

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner

Inter Partes Review No. IPR2017-01115
Patent No. 7,820,161 B1

PETITION FOR *INTER PARTES* REVIEW

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LIST OF EXHIBITS FOR U.S. PATENT NO. 7,820,161

Exhibit No.	Description
1001	U.S. Patent 7,820,161
1002	Declaration of Elena Massarotti, M.D.
1003	Curriculum Vitae of Elena Massarotti, M.D.
1004	Second Declaration of Ronald F. van Vollenhoven, dated January 19, 2010, submitted during prosecution of '161 patent on January 19, 2010
1005	Eisenberg letter to Genetech Oncology & IDEC Pharmaceuticals, dated May 29, 1998
1006	Gryn letter to Parker, dated May 6, 1998
1007	Saleh letter to Comprehensive Cancer Center, dated October 1, 1998
1008	Latov letter to Horvath, dated November 16, 1998
1009	Pestronk letter to Department of Neurology, dated October 12, 1998
1010	Looney letter to Dutcher, dated January 15, 1999
1011	American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, Guidelines for the Management of Rheumatoid Arthritis, Arthritis & Rheumatism, 39(5):713-722 (May 1996)
1012	T. Pincus & C.M. Stein, "No evidence of disease" in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care?, 15 Clinical & Experimental Rheumatology 591 (1997)
1013	William Schwieterman, Immunosuppression in Combination with Monoclonal Antibodies, Biologic Agents in Autoimmune Disease (March 2-4, 1995) ("FDA Conversation")
1014	Kremer, Methotrexate for Rheumatoid Arthritis, Arthritis & Rheumatism, 37(3):316-328 (1994)

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1015	O'Dell, <i>Methotrexate Use in Arthritis</i> , Rheumatic Disease Clinics of North America, 23(4) (1997)
1016	Boers et al., <i>Randomised Comparison of Combined Step-down Prednisolone, Methotrexate and Sulphasalazine with Sulphasalazine Alone in Early Rheumatoid Arthritis</i> , The Lancet, 350:309-18 (1997)
1017	Boers M, Tugwell P, Felson DT, van Riel PL, Kirwan JR, Edmonds JP, et al., <i>World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials</i> , J Rheumatol Suppl; 41:86-9 (1994)
1018	Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al., <i>American College of Rheumatology Preliminary definition of improvement in rheumatoid arthritis</i> , Arthritis Rheum, 38:727-35 (1995)
1019	Kremer, <i>Combination Therapy with Biologic Agents in Rheumatoid Arthritis: Perils and Promise</i> , Arthritis & Rheumatism, 41(9):1548-1551 (1998)
1020	Guidance for Industry Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA) (1999)
1021	Weinblatt et al., <i>A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate</i> , New England Journal of Medicine, 340(4):253-9 (1999)
1022	Maini et al., <i>Therapeutic Efficacy of Multiple Intravenous Infusions of Anti-Tumor Necrosis Factor α Monoclonal Antibody Combined with Low-Dose Weekly Methotrexate in Rheumatoid Arthritis</i> , Arthritis & Rheumatism, 41(9):1552-1563 (1998)
1023	First Declaration of Ronald F. van Vollenhoven, dated July 30, 2007, submitted during prosecution of '161 patent on May 4, 2000

Exhibit No.	Description
1024	IPR2015-00415, Genentech, Inc.'s and Biogen Inc.'s Patent Owner Preliminary Response Under 37 C.F.R. § 42.107
1025	Maloney et al., <i>Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients With Recurrent B-Cell Lymphoma</i> , Blood, 84(8):2457-2466 (1994)
1026	Maloney et al., <i>IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma</i> , Blood, 90(5):2188-2195 (1997)
1027	Bhat et al., WO 95/03770 "Methods for B-Cell Population Control," filed on August 2, 1994, published on February 9, 1995
1028	[exhibit number not used]
1029	Maloney et al., <i>IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients with Relapsed Non-Hodgkin's Lymphoma</i> , Journal of Clinical Oncology, 15(10):3266-3274 (1997)
1030	Edwards et al., <i>Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in which Antibody is also Antigen</i> , British Society for Rheumatology, 37:126-130 (1998)
1031	Edwards, <i>The Case for Killing Cells with ANTI-CD20 in RA</i> , Australian Rheumatology Association Conference, 53 (1998)
1032	[exhibit number not used]
1033	The University College London Hospitals, Treatment of subjects with rheumatoid arthritis with a monoclonal anti-CD20 antibody, October 30, 1998, Letter
1034	The University College London Hospitals, The Joint UCL/UCLH Committees on the Ethics of Human Research, Treatment of subjects with rheumatoid arthritis with a monoclonal anti-CD20 antibody, October 23, 1998, Letter
1035	Letter from the Medicines Control Agency to Edwards, Mabthera (C2B8 Monoclonal anti-CD20), October 2, 1998

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1036	Information for patients undergoing treatment of rheumatoid arthritis by B lymphocyte depletion with an anti-CD20 monoclonal antibody, The University College London Hospitals
1037	Rituxan [®] Label 1997
1038	Kremer, <i>The Changing Face of Therapy for Rheumatoid Arthritis, Arthritis</i> , Rheumatic Disease Clinics of North America, 21(3):845-852 (1995)
1039	Declaration by Jonathan Charles Wright Edwards (filed by the patent challengers in the Opposition to European Patent No. 1 176 981 B1 before the EPO)
1040	Moreland et al., <i>Etanercept Therapy in Rheumatoid Arthritis A Randomized, Controlled Trial</i> , Ann Intern Med., 130:478-486 (1999)
1041	Remicade [®] Label 1998
1042	FDA, 64 Fed. Reg. 7898 (1999)
1043	Buch et al., <i>Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis</i> , Ann Rheum Dis (2011)
1044	Wendler et al., <i>Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients</i> , Arthritis Research & Therapy, 16:R80 (2014)
1045	Edwards et al., <i>Efficacy of B-Cell-Targeted Therapy with Rituximab in Patients with Rheumatoid Arthritis</i> , New England Journal of Medicine, 350(25):2572-81 (2004)
1046	Klareskog et al., <i>Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial</i> , The Lancet, 363:675-681 (2004)
1047	Bathon et al., <i>A Comparison of Etanercept and Methotrexate in Patients with Early Rheumatoid Arthritis</i> , New England Journal of Medicine, 343(22):1586-93 (2000)

Exhibit No.	Description
1048	Gabriel, <i>The Epidemiology of Rheumatoid Arthritis</i> , Rheumatoid Arthritis, 27(2) (2001)
1049	Decision of the Boards of Appeal of the European Patent Office relating to EP1179681, dated June 18, 2015
1050	[exhibit number not used]
1051	Kalden, <i>Rescue of DMARD Failures by Means of Monoclonal Antibodies or Biological Agents</i>
1052	FDA, Rituxan Approval Letter, 97-0244, (November 26, 1997)
1053	Drugs@FDA: FDA Approved Drug Products Approval History for Rituxan (FDA Application No. (BLA) 103705)
1054	1997 Form 10-K405/A filed by IDEC Pharmaceuticals
1055	Internet Archive Capture of Genentech's Website for Rituxan
1056	Declaration from Internet Archive
1057	O'Dell J et al., <i>Treatment of Rheumatoid Arthritis with Methotrexate Alone, Sulfasalazine and Hyrdoxchloroquine, or a Combination of All Three Medications</i> , Treatment of Rheumatoid Arthritis, Vol. 334 No. 20, pp 1287-1291 (1996)

I. INTRODUCTION

Pfizer, Inc. (“Petitioner”) petitions for *inter partes* review (“IPR”) under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 et seq. of claims 1 to 12 of U.S. Patent No. 7,820,161 (“the ’161 patent,” Ex. 1001).

II. PRELIMINARY STATEMENT

The ’161 patent is directed to methods of treating rheumatoid arthritis (“RA”)—an autoimmune disease—by administering more than one intravenous dose of rituximab along with methotrexate. By the time that the earliest application for the ’161 patent was filed, rituximab was an FDA-approved drug, and people of skill in the art knew that rituximab is a biologic agent that targets B cells, and that B cells have a role in RA. Moreover, by that time, methotrexate, which had been described as the “cornerstone” of RA treatment, would have been included in any new RA treatment regimen. In particular, the FDA instructed clinicians and researchers that methotrexate should be “background therapy” with all new emerging biologics used to treat RA. In other words, the ’161 patent claims known uses of old drugs and is therefore obvious over the prior art.

III. MANDATORY NOTICES

1. ***Real parties-in-interest.*** The real party in interest is Petitioner Pfizer, Inc. (“Pfizer” or “Petitioner”).

