Trials@uspto.gov
571-272-7822

Paper 65
Entered: February 21, 2018

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 Owner.

Case IPR2016-01614[1]
Patent 7,820,161 B1

Before FRANCISCO C. PRATS, ERICA A. FRANKLIN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

FRANKLIN, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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

I. INTRODUCTION

On August 15, 2016, Celltrion, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–12 of U.S. Patent No. 7,820,161 B1 (Ex. 1001, "the '161 patent"). Paper 2 ("Pet."). Biogen, Inc. and Genentech, Inc. (collectively, "Patent Owner")[2] did not file a Preliminary Response to the Petition. On February 24, 2017, we instituted an *inter partes* review of claims 1–3, 5–7, and 9–11. Paper 12 ("Dec. Inst."). On June 2, 2017, Biogen, Inc. filed a Patent Owner Response to the Petition. Paper 23 (sealed),[3] Paper 24 (public), (collectively, "PO Resp.").

On March 24, 2017, Pfizer, Inc. filed a Petition in IPR2017-01115, requesting an *inter parties* review of claims 1–12 of the '161 patent. IPR2017-01115, Paper 2.[4] Pfizer, Inc. also filed a Motion for Joinder to join the proceeding with IPR2016-01614. *Id*. at Paper 3. Patent Owner did not file a Preliminary Response to Pfizer, Inc.'s petition. With our authorization, Pfizer, Inc., Biogen, Inc. and Genentech, Inc. filed a Joint Motion to Dismiss the claim challenges not instituted in the IPR2016-01614. *Id*. at Paper 11. On July 11, 2017, we granted the Joint Motion to Dismiss

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[2] *See* Paper 15, Conduct of Proceeding recognizing Biogen, Inc. and Genentech, Inc. as Patent Owner.
[3] *See* Paper 32, "Granting Patent Owner's Motion to Seal and Entry of Protective Order." This Decision relies on the public, redacted version of the Patent Owner Response.
[4] On April 6, 2017, a Notice of Defective Petition was entered explaining that exhibits must be numbered sequentially and according the Petition a filing date of March 24, 2017. IPR2017-01115, Paper 4. On April 11, 2017, a Notice Accepting Corrected Petition was entered recognizing the corrected exhibit numbering. *Id*. at Paper 5.

certain claim challenges raised in Pfizer, Inc.'s petition, instituted an *inter partes* review in IPR2017-01115 for the same claim challenges instituted in IPR2016-01614, and granted Pfizer, Inc.'s Motion for Joinder with IPR2016-01614. *Id*. at Paper 33. Celltrion, Inc. and Pfizer, Inc. (collectively, "Petitioners") filed a Reply to the Patent Owner Response. IPR2016-01614, Paper 38 ("Reply").

Petitioners and Patent Owner each filed a Motion to Exclude Evidence. Papers 48 and 51. Each party filed an Opposition to the other party's Motion to Exclude Evidence. Papers 53 and 56. Each party filed also a Reply to the other party's Opposition to the Motion to Exclude Evidence. Papers 58 and 59. Patent Owner filed a Motion for Observation on Cross-Examination testimony. Paper 49. Petitioners filed a Response ("Opposition") to Patent Owner's Motion for Observation. Each party filed a response to that motion.

With authorization, Petitioners filed a Motion for Additional Discovery seeking to serve Requests for Admission on Patent Owner regarding the FDA label for Patent Owner's drug product Rituxan. Paper 28.[5] Patent Owner filed an Opposition to Petitioners' Motion for Additional Discovery. Paper 29. We granted Petitioners' Motion. Paper 31. Petitioners served the authorized Requests for Admission on Patent Owner and, subsequently, filed Patent Owner's Responses to those requests. Exhibits 1081 and 1082.[6]

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[5] The proposed Requests for Admissions are included in Appendix A of Paper 28.
[6] Petitioners also filed Exhibit 1087 that appears to be a duplicate of Exhibit 1081.

On October 31, 2017, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 62 ("Tr.").

