rituximab, to manufacturing facilities, or to other resources needed to conduct trials. In other words, due to constraints unrelated to the claimed use of rituximab and methotrexate to treat RA, other parties could not commercialize rituximab for the use of RA, and therefore, Patent Owner's commercial success is not due to the claimed combination, but to others' inability to enjoy that success. *See, e.g., Ruiz v. Chance Co.*, 357 F.3d 1270, 1277 (Fed. Cir. 2004) ("[A]ny commercial success was not due to Chance's allege unique combination, but rather due to Chance's expertise with screw anchors combined with being the first large screw anchor manufacturer to enter the underpinning market.").

B. The Method Claimed in the '161 Patent Did Not Meet a Long-Felt But Unmet Need.

With respect to Patent Owners' allegations that the claimed methods met a long-felt need, Patent Owners have failed to show that the clinical efficacy of rituximab is due to the combination of rituximab and methotrexate and not to rituximab alone. Patent Owners stated that the only way for a combination to be proven to have better efficacy than either agent alone is by conducting a trial with three arms: one arm for each agent, and one arm for the combination. (POR at 17-18; Ex. 2085 (Silverman Dec.) at ¶ 93; Ex. 1063 (Silverman Depo.) at 132:7-

133:11; 137:14-22.) However, none of the studies that Patent Owners cite included these three arms. Instead, these studies compared the combination of rituximab plus methotrexate to the combination of methotrexate and placebo. (*See* Ex. 1005; Ex. 1006.) Because Patent Owners have not introduced any comparison of the claimed method with treatment of rituximab alone, Patent Owners have not shown that there is any nexus to the claimed method. Coupled with Dr. Boers's statistics demonstrating that many patients are currently treated with rituximab alone, and not in combination with methotrexate, the only reasonable conclusion is that, to the extent that use of rituximab to treat RA met a long-felt need, there is no nexus to the claimed method.

Setting aside the nexus deficiency, Patent Owners argue that the claimed methods filled a long-felt need because "at the time of the invention, no single therapy regimen or combination of therapies had been consistently associated with a halt in progression or loss of joint structure and function." (POR at 57.) Patent Owners' arguments fail for a number of reasons.

First, Patent Owners' discussion regarding the known "associations" as of the priority date are irrelevant to the long-felt need inquiry because as of the priority date, other therapy regimens had been introduced that are known to be equally effective as rituximab. (Boers2 at ¶ 22 (discussing sulfasalazine, glucocorticoids, infliximab and etanercept).) For example, both infliximab and

etanercept were introduced for use in RA before the filing date of the '161 patent, both of these agents were FDA approved for use in RA before FDA approval of rituximab to treat RA, and both of these agents were shown to be effective, when used in combination with methotrexate, before efficacy had been shown with rituximab and methotrexate. (Exs. 1072 and 1071.) Both of these agents in combination with methotrexate also have been shown to halt erosive progression, the particular benefit that Patent Owners call out as "associated" with rituximab and methotrexate:

- Regarding infliximab plus methotrexate: "This study demonstrates that treatment of early RA with the combination of MTX and infliximab improves the signs and symptoms of disease activity, inhibits the radiographic progression of joint damage, and improves physical function better than MTX therapy alone over 1 year." (Ex. 1072 at 3440.)
- Regarding etanercept plus methotrexate: "Radiographic data at 24 and 52 weeks indicated that patients in the combination and etanercept treatment groups had significantly less progression of disease for all measured radiographic endpoints compared with patients in the methotrexate group. Furthermore, the combination provided a

significantly better result than either monotherapy concerning changes in total Sharp score at 52 weeks of treatment." (Ex. 1071 at 680.)

Further, the efficacy of infliximab, etanercept, and rituximab are equivalent: "These mechanistically discrete therapies seem to convey similar efficacy." (Ex. 1070 at 2031.)

Patent Owner does not refute that infliximab and etanercept were shown to have similar efficacy to rituximab; instead, Patent Owners contend that this efficacy is irrelevant because it was not known as of the filing date of the '161 patent. (POR at 60.) Patent Owners' argument is legally incorrect. The Federal Circuit has held that the timeline of events, including when drugs were first used, when they were approved by FDA, and when their benefits first became known are relevant to the long felt-need inquiry. Because of the timeline here, with both infliximab and etanercept passing every milestone before rituximab, no claim to a method of treating RA with rituximab (with or without methotrexate) met a long-felt need. *See Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 752 F.3d 967, 979 (Fed. Cir. 2014) ("On long-felt need, three other drugs for treating hepatitis B were invented before the filing date of entecavir [the claimed drug]. These three drugs also gained FDA approval before entecavir. Finally, entecavir's inventors did not know about its hepatitis B property until four years after the filing date, and by then the first FDA-approved hepatitis B treatment was

launched…Therefore, we agree with the district court that the evidence of long-felt need is of limited value to [the patentee].").

Second, even with the success of the biologic therapies for RA, there still exists a need for better treatments for RA: "There is still a considerable unmet need in rheumatoid arthritis; full or stringent remission is not typical, nor is it usually sustained without continuing treatment, and as such it should now be the priority of research efforts." (Ex. 1070 at 2023.) No treatment has yet fully met the need to effectively treat RA, and thus any need remains unmet.