2. ***Related matters.*** The Board has instituted review of claims 1–3, 5–7, and 9–11 of the ’161 patent in *Celltrion, Inc. v. Biogen, Inc.*, No. IPR2016-01614

(PTAB), and Petitioner has moved to join this Petition with that proceeding. The '161 patent was also challenged in IPR2015-00415.

The PTAB instituted the IPR for claims 1, 2, 5, 6, 9, and 10 of the '161 patent in that proceeding on July 17, 2015. That proceeding was terminated on October 1, 2015, following a Request for Adverse Judgment by the Petitioner. Celltrion, Inc. ("Celltrion") challenged the '161 patent in IPR2015-01744, in a petition filed on August 17, 2015, which was accompanied by a motion for joinder to IPR2015-00415. After the IPR2015-00415 petitioner terminated IPR2015-00415, but before an institution decision on Celltrion's petition, Celltrion dismissed without prejudice IPR2015-01744 and its motion for joinder.

3. *Lead and Back-Up Counsel.* Petitioner identifies the following:

- *Lead counsel:* Jovial Wong (Reg. No. 60,115)
- *Back-up counsel:* Charles B. Klein*
- *Back-up counsel:* Eimeric Reig-Plessis*

* Back-up counsel to seek *pro hac vice* admission.

4. *Service Information.* Petitioner identifies the following:

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Please address all correspondence to lead counsel at the address shown above.

Petitioner consents to electronic service at the above listed email address.

IV. REQUIREMENTS FOR REVIEW

a. ***Grounds for standing.*** Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition. The Commissioner is hereby authorized to charge all fees due in connection with this matter to Deposit Account No. 50-1814.

b. ***Identification of challenge.*** Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancelation of claims 1–12 of the '161 patent pursuant to the following statement of the precise relief requested:

In Ground 1, Petitioner requests *inter partes* review and cancellation of claims 1-12 as obvious over Edwards 1998 in view of the FDA Conversation and the Rituxan® label.

In Ground 2, Petitioner requests *inter partes* review and cancellation of claims 1-12 as obvious over Edwards 1998 in view of O'Dell, and further in view of the Rituxan® label.

In Ground 3, Petitioner requests *inter partes* review and cancellation of claims 1-12 as obvious over Edwards 1998 in view of Kalden and further in view of the Rituxan[®] label.

Petitioner notes that the Board previously instituted review of claims 1, 2, 5, 6, 9, and 10 under Grounds 2 and 3 in IPR2015-00415, finding that the Petitioner in that proceeding had established that it would likely prevail in showing that the claims were *prima facie* obvious over the combinations of prior art in Grounds 2 and 3.

This petition is supported by the Expert Declaration of Elena Massarotti, M.D. (Ex. 1002.) Dr. Massarotti is a Professor of Medicine at Harvard Medical School and a Physician at the Brigham and Women's Hospital. The petition and supporting declaration show that there is at least a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims. *See* 35 U.S.C. § 314(a).

V. SUMMARY OF THE '161 PATENT AND PROSECUTION HISTORY

The '161 patent (Ex. 1001) issued on October 26, 2010, from Application Ser. No. 09/564,288 ("the '288 application"), which was filed on May 4, 2000. The '288 application claims priority to two provisional applications filed on May 7, 1999, and June 17, 1999. The earliest priority date associated with the '161 patent is May 7, 1999. Therefore, any publication prior to May 7, 1998, qualifies as prior art under 35 U.S.C. § 102(b), and any publication prior to May 7, 1999, qualifies as prior art under 35 U.S.C. § 102(a).

A. The Claims of the '161 Patent

1. Independent Claims 1, 5, and 9

Independent claim 1 reads as follows:

A method of treating rheumatoid arthritis in a human comprising:

- (a) administering to the human more than one intravenous dose of a therapeutically effective amount of rituximab; and
- (b) administering to the human methotrexate.

Independent claim 5 reads as follows:

A method of treating rheumatoid arthritis in a human comprising:

- (a) administering to the human more than one intravenous dose of a therapeutically effective amount of an antibody that binds to the CD20 antigen on human B lymphocytes;
 - (b) administering to the human methotrexate;
- wherein the CD20 antibody administration consists of intravenous administration of the CD20 antibody, and the CD20 antibody is rituximab.

Independent claim 9 reads as follows:

A method of treating rheumatoid arthritis in a human comprising:

- (a) administering to the human more than one intravenous dose of a therapeutically effective amount of an antibody that binds to the CD20 antigen on human B lymphocytes; and
 - (b) administering to the human methotrexate;
- wherein the therapeutically effective amount of the CD20 antibody is administered intravenously, and the CD20 antibody is rituximab.

2. Dependent Claims 2-4, 6-8, and 10-12

Claims 2, 6, and 10 depend from claims 1, 5, and 9, respectively, and add the limitation that the dose of rituximab is “from about 250 mg/m² to about 1000 mg/m².” Claims 3, 7, and 11 depend from claims 1, 5, and 9, respectively, and add the limitation that the method further comprises administering to the human a glucocorticosteroid. Claims 4, 8, and 12 depend from claims 1, 5, and 9, respectively, and further require an initial dose of rituximab followed by a subsequent dose, where the subsequent dose exceeds the initial dose.

B. Specification of the '161 Patent

The '161 patent characterizes the alleged invention as follows: “[t]he present invention concerns treatment of autoimmune diseases with antagonists which bind to B cell surface markers, such as CD19 or CD20.” (Ex. 1001 at 1:13-15.)

The specification provides three examples of treating autoimmune diseases with rituximab (*i.e.*, RITUXAN[®]).¹ Example 1 relates to patients with RA, example 2 relates to patients with autoimmune hemolytic anemia (AIHA), and example 3 relates to patients with adult immune thrombocytopenic purpura (ITP). (*Id.* at 27:34-

¹ See Ex. 1001 at 8:61-64 (“The terms ‘rituximab’ or ‘RITUXAN[®]’ herein refer to the genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen and designated ‘C2B8’ in U.S. Pat. No. 5,736,137 . . .”).

29:41.) All of these examples recommend three specific intravenous dosing schedules: (1) 50 mg/m² on day 1 and 150 mg/m² on days 8, 15, and 22; (2) 150 mg/m² on day 1, and 375 mg/m² on days 8, 15, and 22; and (3) 375 mg/m² on days 1, 8, 15, and 22. (*Id.* at 27:52-59; 28:8-15; 29:3-9.)

C. Prosecution History of the '161 Patent

The application leading to the '161 patent was originally filed on May 4, 2000, with 26 claims, directed to treating fifty-nine autoimmune diseases, including RA, with rituximab. None of the claims were directed to a method of treating RA with the combination of rituximab and methotrexate. After a series of rejections, examiner interviews, restriction requirements, responses to rejections, claim amendments, and submissions of declarations, the applicants added claims directed to treatment of RA with rituximab plus methotrexate on May 20, 2005, five years after the original application was filed.

After still further rejections, examiner interviews, restriction requirements, responses to rejections, claim amendments, and submissions of declarations, the application was finally allowed on June 18, 2010, almost nine years after the first rejection on the merits issued and more than ten years after the application was filed. All told, the examiner issued five separate office actions, each with multiple obviousness rejections citing more than ten prior art references directed toward (1) methods of treating RA and other autoimmune diseases with agents targeted at

antigens on CD20 B cells, (2) the superiority of methotrexate over other options as a treatment for RA, (3) the use of methotrexate in combination with other RA therapies and the suggestion to use methotrexate in combination with all new RA therapies; and (4) the use of rituximab to treat B-cell mediated diseases other than non-Hodgkin's lymphoma ("NHL"), for which it was approved.

During prosecution, the applicants submitted to the Patent and Trademark Office six proposals that Biogen/IDEC, the owner of Rituxan[®], had received from independent researchers directed toward the use of rituximab to treat a variety of autoimmune diseases, including RA: (1) a proposal to use rituximab to treat RA by Dr. Jeffrey Gryn, M.D., of the Cooper Cancer Institute, dated May 6, 1998 (Ex. 1006); (2) a proposal to use rituximab to treat lupus by Dr. Robert Eisenberg, M.D., of the University of Pennsylvania School of Medicine, dated May 29, 1998 (Ex. 1005); (3) a proposal to use rituximab to treat thrombocytopenic purpura by Dr. Mansoor Saleh, M.D., of the University of Alabama, dated October 1, 1998 (Ex. 1007); (4) a proposal to use rituximab to treat autoimmune neuropathy by Dr. Norman Latov, M.D., Ph.D., of Columbia University, dated November 16, 1998 (Ex. 1008); (5) a proposal to use rituximab to treat polyneuropathies associated with serum IgM autoantibodies by Dr. Alan Pestronk, M.D., of Washington University School of Medicine, dated October 12, 1998 (Ex. 1009); and (6) a proposal to use

rituximab to treat B-cell-mediated autoimmune diseases by Dr. John Looney, M.D., of the University of Rochester, dated January 15, 1999 (Ex. 1010).