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a). and 37 C.F.R. § 42.73. Having considered the record before us, we determine Petitioners have not proved by a preponderance of the evidence that any of the challenged claims of the '161 patent are unpatentable. *See* 35 U.S.C. § 316(e). Additionally, the Motions to Exclude Evidence by Petitioners and Patent Owner are dismissed as moot.

A. Related Proceedings

Patent Owner provided notice that the '161 patent is at issue in "*Genentech, Inc.*, *Biogen, Inc.*, and *City of Hope v. Sandoz, Inc.* and *Sandoz International GMBH*, Case No. 2:17-cv-13507, in the District Court for the District of New Jersey." Paper 63. Petitioners provided notice that the '161 patent is at issue in "*Genentech, Inc. v. Celltrion, Inc.*, Case No. 1:18-cv-00574 (D. N.J. 2018), *Celltrion, Inc. v. Genentech, Inc.*, Case No. 3:18-cv-00276 (N.D. Cal. 2018) and *Genentech, Inc. v. Sandoz, Inc.*, Case No. 1-17-cv-13507 (D. N.J. 2018)." Paper 64. Petitioners and Patent Owner identify two previous Board proceedings involving a challenge to claims of the '161 patent: Case IPR2015-00415 (terminated on Oct. 1, 2015, pursuant to a Request for Adverse Judgment by petitioner Boehringer Ingelheim Int'l GmbH), and Case IPR2015-01744 (terminated on Oct. 6, 2015, pursuant to a Motion to Dismiss filed by petitioner Celltrion, Inc). Pet. 2, Paper 6, 2.

B. The '161 Patent

The '161 patent relates to a method for treating rheumatoid arthritis ("RA") by administering more than one intravenous dose of a therapeutically effective amount of rituximab and administering methotrexate. Ex. 1001, Abstract. Rituximab, i.e., Rituxan, refers to the genetically engineered chimeric murine/human monoclonal antibody, i.e., "C2B8," directed against the CD20 antigen. *Id*. at 2:29–32. The CD20 antigen, also referred to as human B-lymphocyte-restricted differentiation antigen, Bp35, is expressed on greater than 90% of B cell non-Hodgkin's lymphomas ("NHL"). *Id*. at 1:36–40. Studies have shown that rituximab binds human complement and lyses lymphoid B cell lines through complement-dependent cytotoxicity. *Id.* at 2:35–39. At the time of the invention, Rituxan was indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B cell NHL. *Id*. at 2:33–35. The Specification describes methotrexate as an anti-metabolite, immunosuppressive, and chemotherapeutic agent. *Id*. at 10:7, 30–31; 27:48–49.

C. Illustrative Claims

Claims 1 and 3 are illustrative and are reproduced below:

> 1. 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.
>
> 3. The method of claim 1, comprising administering to the human a glucocorticosteroid.

Ex. 1001, 29:43–46, 30:4–5.

D. The Instituted Ground of Unpatentability

We instituted an *inter partes* review of claims 1–3, 5–7, and 9–11 of the '161 patent under 35 U.S.C. § 103(a) as unpatentable over Edwards,[7] the Rituxan Label,[8] O'Dell,[9] and Kalden.[10]

Petitioners also rely upon the declarations of Maarten M. Boers, M.D. (Exs. 1002, 1064, and 1086), Jack Goldberg, M.D. (Ex. 1028), Jonathan Charles Wright Edwards, M.D. (Ex. 1075), and Vibeke Strand, M.D. (Ex. 1084). Patent Owner relies upon the declarations of Gregg Silverman, M.D. (Ex. 2085) and Ryan Sullivan, Ph.D. (Ex. 2084).