IV. Patent Owners' Other Arguments Fail To Overcome the Obviousness of the Claims.

A. The Claims Are Obvious Even with Patent Owners' Proposed Definition of a POSA.

Patent Owners argue that Petitioner's proposed definition of a POSA imbues that POSA with "unrealistic insight" because a POSA would not have treated "all" autoimmune disorders. (POR at 11; Ex. 2085 (Silverman Dec.) at ¶ 48.) Dr. Boers, however, never opined that POSAs would have experience with "all" autoimmune disorders. He opined that a POSA would have experience with "other autoimmune disorders." Dr. Silverman agreed at his deposition, asserting that rheumatologists "are charged with having a more in-depth understanding of 100 different diseases that can involve degenerative, metabolic, genetic, inflammatory diseases as well as immunologic diseases…" (Ex. 1063 (Silverman Depo.) at

15:20-16:4.) Dr. Silverman also stated that rheumatologists have formal training in and understanding of auto-immune diseases. (*Id.* at 30:10-21.)

Regardless, Dr. Boers has reconsidered his opinions in light of Patent Owners' proposed definition of a POSA and confirms that his opinions in both of his declarations are unaffected. (Boers2 at ¶ 27.)

B. Exhibit 1037 is a Printed Publication, but Regardless, the Claims Are Obvious Even Without Reliance on the Contested Exhibit 1037.

Patent Owners argue that Petitioner has not met its burden to prove that Exhibit 1037 is a printed publication. Petitioner believes that the evidence presented in the Petition suffices to show the printed publication status of Exhibit 1037.

Pursuant to the Board's order, Patent Owner responded to Petitioner's additional discovery regarding the printed publication status of Exhibit 1037. (Exs. 1081 and 1082.) Patent Owners' responses failed to provide any information, one way or the other, as to whether Exhibit 1037 was publicly available. Patent Owners admitted that they have a copy of a label that was included with shipments of Rituxan® sold in the U.S. before the priority date (*see* Ex. 1081 at RFA 16), but refused to provide that label to Petitioners. Patent Owners also denied that the text of that label was identical to the text of the label in Exhibit 1037 but did not explain what the alleged differences were, leaving Petitioner and the Board to

speculate on what differences could exist between a label posted on the FDA's website as the approved label and the label that Patent Owners included with a pharmaceutical product.

Based on the information available to the Board and Petitioners, the alleged differences must be negligible: Petitioner has compared the label that is posted on the FDA's website (Ex. 1037) with the label that was posted on Genentech's website in 1998 (Ex. 1055), and found only minor differences. For example, in two instances Ex. 1037 says "Rituxan™ (Rituximab)" where Ex. 1055 says "RITUXAN, and in one place, Ex. 1037 uses the symbol "≥" where Ex. 1055 says "greater than or equal to." (Compare Ex. 1037 with Ex. 1055.) A computer-generated comparison between the two Exhibits confirms that there are no differences—aside for the placement of a period—between the two labels in the "Dosage and Administration" and "Adverse Events" sections, the two sections relied upon by Petitioner. (Exs. 1079 and 1080.)

Regardless, Exhibit 1055 provides a virtually identical reference to Exhibit 1037, aside for some negligible differences as noted above, and Petitioner explained in the Petition that its challenge may incorporate either of these sources for the same information: "All references to the Rituxan® label in this Petition should be understood to refer both to the label at Exhibit 1037, and to the Genentech website label at Ex. 1055; both versions reflect the same content."

(Petition at note 2.) Despite the differences in formatting between the two exhibits, they disclose the same information, and therefore, if one is a printed publication, then the other is also a printed publication. *See In re Klopfenstein*, 380 F.3d 1345 (Fed. Cir. 2004), holding that a "printed slide presentation" was a printed publication when it had been displayed in a different format—"pasted onto poster boards"—at a presentation. Moreover, the existence of the printed publication at Ex. 1055 with the identical language to the printed publication at Ex. 1037 provides corroboration that both are what they purport to be. And, Patent Owners were on notice that the challenges to the '161 patent relied on either Ex. 1037 or Ex. 1055 based on the explicit language in the Petition.

Further, Petitioner relies on Exhibit 1037 to disclose the dose of Rituxan® that was approved by FDA to treat NHL, and for the unremarkable proposition that steroids effectively treat hypersensitivity reactions. Both of these assertions were common knowledge in 1999 (Boers2 at ¶¶ 23-24) and therefore, Petitioner's challenge is unaffected by the printed publication status of Exhibit 1037.

C. The Claims Are Obvious Even Though Dr. Boers, as an Individual, was Unaware of Dr. Edwards's Publication Recommending the Use of Rituximab To Treat RA.

As part of their Response, Patent Owners contend that "even Dr. Boers himself had no expectation that RA could be successfully treated with rituximab." (POR at 25.) Patent Owners have misrepresented Dr. Boers's statement during his

deposition, which was actually directed to the dosage of rituximab, and not to the drug itself. (*See* Ex. 2016 at 23:7-11.) Dr. Boers's personal beliefs, however, are irrelevant to the expectation of a POSA. A POSA is a theoretical legal construct that presumes knowledge of every relevant prior reference. *See, e.g., In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) ("The legal construct also presumes that all prior art references in the field of the invention are available to this hypothetical skilled artisan."). Recourse to the knowledge or expectation of any individual is inappropriate. *See, e.g., Bristol-Myers Squibb*, 752 F.3d at 978, explaining that the skill of the inventor is irrelevant. Thus, Dr. Boers's own knowledge in 1999 is irrelevant to the obviousness inquiry. Dr. Boers is, however, an expert in the field of RA treatment and is qualified to offer on opinions on what the theoretical POSA would have expected.

Dated: August 23, 2017

/Elizabeth J. Holland/
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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petitioner's Reply to Patent Owners' Response contains 5,592 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: August 23, 2017

/Elizabeth J. Holland/
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e), I certify that on this 23rd day of August, 2017, I served a copy of this PETITIONER'S REPLY TO PATENT OWNERS' RESPONSE along with all supporting exhibits by email on the following:

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