The examiner finally allowed the application after the applicant submitted a series of declarations by Dr. Ronald van Vollenhoven in which he opined that the combination of methotrexate and rituximab produced unexpectedly long-lasting results. (Exs. 1004, 1023.)

VI. BACKGROUND ON THE USE OF RITUXIMAB TO TREAT RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic autoimmune disease that causes pain, stiffness, swelling and limited motion and function of joints. (Ex. 1002 ¶ 31.) RA can affect any joint, but the small joints in the hands and feet tend to be involved most often. (*Id.*) Two-thirds of RA patients are female. (*Id.*)

A. RA Treatment Regimens in the Early 1990s, Prior to the Introduction of Biologic Therapies

Before the earliest priority date of the '161 patent (May 7, 1999), the typical practice to treat RA, outlined in the 1996 Guidelines for the Management of Rheumatoid Arthritis, written by the American College of Rheumatology Ad Hoc Committee on Clinical Guidelines (Ex. 1011, "ACR Guidelines"), was to treat the symptoms by administering an agent such as a corticosteroid or non-steroidal anti-inflammatory drug ("NSAID"), along with a disease modifying anti-rheumatic drug ("DMARD") to attempt to halt or slow progression of the disease. (Ex. 1002 ¶¶ 32-

33; Ex. 1011 at 716-19.) The ACR Guidelines is a printed publication that is prior art under 35 U.S.C. § 102(b).

Corticosteroids had been used to treat RA patients for many years prior to the earliest filing date of the '161 patent. (Ex. 1002 ¶ 33.) As of 1999, approximately 50% of RA patients, both those in regular treatment and those in clinical trials, were on a chronic low dose of oral prednisone, one of the most commonly prescribed corticosteroids. (*Id.*; Ex. 1012 at 591.) Corticosteroids were used in combination therapy with other drugs, usually DMARDs. (Ex. 1002 ¶ 33; Ex. 1012 at 719.)

Examples of DMARDS include intravenous leflunomide, sulfasalazine, and methotrexate. (Ex. 1002 ¶ 33.) Methotrexate is a drug used in the treatment of autoimmune diseases, including RA. (*Id.* ¶ 33-34.) The efficacy and safety of methotrexate as a treatment for RA had been established long before the filing date of application for the '161 patent. (*Id.* ¶ 33 (citing O'Dell, *Methotrexate Use in Rheumatoid Arthritis*, 23 RHEUMATIC DISEASE CLINICS OF NORTH AMERICA 4, (1997) (Ex. 1015, at 779 "O'Dell").) O'Dell begins, "[t]o overstate the importance of methotrexate in the contemporary management of rheumatoid arthritis (RA) would be difficult." (Ex. 1015 at 779.) O'Dell is a printed publication and is prior art to the '161 patent under 35 U.S.C. §102(b). It was not before the examiner during prosecution.

The “ability of patients to tolerate [methotrexate] safely with long-term use” distinguished methotrexate from other DMARDs used to treat RA. (Ex. 1015 at 788.) Indeed, methotrexate “simultaneously revolutionized and revitalized the treatment of patients with RA.” (*Id.* at 779.) O’Dell further stated that methotrexate was “the disease-modifying antirheumatic drug (DMARD) most commonly used to treat RA” and was “not only the most commonly used but also the first prescribed DMARD by most rheumatologists in the United States for the treatment of RA.” (*Id.*)

The types of drugs administered and their dosing schedule depended on a patient’s response to treatment, which was continuously monitored by physicians based on criteria developed by the ACR. (Ex. 1002 ¶ 34.) Adjustments to the type of drugs, their combinations, and their doses, were made as necessary. (*Id.*) These adjustments consisted of combination therapies with more than one DMARD, monotherapy with a new DMARD, or, once they were introduced, therapy with a biologic agent. (*Id.* ¶¶ 39-44.) Therapy with a biologic agent could be either monotherapy or combination therapy with a DMARD. (Ex. 1002 ¶¶ 38-39; Ex. 1019 at 1548.)

“No Evidence of Disease” in Rheumatoid Arthritis Using Methotrexate in Combination with Other Drugs: A Contemporary Goal for Rheumatology Care is an editorial by Pincus, et al., that was published in *Clinical and Experimental*

Rheumatology in 1997. (Ex. 1012, “Pincus.”) Pincus is a printed publication and prior art to the ’161 patent under 35 U.S.C. § 102(b). It was not before the examiner during prosecution. Like the other publications excerpted above, Pincus highlighted the importance of methotrexate treatment for RA. For example, Pincus stated that “[r]ecognition of the superiority of methotrexate to other DMARDs has emerged from long term observational studies in the clinic rather than from clinical trials.” (*Id.* at 591.) Pincus also compared the goal of remission in RA to the goal of remission in Non-Hodgkins Lymphoma (“NHL”). (*Id.*) Pincus suggested that the goal of remission in RA may be reached with combination therapy, in much the same way that remission is reached in NHL: “In attempts to restore a patient to a status of ‘no evidence of disease’ in Hodgkin’s disease or hypertension, clinicians may use 1, 2, 3, 4 or more drugs as appear required for disease control, a phenomenon which may be applicable in RA.” (*Id.* at 592.)

Kremer, *The Changing Face of Therapy for Rheumatoid Arthritis*, published in RHEUMATIC DISEASE CLINICS OF NORTH AMERICA, Vol. 21, No. 3 (1995) (“Kremer 1995,” Ex. 1038), described the dosage of methotrexate that was typically given to RA patients: “Most clinicians begin therapy with 7.5 mg weekly and increase the dosage at 1- or 2- month intervals to achieve maximal efficacy.” (*Id.* at 847.) In other words, patients should be titrated onto methotrexate. (O’Dell, Ex. 1015 at 788.) Kremer 1995 is a printed publication and prior art to the ’161

patent under 35 U.S.C §102(b). It was not before the examiner during prosecution. As of 1999, titrating patients onto medications that may have unwanted side effects, as is done with methotrexate to treat RA, was a common method of introducing a therapeutic agent to a patient. (Ex. 1002 ¶¶ 33-34.)

In the 1990s prior to the advent of biologic therapies to treat RA, methotrexate was used to treat the most difficult cases of RA, as it was known to produce the best and longest-lasting effects with a low risk of toxicity (assuming patients are properly titrated onto the medication). (*Id.* ¶¶ 33-34, 36.) Even patients who did not fully respond to methotrexate were treated with methotrexate because it was the best option available at that time. (*Id.* ¶ 40.) Because of the efficacy and widespread use of methotrexate, it was understood that new therapies should be compared to both methotrexate as “background therapy” and to placebo during clinical trials. (Ex. 1002 ¶¶ 43, 46; Ex. 1019 at 1548.) “Background therapy” refers to a treatment component that is held constant (here, methotrexate) even while other treatment components are added to or removed from a treatment regimen. (Ex. 1002 ¶ 34.)

B. Biologics and Combination Therapy with Methotrexate

The first biologic agent with an indication to treat RA was approved in the United States in 1998 under the brand name Enbrel[®]. (Ex. 1002 ¶¶ 38, 45.) The active ingredient in Enbrel[®] is etanercept, a tumor necrosis factor alpha (TNF α) blocking agent. (*Id.* ¶ 45.) Later TNF α -inhibitors include infliximab (Remicade[®]),

approved in 1998, and adalimumab (Humira[®]), approved in 2002. (*Id.* ¶ 38) Rituxan[®] (rituximab) was approved to treat NHL in 1997 and was approved to treat RA in 2006. (*Id.* ¶ 45.)

A March 1995 conversation between an FDA representative and prominent physicians and researchers working on new RA therapies illustrates the thinking regarding biologics therapy for RA at that time. (Ex. 1013, *Immunosuppression in Combination with Monoclonal Antibodies*, “the FDA Conversation.”) The FDA Conversation was published in a book, Proceedings: Early Decision in DMARD Development IV, by the Arthritis Foundation in 1996, and is therefore a printed publication and prior art to the ’161 patent under 35 U.S.C § 102(b). The FDA Conversation was not before the examiner during prosecution. As described in that publication, the FDA representative advocated that phase I studies with new biologics be done without combination with methotrexate to establish the safety of the new biologic. (Ex. 1013 at 292.) Phase II trials, however, were to be done with “methotrexate as background therapy.” (Ex. 1002 ¶ 46; Ex. 1013 at 294.) The FDA representative further explained that it had become “standard” to do phase I nonclinical studies with a single agent to establish safety and “then go with methotrexate.” (Ex. 1002 ¶ 46; Ex. 1013 at 295). As reflected in the FDA Conversation, methotrexate was used concomitantly with new biologics because (1) the progressive nature of the disease made it difficult to recruit patients who were

willing to discontinue methotrexate even if methotrexate provided only minimal benefit (*see* Ex. 1013 at 295 (comment by Dr. Joseph Markenson, an attending rheumatologist at the Hospital for Special Surgery in NY)); (2) it was ethically unsound to remove patients from methotrexate therapy even if it had only minimal effect in this progressive disease (*id.*; *see also id.* at 294 (comment by Dr. Michael Weinblatt of Brigham and Women’s Hospital in Boston)); and (3) it would be difficult to assess a new therapy on patients who were recently taken off of methotrexate because of the expectation of a disease “flare” upon withdrawal. (*Id.* at 294-95; *see also* Ex. 1002 ¶ 41.)

Prominent researchers touted the potential benefits of methotrexate and of combination therapy with biologic agents and methotrexate. For example, O’Dell taught: “Even though few would argue that methotrexate is the single most effective DMARD available, clearly if obtaining or at least approaching remission for patients is the goal, methotrexate alone isn’t the answer. Many clinicians, therefore, have added other DMARDs to methotrexate in patients who have had partial responses, a use of so-called combination therapy.” (Ex. 1015 at 782-83.) Methotrexate was the “cornerstone” and should be the “foundation” of most combinations and was “the standard against which combinations should be measured.” (*Id.* at 790.) Indeed, “[b]ecause methotrexate is the single most effective DMARD and because most patients with RA who receive methotrexate obtain a response, albeit sometimes an

incomplete response, it follows that the combination therapies most commonly used in clinical practice included methotrexate.” (*Id.*) The paper concluded: “[c]ontinued research on combinations of DMARDs, as well as combinations that include biologic agents and methotrexate and possibly other DMARDs, is necessary.” (*Id.* at 792.)

Kalden, *Rescue of DMARD Failures by Means of Monoclonal Antibodies or Biological Agents*, CLINICAL AND EXPERIMENTAL RHEUMATOLOGY (1997) (Ex. 1051, “Kalden”) taught that, in practice, new biologic agents were, in fact, being used successfully in combination therapy with methotrexate. Kalden is a printed publication and is prior art under 35 U.S.C. §102(b). It was not before the examiner during prosecution. As of 1997, “[i]nitial attempts [were] presently being conducted to test combination therapies, using monoclonal antibodies directed against the proinflammatory cytokines and cell surface molecules, and long-acting rheumatic drugs such as methotrexate.” (*Id.* at S-91.) One study on combination therapy with a biologic agent and methotrexate “demonstrated that combination therapy might be an important therapeutic approach for RA patients whose disease is not completely controlled by MTX alone.” (*Id.* at S-96 (citation omitted).) Kalden concluded by stating that biologic agents may be of “special value” in combination with methotrexate and other immunosuppressive compounds. (*Id.*)

Other prior art literature, both from regulatory agencies and from academic or clinical researchers, further underscores the general understanding that new biologics would and should be tested with methotrexate. (*See, e.g.*, Ex. 1019 at 1548 (“Virtually all of the new treatment modalities are currently being tested with [methotrexate] in patients who have active disease despite an adequate weekly dose of the drug... Most of the new biotechnology-derived therapeutic interventions are being studied as both monotherapy and combination therapy with [methotrexate].”); Ex. 1012 at 593 (stating that new drugs and biotechnology products, in particular, “should be tested in combination with methotrexate for approval in marketing, particularly as this is how they are likely to be used”); Ex. 1020 at 18 (it was “inevitable that new agents [would] be used in combination with methotrexate in clinical practice unless a contraindication exists.”); *see also* Ex. 1002 ¶¶ 45-48.)

C. The Use of Rituximab To Treat RA

Rituximab is a monoclonal antibody patented by IDEC Pharmaceuticals (now Biogen) in the early 1990s and developed in conjunction with Genentech since 1995. (Ex. 1002 ¶ 54.) Rituximab is sold under the brand name Rituxan[®] in the United States and Mabthera[®] in Europe. (*Id.*) Early in its development, rituximab was also known as “IDEC-C2B8” and is referred to by that name in some publications. (*Id.*) Rituximab’s efficacy in treating RA is derived from its well-publicized ability to destroy mature B-cells without being toxic to patients. (*Id.*)

In 1997, the FDA approved the use of rituximab for the treatment of patients with relapsed or refractory low-grade or follicular B-cell NHL. (*Id.* ¶ 55.) The FDA-approved product insert for rituximab, dated November 1997 (“Rituxan[®] label”), is a printed publication and constitutes prior art to the ’161 patent under 35 U.S.C. § 102(b) as it was accessible to the public prior to May 1998.² (Ex. 1037.)

² The label bears a copyright date of 1997. Further, the label and its associated Approval Letter, Ex. 1052, are available on the FDA’s website as part of the November 26, 1997 approval package. (Ex. 1053, Approval History BLA 103705, Drugs@FDA (last visited July 6, 2016), https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.)

Pursuant to FDA regulations, Genentech was required to include this with its Rituxan[®] product as of December 1997, when Genentech began selling Rituxan[®] in the U.S. (See Ex. 1054, IDEC Pharms. Corp. Annual Report (Form 10-K/A) (Mar. 3, 1998) at 34 (“During 1997, the joint business recorded an operating loss due to significant shared expenses related to the product launch of Rituxan in the United States in December 1997.”); *see also* 21 C.F.R. §§ 201.59 (1997) (forbidding the marketing of any drug without the required labeling).) Therefore, the Rituxan[®] label was a publicly available printed publication as of December 1997. Even if Genentech failed to market Rituxan[®] with its label, a copy of the label was posted on Genentech’s website, www.gene.com, as least as early as January 23, 1998. (*See*

The Rituxan[®] label provided that the recommended dosage of rituximab is “375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15 and 22)” (id. at 2; Ex. 1002 ¶ 55) and that “[a]dministration of RITUXAN resulted in a rapid and sustained depletion of circulating and issue-based B cells.” (Ex. 1037 at 1.) “Among the 166 patients in the pivotal study, circulating B-cells . . . were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients.” (*Id.*) The label also provided that “Rituxan is associated with hypersensitivity reactions.... Medications for the treatment of

Ex. 1055, “Rituxan label B”; Ex. 1056, declaration from the Internet Archive attesting to the veracity of the post from January 23, 1998.) Genentech’s website was organized such that the label could be easily located. Therefore, the label was broadly disseminated and publicly accessible before May 1998 to anyone with a browser and an Internet connection. For this additional reason, it is printed publication and prior art under section 102(b). *See, e.g., Suffolk Techs., LLC v. AOL Inc.*, 752 F.3d 1358, 1364-65 (Fed. Cir. 2014) (finding that an online document constitutes a printed publication; *Voter Verified, Inc. v. Premier Election Sols., Inc.*, 698 F.3d 1374, 1380-81 (Fed. Cir. 2012) (same). 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.

hypersensitivity reactions, e.g., epinephrine, anti-histamines and corticosteroids should be available for immediate use in the event of a reaction during administration.” (*Id.* at 1; see also Ex. 1002 ¶ 56.) Further, the label reported that these hypersensitivity reactions occur in approximately 80% of patients upon the first infusion and in approximately 40% of patients in subsequent infusions. (Ex. 1037 at 1; see also Ex. 1002 ¶ 56.)

Other prior art also described the efficacy of rituximab in depleting B cells in NHL. (See, e.g., Maloney et al., Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma, 84 BLOOD 8 (1994) (Ex. 1025) (“Maloney 1994”); Ex. 1026; see also Ex. 1002 ¶ 57) Further, the prior art suggested using rituximab for autoimmune diseases in which B cells play a role: “Additional potential applications include ... possible treatment of patients with autoimmune diseases caused by autoreactive antibodies.” Maloney et al., IDECC2B8: Results of a Phase I Multiple Dose Trial in Patients with Non-Hodgkin’s Lymphoma, J. CLINICAL ONCOLOGY, vol. 15, No. 10 (1997) (“Maloney 1997,” Ex. 1029 at 3274; see also Ex. 1002 ¶ 57-58.) Both Maloney 1994 and Maloney 1997 are printed publications and prior art to the ’161 patent under 35 U.S. C. § 102(b).

In addition, the prior art described the use of rituximab to treat RA. For example, Edwards et al., *Rheumatoid Arthritis: The Predictable Effect of Small*

Immune Complexes in Which Antibody Is Also Antigen, BRIT. J. RHEUMATOLOGY, 1998(37): 126-130 (“Edwards 1998,” Ex. 1030), proposed treating RA by killing B-cells, citing Maloney 1994 and its use of rituximab: “[r]ecent reports indicate that destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody with minimal unwanted effects, since B cells are produced rapidly and Ig levels are maintained in the short term.” (Ex. 1030 at 129-30; *see also* Ex. 1002 ¶¶ 63, 65 (citing WO 95/003770, Ex. 1027 at 2:4-5 (“in other diseases, such as rheumatoid arthritis and lupus nephritis, the primary mediator may be B-cells”))).) Edwards 1998 was published in February 1998 and is a printed publication and prior art to the ’161 patent under 35 U.S.C. § 102(b).

VII. CLAIM CONSTRUCTION

Because the ’161 patent has not yet expired, and will not expire during the pendency of this proceeding, the challenged claims should be given their broadest reasonable construction in light of the patent specification. 37 C.F.R. § 42.100(b).

No terms in the claims of the ’161 patent require construction. Petitioner notes, however, that claim 1 is directed to a method of treating RA comprising administering intravenously more than one dose of a therapeutically effective amount of rituximab and administering methotrexate. Claims 5 and 9 each replace the term “rituximab” in claim 1 with “an antibody that binds to the CD20 antigen on human B lymphocytes,” and also state that “the CD20 antibody is rituximab.” Thus,

a POSA would have understood that “rituximab” is a CD20 antibody that binds to the CD20 antigen on human B lymphocytes. (Ex. 1002 ¶ 54.) The three independent claims differ in form, but not in substance: claims 5 and 9 each state twice that the administration of rituximab is “intravenous,” while claim 1 states that only once; claim 9 states twice that the dose of rituximab should be a “therapeutically effective amount,” while claim 5 states that only once. Therefore, claims 1, 5, and 9 are identical in scope. (*Id.* ¶ 68.)

Similarly:

- claims 2, 6, and 10, which depend on claims 1, 5, and 9, respectively, each requires that the dose of rituximab is in the range from about 250 mg/m² to about 1000 mg/m², and are identical in scope (*id.* ¶ 69);
- claims 3, 7, and 11, which depend on claims 1, 5, and 9, respectively, each requires further administration of a glucocorticosteroid, and are identical in scope (*id.* ¶ 70); and
- claims 4, 8, and 12, which depend on claims 1, 5, and 9, respectively, each requires an initial dose of the antibody followed by a subsequent dose wherein the subsequent dose exceeds the initial dose, and are identical in scope. (*Id.* ¶ 71.)

VIII. GROUND 1: OBVIOUSNESS OVER EDWARDS 1998 IN VIEW OF THE FDA CONVERSATION AND THE RITUXAN® LABEL (CLAIMS 1-12)**A. Scope and Content of the Prior Art**

The scope and content of the prior art is described above, in section VII.

B. Level of Ordinary Skill in the Art

As Dr. Massarotti explains, RA is a chronic inflammatory disorder that affects tens of millions of people worldwide, causing pain, stiffness and swelling of joints, most often in the hands and feet. (Ex. 1002 ¶ 31.) RA is an autoimmune disease, the cause of which is not known. (*Id.*) The disorder has been the subject of substantial research and published literature concerning the treatment of patients and new RA therapies. (*Id.*) Many practicing rheumatologists are involved with clinical trials involving new drugs and methods of treatment. (*Id.*) For these reason, doctors in the field of rheumatology tend to be well informed about current trends and developing therapies for treating RA. (*Id.*)

In light of the specification, the references of record, and other available evidence, a person of ordinary skill at the time of the alleged invention would have been a practicing rheumatologist with a medical degree (M.D. or equivalent) and: (i) at least 5 years of experience treating RA patients; (ii) an understanding of the pathophysiology of RA and other auto-immune disorders, including those in which B-cells were thought to play a role; and (iii) an understanding of all of the available

and proposed methods of treating RA and other auto-immune disorders, including those in which B-cells were thought to play a role, and how they work to treat such disorders. (*Id.* ¶ 30) A person of ordinary skill in the art would also have had an understanding of clinical trials for RA treatments, including how the trials are designed and how to interpret results. (*Id.*)

C. Differences Between the Claims and the Prior Art

The prior art, *e.g.*, Edwards 1998, explicitly suggested the use of rituximab to treat RA. (Ex. 1002 ¶ 76.) The prior art, *e.g.*, the FDA Conversation, also directed physicians to use background methotrexate therapy with all biologic agents. (*Id.*) The Rituxan[®] label provided the approved dosing regimen for rituximab to treat NHL and disclosed the concomitant treatment with corticosteroids. (*Id.* ¶ 82.) Details about how rituximab should be administered to treat RA, including the precise doses and the coadministration with steroids, would have been obvious to a POSA, as described below. (*Id.* ¶¶ 78-82.)

D. Conclusion of Obviousness³

A POSA would have been motivated to treat RA with the combination of rituximab and methotrexate with a reasonable expectation of success because, for

³ Petitioner notes that EP1613350, the European counterpart to the '161 patent, was revoked in proceedings at the European Patent Office for reasons similar to those

example, Edwards 1998 stated that RA could be treated successfully with an agent that kills B cells, such as rituximab, and the FDA Conversation advised that methotrexate should be used as background therapy with biologic agents to treat RA. (Ex. 1002 ¶¶ 77-78.) A POSA would have been motivated to treat RA with doses of rituximab that were at or around the doses used to treat NHL, and would have reasonably expected success, because those doses were known to be safe and effective in killing B cells. (*Id.*) “Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.” *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir.), *cert. denied*, 135 S. Ct. 878 (2014) (citations omitted).

As Dr. Massarotti explains, a POSA would have been motivated to use combination therapy with rituximab and methotrexate because, as of at least 1996, physicians used methotrexate as “background therapy” with all new biologic agents because it was not feasible ethically or practically to take RA patients off of methotrexate. (*Id.* ¶¶ 41-44, 46-47, 77.) This motivation is consistent with the FDA’s advice that a biologic such as rituximab should be administered with methotrexate. (*Id.* ¶¶ 46-49, 52, 77-78; Ex. 1013; Ex. 1020 at 18.) Further, because rituximab and

presented in this Petition. (*See* Ex. 1049, the decision affirming the revocation of that patent.)

methotrexate work via different mechanisms, a POSA would have understood that the two drugs may have an additive effect and would not have expected methotrexate to interfere with the action of rituximab. (Ex. 1002 ¶ 74; *see also id.* ¶¶ 50-53.) Rather, it was expected that rituximab would work in the presence of methotrexate just as the other biologic agents worked in the presence of methotrexate. (*Id.*)

In a case with facts similar to those in this case, a patent claiming combination therapy with a new drug and an old drug to treat diabetes was found to be obvious because (1) combination therapy was often used to treat diabetes; (2) the old drug was the most commonly used drug for combination therapy; and (3) the two drugs worked with different mechanisms of action and therefore, with combination therapy, “[c]linical efficacy would be additive.” *Novo Nordisk A/S v. Caraco Pharmaceutical Lab.*, 775 F. Supp. 2d 985, 1006 (E.D. Mich. 2011), *aff’d* by 719 F.3d 1346 (Fed. Cir. 2013).

In this case, the prior art taught that (1) combination therapy was often used to treat RA; (2) methotrexate was the most commonly used drug for combination therapy; and (3) methotrexate was not expected to interfere with the activity of biologic agents and thus its therapeutic effect may be additive. (Ex. 1002 ¶¶ 33-34, 36, 40, 47, 78.) The prior art also taught that rituximab should be used to treat RA. (*Id.* ¶¶ 58-60.) Therefore, it would have been obvious to treat RA with combination

therapy consisting of methotrexate and any new biologic agent, including rituximab.

To the extent that Patent Owner argues that POSAs would not have agreed with the Edwards 1998 proposal to treat RA with rituximab, as it did in its Preliminary Response in IPR2015-00415, real-world evidence suggests otherwise. For example, Dr. Gryn had the idea to treat RA with rituximab and suggested that use to Biogen, which held a monopoly on rituximab in 1998. (Ex. 1006; *see also* Ex. 1002 ¶ 61.) Similarly, both Dr. Looney and Maloney 1994 independently proposed using rituximab to treat autoimmune diseases. (Ex. 1010; Ex. 1025; *see also* Ex. 1002 ¶ 61.)

Moreover, the proposal in Edwards 1998 to treat RA with rituximab was well received by POSAs. (Ex. 1002 ¶ 60.) Dr. Edwards, the author of that proposal, succeeded in securing funding from the University College London Hospitals to conduct a trial to treat subjects with RA with rituximab in October 1998. (Ex. 1033.) He also succeeded in securing approval from that University's ethics committee (Ex.1034), and permission to use rituximab off-label during that trial to treat RA from the UK Medicines Control Agency. (Ex. 1035.).

These real-world facts are probative evidence that a POSA would have been motivated to treat RA with rituximab using the dosing schedule set forth in the Rituxan[®] label. *See, e.g., Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d

1319, 1338 (Fed. Cir. 2004) (holding that evidence of what a POSA did demonstrated the obviousness of a claimed combination, even absent public distribution of the evidence). Contemporaneous invention, “though not determinative of statutory obviousness, [is] strong evidence of what constitutes the level of ordinary skill in the art.” *Geo. M. Martin Co. v. All. Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1306 (Fed. Cir. 2010) (citations omitted).

1. Independent Claims 1, 5, and 9 Are Obvious

Claims 1, 5, and 9 are identical in scope and each requires the administration of more than one dose of intravenous rituximab and methotrexate to treat RA. The prior art renders the combination of rituximab and methotrexate obvious, as explained above. It also would have been obvious to use more than one dose of intravenous rituximab based on the Rituxan[®] label, which specifies a total of four doses of intravenous rituximab to treat NHL, and states that this dosing schedule is effective for depleting B cells, which was also the goal in treating RA. Therefore, independent claims 1, 5, and 9 are obvious over Edwards 1998 in view of the FDA Conversation and the Rituxan[®] label. (Ex. 1002 ¶ 79.)

2. Claims 2, 6, and 10 Are Obvious

Claims 2, 6, and 10 depend from claims 1, 5, and 9, respectively, and further require that each dose of rituximab is “from about 250 mg/m² to about 1000 mg/m².” The Rituxan[®] label specified a suggested rituximab dose of 375 mg/m², which falls

within the claimed dosage range. (Ex. 1037 at 2.) The suggested dosage for NHL was known to be effective for depleting B cells, which was also the goal in treating RA. (Ex. 1002 ¶ 86.) It would therefore have been obvious to use a 375 mg/m² dose, which falls within the claimed range. For the reasons discussed above with respect to claims 1, 5, and 9, claims 2, 6, and 10 are obvious over Edwards 1998 in view of the FDA Conversation and the Rituxan[®] label. (*Id.*)

Further, a skilled practitioner would have known how to optimize the dose of rituximab to treat RA patients. (Ex. 1002 at ¶ 80.) The broad range of doses recited in claims 2, 6, and 10 includes many of the preferred doses for rituximab that would have been used by a person of ordinary skill. (*Id.*) In fact, two of the five doses tested by Maloney 1994 to deplete B cells (250 and 500 mg/m²) fall squarely within the claimed range. (*See* Ex. 1025 at 2457.)

Real-world evidence confirms that a POSA would have been motivated to use the NHL-approved dose to treat diseases by depleting B-cells. (*Id.* ¶ 61.) For example, Dr. Gryn suggested that dose in his proposal to treat RA (Ex. 1006.), Dr. Latov suggested that dose to treat neuropathy (Ex. 1008.), Dr. Pestronk suggested that dose to treat neuropathies (Ex. 1009.), and Dr. Looney suggested that dose to treat B-cell mediated autoimmune diseases, including lupus. (Ex. 1010.)

3. Claims 3, 7, and 11 Are Obvious

Claims 3, 7, and 11 depend from claims 1, 5, and 9, respectively, and further require administering a glucocorticosteroid. The use of corticosteroids to treat hypersensitivity reactions during infusion of biologic therapeutic agents was well known as of 1999. The Rituxan[®] label indicates that corticosteroids should be available to treat immediate hypersensitivity reactions that occur with the first infusion of rituximab in the majority of patients (approximately 80%), and during subsequent infusions in some patients (approximately 40%). (Ex. 1037 at 1; *see also* 1998 Remicade[®] label, Ex. 1041 (“Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids, and/or epinephrine) should be available for immediate use in the event of a reaction.”).) Therefore, for the reasons discussed above with respect to claims 1, 5, and 9, it would have been obvious to treat patients with rituximab, methotrexate, and a corticosteroid, and claims 3, 7, and 11 are obvious over Edwards 1998 in view of the FDA Conversation and the Rituxan[®] label. (*Id.*)

Alternatively, a POSA as of 1998 would have known that approximately 50% of RA patients are treated with corticosteroids concomitantly with other treatments (Ex. 1012 at 591), including combination treatments. (Ex. 1011 at 714.) Therefore, the addition of corticosteroids to the rituximab-methotrexate combination would

have been obvious over either the prior art or the knowledge of a POSA as of 1999. For this additional reason, claims 3, 7, and 11 are obvious over the prior art.

4. Claims 4, 8, and 12 Are Obvious

Claims 4, 8, and 12 depend on claims 1, 5, and 9, respectively, and further require an initial dose of rituximab followed by a subsequent dose, where the subsequent dose exceeds the initial dose. A POSA would have been motivated to administer an initial dose of rituximab that is lower than a subsequent dose of rituximab in accordance with the general medical principle that patients should be titrated up slowly on medications to minimize unwanted side effects. (Ex. 1002 ¶¶ 33-34.) Kremer 1995 and O'Dell taught that RA patients should begin therapy at low doses of methotrexate and work up to a clinically effective dose, illustrating that this general principle had been applied to the treatment of RA. (Ex. 1002 ¶ 82; Ex. 1015 at 788; Ex. 1038 at 1549.) Therefore, for the reasons described above with respect to claims 1, 5, and 9, claims 4, 8, and 12 are obvious over Edwards 1998 in view of the FDA Conversation, the Rituxan[®] label and the knowledge of a POSA. (Ex. 1002 ¶ 82.)

Real-world evidence confirms that a POSA would have titrated up the amount of rituximab when beginning treatment: in his 1998 study, Dr. Edwards dosed patients with four doses of rituximab; the first dose was smaller than the remaining

doses (Ex. 1036). Dr. Edwards’s dosing schedule is identical to that of Example 1(B) of the ’161 patent. (*Id.*; Ex. 1001.)

IX. GROUNDS 2 AND 3: OBVIOUSNESS OVER EDWARDS 1998 AND EITHER O’DELL OR KALDEN, IN VIEW OF THE RITUXAN® LABEL

The following analysis of obviousness for Grounds 2 and 3 is substantially identical to that set forth in the institution decision in IPR2015-00415 for claims 1, 2, 5, 6, 9, and 10. The arguments presented below for claims 3, 4, 7, 8, 11, and 12 were not presented in IPR2015-00415.

A. No Differences Exist Between the Challenged Claims and the Prior Art

1. **“A method of treating rheumatoid arthritis in a human comprising . . . administering to the human more than one intravenous dose of a therapeutically effective amount of [rituximab]” (all claims)⁴**

As of the earliest priority date for the ’161 patent, a person of ordinary skill would have been aware of: (i) rituximab’s ability to destroy mature B-cells without being toxic to human patients (Exs. 1025, 1026, 1030); and (ii) research showing

⁴ Claims 5 and 9 of the ’161 patent replace the term “rituximab” in claim 1 with: (i) “an antibody that binds to the CD20 antigen on human B lymphocytes;” and (ii) a “wherein” clause stating that “the CD20 antibody is rituximab.” Accordingly, the scope of the three independent claims is identical. (*See supra* Section V.A.1.)

that B-cells are involved in the pathophysiology of RA (Exs. 1030, 1031; *see also* Ex. 1002 ¶¶ 76-77.).

The 1998 Edwards reference proposed treating RA by depleting B-cells with anti-B-cell (CD20) antibodies and specifically rituximab (a/k/a IDEC-C2B8). (*See* Ex. 1030 at 129-30).

A person of ordinary skill would also have been aware that rituximab was “formulated for intravenous administration” and that the recommended dosage approved by the FDA was “375 mg/m² given as an IV [intravenous] infusion once weekly for four doses (days 1, 8, 15, and 22).” (*See* Ex. 1037.)

The FDA-approved recommended dosing regimen for rituximab would have been the starting point for a person of ordinary skill using rituximab to treat RA. (Ex. 1002 ¶ 78.) Indeed, the patentees acknowledged that the logical starting point for using rituximab to treat RA would have been the standard dosing regimen provided on the FDA label. (*See* Ex. 1001 at 27:59, 28:15, and 29:9 (proposing doses of “375 mg/m² IV days 1, 8, 15, & 22” for treating three separate autoimmune diseases, including rheumatoid arthritis).)

With the possible exception of early Phase I clinical studies designed to identify the safest and most effective dose (*e.g.*, Ex. 1025), a person of ordinary skill would have understood from the prior art that any therapeutically effective dosing

regimen for treating RA must involve more than one intravenous dose of rituximab, particularly given the chronic nature of RA. (Ex. 1002 ¶¶ 76, 79-82.)

2. “administering to the human methotrexate” (all claims)

The prior art establishes that, as of the earliest priority date for the ’161 patent, methotrexate was the “gold standard” for treating RA (Ex. 1057 at 1290) and had achieved a position of “therapeutic dominance” due to its demonstrated efficacy and long-term tolerability. (Ex. 1038 at 847; Ex. 1002 ¶¶ 76-78.) In fact, methotrexate was “not only the most commonly used but also the first prescribed DMARD by most rheumatologists in the United States for the treatment of RA.” (Ex. 1015 at 779.) Indeed, “[t]o overstate the importance of methotrexate in the contemporary management of rheumatoid arthritis (RA) would be difficult.” (*Id.* at 779.) The administration of methotrexate to treat RA patients was well known in the prior art.

3. Combining Rituximab and Methotrexate as Therapeutic Agents for Treating RA (all claims)

Combinations therapies involving monoclonal antibodies and methotrexate were discussed publicly by the FDA as early as 1995. In the FDA Conversation, a representative from the FDA’s Center for Biologics Evaluation and Research stated: “If the Phase I studies off methotrexate are shown to be safe, and this is agreed upon by the regulatory agency and the sponsor, I think it is perfectly appropriate to go into a methotrexate-treated patient population, provided that what you have learned in Phase I is employed in Phase II.” (Ex. 1013 at 295.) The FDA and the

rheumatologists who participated in that discussion were well aware of combination therapies for RA that involved biologic agents and methotrexate. (*See id.* at 294-95; Ex. 1002 ¶¶ 76-78.)

A person of ordinary skill at the time of the priority date would be aware that methotrexate was the “cornerstone” and “foundation” for combination RA therapies. (Ex. 1015 at 790, 792; *see also* Ex. 1002 ¶ 77.) Moreover, a person of ordinary skill would have been aware of studies demonstrating that combination therapies involving methotrexate would be an “important therapeutic approach for RA patients.” (*See* Ex. 1051 at S-96 (discussing studies showing the promise of combining drugs with methotrexate to treat RA).) Such experimental data, as well as the initial clinical data regarding combination therapies, led skilled practitioners to conclude that “biological agents such as anti-CD4 monoclonals or other anti-inflammatories might be of special value in combination with drugs such as MTX [methotrexate] and other immunosuppressive compounds.” (*Id.*)

The prior art taught that biological agents and other RA drugs “should be tested in combination with methotrexate for approval in marketing, particularly as this is how they are likely to be used.” (Ex. 1012 at 593.) Indeed, the prior art identified a straightforward economic incentive to combine methotrexate with other RA drugs during pharmaceutical development: “[T]he 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.)

Because methotrexate was well-accepted as the most efficacious and well-tolerated RA therapy at the relevant time, “virtually all” new RA treatments were being tested in combination with methotrexate. (Ex. 1019 at 1548.) This was also true of biological therapies for RA. (*See id.* (“Most of the new biotechnology-derived therapeutic interventions are being studied as both monotherapy and combination therapy with MTX.”))

By February 1999, the FDA stated it was “inevitable” that new therapeutic agents for RA would be used in combination with methotrexate. (Ex. 1020 at 18 (“[S]ince methotrexate therapy is used to treat many RA patients, it is inevitable that new agents will be used in combination with methotrexate in clinical practice unless a contraindication exists.”).) Indeed, absent a prohibition on concurrent methotrexate, the FDA told those skilled in the art that “data regarding use of the investigational agent in combination with methotrexate are needed to evaluate the potential for immunosuppression from combination therapy.” *(Id.)* Put simply, the FDA told the industry that combining new RA drugs with methotrexate was expected in order to obtain approval for new treatments.

It would have been obvious to a person of ordinary skill as of the priority date to treat RA with rituximab, or any other biologic or drug for treating RA, in combination with methotrexate. (Ex. 1002 ¶¶ 78-82.) The motivation to combine rituximab and other biologic agents with methotrexate can be found in the prior art (*id.*), which described the benefits of such combination therapies for treating RA as discussed above. (Ex. 1051 at S-96 (stating that combination therapies involving biologic agents and methotrexate might be of “special value”).) The prior art also discussed an economic incentive to drug developers to combine new RA treatments with methotrexate. (*E.g.*, Ex. 1012 at 593 (suggesting that the widespread use of methotrexate made it “advantageous from both a clinical and a business standpoint to develop most drugs in RA at this time for use in combination with methotrexate.”).)

4. “an antibody that binds to the CD20 antigen on human B lymphocytes” (claims 5 and 9)

It was known in the prior art that rituximab is an antibody that binds to the CD20 antigen on human B lymphocytes. (*See, e.g.*, Ex. 1037 at 1 (“The RITUXAN (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD antigen found on the surface of normal and malignant B lymphocytes.”); Ex. 1026 at 2188 (“IDEC- C2B8 [rituximab] is a chimeric monoclonal antibody (MoAb) directed against the B-cell specific antigen

CD20”).) This element does nothing more than describe what rituximab is and does. (*See* Ex. 1002 ¶¶ 68, 79.)

5. **“wherein the CD20 antibody administration consists of intravenous administration of the CD20 antibody, and the CD20 antibody is rituximab” (claim 5) and “wherein the therapeutically effective amount of the CD20 antibody is administered intravenously, and the CD20 antibody is rituximab” (claim 9)**

Claims 5 and 9 of the ’161 patent each contain “wherein” clauses. The “wherein” clause of claim 9 states that: (i) the CD20 antibody administration be both of a “therapeutically effective amount” and delivered intravenously; and (ii) the CD20 antibody is rituximab. The “wherein” clause of claim 5 does not include the term “therapeutically effective amount” and only states that: (i) the CD20 antibody administration is delivered intravenously; and (ii) the CD20 antibody is rituximab. The “wherein” clauses of claims 5 and 9 do nothing more than make explicit that the CD20 antibody is rituximab and, as a result, claims 5 and 9 are identical in scope to claim 1. In any event, as discussed above, it would have been obvious to administer a therapeutically effective amount of rituximab to treat RA, and it was known that rituximab is administered intravenously. (*See supra* Section X.D.1; *see also* Ex. 1002 ¶ 79.)

6. “each administration of rituximab is a dose in the range from about 250 mg/m² to about 1000 mg/m²” (claims 2, 6, and 10)

Claims 2, 6, and 10 recite a broad range of rituximab doses. The recommended dose on the Rituxan[®] label falls squarely within this range. (*See* Ex. 1037 at 2 (recommending “375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22)”)). As discussed above, the dosing regimen provided in the Rituxan[®] label would have been the logical starting point for the use of rituximab to treat RA (*see supra* Section X.D.2; *see also* Ex. 1002 ¶¶ 34, 67, 80), as confirmed by the patentees’ statements in the ’161 patent (*see* Ex. 1001 at 27:35-67.).

Further, a skilled practitioner would have known how to optimize the dose of rituximab to treat RA patients. (Ex. 1002 ¶ 80.) The broad range of doses recited in claims 2, 6, and 10 includes many of the preferred doses for rituximab that would have been used by a person of ordinary skill. (*Id.*) In fact, two of the five doses tested by Maloney 1994 (250 and 500 mg/m²) fall squarely within the claimed range. (*See* Ex. 1025 at 2457.)

7. “comprising administering to the human a glucocorticosteroid” (claims 3, 7, and 11)

Claims 3, 7, and 11 depend from claims 1, 5, and 9, respectively, and further require administering a glucocorticosteroid. The use of corticosteroids to treat hypersensitivity reactions during infusion of biologic therapeutic agents was well

known in 1999. (Ex. 1037 at 1.) The Rituxan[®] label indicates that corticosteroids should be available to treat immediate hypersensitivity reactions that occur with the first infusion of rituximab in the majority of patients (approximately 80%), and during subsequent infusions in some patients (approximately 40%). (Ex. 1037 at 1; *see also* 1998 Remicade[®] Label, Ex. 1041 at 5 (“Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids, and/or epinephrine) should be available for immediate use in the event of a reaction.”).) Alternatively, a POSA would have known that approximately 50% of RA patients are treated with corticosteroids concomitantly with other treatments (Ex. 1012 at 591), including combination treatments (Ex. 1011 at 2.). Therefore, the addition of corticosteroids to the rituximab-methotrexate combination would have been obvious over the prior art. Therefore, for this additional reason, claims 2, 6, and 10 are obvious over the prior art. (Ex. 1002 ¶ 81.)

8. “comprising an initial dose of the rituximab followed by a subsequent dose, wherein the mg/m² dose of the rituximab in the subsequent dose exceeds the mg/m² dose of the rituximab in the initial dose” (claims 4, 8, and 12)

Claims 4, 8, and 12 depend on claims 1, 5, and 9, respectively, and further require an initial dose of rituximab followed by a subsequent dose, where the subsequent dose exceeds the initial dose. A POSA would have been motivated to administer an initial dose of rituximab that is lower than a second dose of rituximab in accordance with the general medical principle that patients should be titrated

slowly up on medications to minimize unwanted side effects. (Ex. 1002 ¶ 38.) O’Dell taught that RA patients should begin therapy at low doses of methotrexate and work up to a clinically effective dose, illustrating that this general principle had been applied to the treatment of RA. (Ex. 1015 at 788.) Therefore, claims 4, 8, and 12 are obvious over the prior art. (Ex. 1002 ¶ 82.)

X. LACK OF SECONDARY CONSIDERATIONS

Petitioner is not aware of any secondary considerations that would support a finding of non-obviousness. Further, even if such secondary considerations exist, they cannot overcome the strong *prima facie* case of obviousness from the prior art, which discloses the use of rituximab to treat RA by depleting B cells, the dosing schedule for rituximab, and combination therapy with methotrexate to treat RA. The claimed invention is nothing more than the predictable use of prior art therapies according to their established functions, and secondary evidence cannot render such subject matter patentable. “Where the inventions represented no more than the predictable use of prior art elements according to their established functions, ... the secondary considerations [are] inadequate to establish nonobviousness as a matter of law.” *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (internal citations omitted).

A. No Unexpected Results

Patent Owner may point to the July 30, 2007 declaration of Dr. van Vollenhoven, submitted during prosecution of the '288 application, for the proposition that combination therapy with rituximab plus methotrexate produced longer-lasting effects than therapy with rituximab alone. (Ex. 1023 ¶¶ 32-34; clinical study attached as Ex. 1045.) This declaration does not demonstrate unexpected results because, as Dr. Massarotti explains, Dr. van Vollenhoven's assertions are not supported by the 2004 clinical study on which he relied. (Ex. 1002 ¶¶ 84-86.)

The 2004 study was designed to separately compare each of the following three treatment arms to monotherapy with methotrexate as a control: rituximab alone, rituximab plus methotrexate combination therapy, and rituximab plus cyclophosphamide combination therapy. (*Id.* ¶ 85.) The study concluded that each of the three treatments resulted in clinical improvements over methotrexate alone. (Ex. 1045 at 2572; *see also* Ex. 1002 ¶ 85.)

In his declaration, Dr. van Vollenhoven compared the three treatment arms to each other (Ex. 1023 ¶¶ 32-34) – a comparison that was not done in the 2004 report. Dr. van Vollenhoven's comparison is improper because he has not shown that the study was powered sufficiently to detect differences between the groups. (Ex. 1002 ¶ 91.) Even if the study had been powered to detect such a difference, the differences between the treatment groups were minimal at 24 weeks, evidencing no unexpected

results from the use of rituximab and methotrexate at that time point. (*Id.* ¶ 86.) While there were differences between the treatment groups at the 48 week time point, the data reported in the study for that time point are insufficient to conclude that rituximab plus methotrexate actually resulted in longer-lasting results, for at least three reasons.

First, the 48-week time point was part of an extension of the study and was not a primary or even secondary endpoint of the original study. (*Id.* ¶ 86.) In general, such post-hoc comparisons are not given the same weight as comparisons regarding endpoints that were originally included in the study protocol. Second, not all of the patients completed 48 weeks of treatment, skewing the results in a way that is not accounted for in either the 2004 report or in Dr. van Vollenhoven's declaration. (*Id.* ¶ 86.) Third, as explained, the study was not powered to detect differences between the three treatment groups. (*Id.* ¶ 85.) Therefore, Dr. van Vollenhoven's opinion that the study evidences unexpected results with the combination of methotrexate plus rituximab is unfounded. (*Id.*)

Assuming, arguendo, that the 2004 report does suggest that the combination of methotrexate plus rituximab resulted in better outcomes than monotherapy, such results would not have been unexpected: combination therapy was frequently used to treat RA precisely because it often worked better than monotherapy. (Ex. 1002 ¶ 88.) Additive results are not unexpected results. *See, e.g., Merck & Co. v. Biocraft*

Labs., Inc., 874 F.2d 804, 808 (Fed. Cir. 1989) (“Given the prior art teaching that both amloride and hydrochlorathiazide are natriuretic [inducing sodium excretion], it is to be expected that their coadministration would induce more sodium excretion than would either diuretic alone.”).

Further, rituximab is currently used both with and without methotrexate—a clear indication that, in practice, co-treatment with methotrexate is not necessarily superior. In other words, after years of administering rituximab with methotrexate in clinical practice, no synergistic effect has been observed. In a recent review of almost 2,500 RA patients on rituximab, 23% were on rituximab monotherapy, *i.e.*, without methotrexate, and the efficacy of treatment for this group did not differ from patients co-treated with methotrexate. (Ex. 1044 at 7; *see also* Ex. 1002 ¶ 87.) Finally, the Updated Consensus Statement on the use of rituximab in patients with rheumatoid arthritis, written by 17 practicing rheumatologists including Dr. van Vollenhoven, for the Rituximab Consensus Expert Committee (2011), while noting that rituximab is licensed for use with methotrexate, also noted that studies have described the successful use of rituximab without methotrexate. (Ex. 1043 at 5; *see also* Ex. 1002 ¶ 87.)

Thus, there is no evidence of unexpected results.

B. No Long-Felt Need

The claimed regimen did not meet any long-felt need. (Ex. 1002 ¶ 89.) As Dr. Massarotti explains, in the late 1990s, there was a need to treat RA patients who only partially responded to methotrexate. (*Id.*) That need was met by the introduction of the TNF α -inhibitors. (*Id.*) To the extent that there was a need for an additional treatment option for RA even after the introduction of the TNF α -inhibitors, for example, for patients that are inadequate responders to TNF α -inhibitors, that need was met when rituximab was approved and marketed for NHL, as demonstrated by the many independent physicians who used rituximab off-label to treat various B-cell-mediated diseases. (Exs. 1005-1010, 1035; *see also* Ex. 1002 ¶ 89.) Therefore any long-felt need was met when rituximab was first approved, and certainly no later than when Edwards 1998 published and publicly advocated the use of rituximab to treat RA. (Ex. 1002 ¶ 90.)

C. No Skepticism by POSAs

Petitioner is not aware of any skepticism regarding the claimed method by POSAs. To the contrary, the evidence suggests that many people simultaneously treated (or suggested treatment of) RA with rituximab, indicating that skilled persons would not have been skeptical that the claimed method would work. (Ex. 1002 ¶ 91.) For example, Dr. Edwards sought and received approval from three independent boards prior to treating his RA patients with rituximab. (Ex. 1033 (approval from

hospital funding board); Ex. 1034 (approval from hospital ethics board); Ex. 1035 (approval from UK Medicines Agency to use rituximab off label to treat RA.) Further, other physicians also treated or suggested treating RA patients with rituximab within a few months of the filing date of the patent. (*See, e.g.*, Gryn letter, Ex. 1006.) These simultaneous uses of rituximab to treat RA confirm that a person of ordinary skill as of 1998 not only would not have been skeptical, but also would have had a reasonable expectation of success in practicing the claimed methods.

XI. CONCLUSION

For the foregoing reasons, the Board should institute inter partes review and cancel claims 1-12 of the '161 patent as unpatentable.

Dated: March 24, 2017

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 7,820,161 B1 contains 10,528 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).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on March 24, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by overnight courier service on the Patent Owner at the correspondence address of record for U.S. Patent No. 7,820,161 B1, as follows, and at another address known as likely to affect service by email.

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