II. PATENTABILITY ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter*

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[7] Edwards et al., *Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in Which Antibody is Also Antigen*, 37 BRITISH J. RHEUMATOLOGY 126–130 (1998) (Ex. 1030).
[8] IDEC Pharmaceuticals Corporation and Genentech, Inc., Product label for Rituxan (1997) (Ex. 1037). Petitioners explain that they rely also upon Exhibit 1055 when referring to the Rituxan Label. Pet. 19 n.2.
[9] O'Dell, *Methotrexate Use In Rheumatoid Arthritis,* 23 RHEUMATIC DISEASE CLINICS OF NORTH AMERICA 779–796 (1997) (Ex. 1015).
[10] Kalden et al., *Rescue of DMARD failures by means of monoclonal antibodies or biological agents*, 15 J. CLINICAL AND EXPERIMENTAL RHEUMATOLOGY S91–S98 (1997) (Ex. 1051).

partes review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In the Petition, Petitioners assert that no terms of the challenged claims require construction. Pet. 22. However, Petitioners note that a person of skill in the art would have understood that "rituximab," recited in claim 1, is "a CD20 antibody that binds to the CD20 antigen on human B lymphocytes." Pet. 22–23. Indeed, claims 5 and 9 recite "an antibody that binds to the CD20 antigen on human B lymphocytes" and explain that "the CD20 antibody is rituximab." *Id*. at 23. In the Institution Decision, we agreed with Petitioners that no claim terms required construction for purposes of that decision. Dec. 5 (citing *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy)). The parties do not assert otherwise in the Patent Owner Response or in Petitioners' Reply. Accordingly, because the parties identify no controversy as to the scope of any claim terms, we conclude that, for the purpose of this Final Written Decision, no claim term requires express construction.

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v.*

VSI Int'l Inc., 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) and *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioners assert that a person of ordinary skill in the art at the time of the invention should be defined as:

> 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. ([Ex. 1002] ¶ 34) 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.*)

Pet. 24–25 (citing Ex. 1002 ¶ 34).

Patent Owner asserts that the person of ordinary skill in the art at the time of the invention should be defined as:

> [A] practicing rheumatologist with a medical degree and:
> (i) at least 2-3 years of experience treating RA patients;
> (ii) an understanding of immunology and the pathophysiology of RA, as disclosed in the prior art; and
> (iii) knowledge about the available methods of treating RA, as disclosed in the prior art.

PO Resp. 9–10. Further, Patent Owner asserts that we should reject the portion of Petitioners' proposed definition requiring an understanding of "all of the available and proposed methods of treating RA and other auto-immune disorders … and how they work to treat such disorders." *Id.* at 10 (quoting Pet. 24). According to Patent Owner, rheumatologists at the time

of the invention did not study or treat all autoimmune disorders, as such disorders are expansive and involve different pathophysiologies. PO Resp. 10–11 (citing Ex. 2085 ¶¶ 46–49). Patent Owner, thus, contends that Petitioners' proposed definition of a person of ordinary skill instead describes a person having "extraordinary insight." *Id*. at 10.

The proposed definitions asserted by Petitioners and Patent Owner suggest that the level of skill in the art is considerably high. Petitioners' definition is more limiting than Patent Owner's definition in that it requires, for example, the person of ordinary skill in the art to have more years of experience in treating RA patients and an understanding of "all of the available and proposed methods of treating RA and other auto-immune disorders … and how they work to treat such disorders." Pet. 24.

Based on the record as a whole, we determine that a person of ordinary skill in the art is not so limited. The invention and the cited references are directed to standard and proposed methods of treating RA and not all "other auto-immune disorders." In terms of years of experience, we recognize rheumatology as a specialized area of medicine, wherein acquiring at least three years of experience would be sufficiently significant. Accordingly, we find that the record as a whole supports defining the level of ordinary skill in the art as: a practicing rheumatologist with a medical degree (M.D. or equivalent) and: (i) at least three years of experience treating RA patients; (ii) an understanding of the immunology and the pathophysiology of RA; and (iii) an understanding of the available and proposed methods of treating RA, including relevant clinical trials for such treatment. We also note that the applied prior art reflects the appropriate

level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Moreover, we have reviewed the credentials of Drs. Boers (Ex. 1002) and Silverman (Ex. 2085) and consider each of them to be qualified to provide an opinion on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention.

C. The Combination of Edwards, the Rituxan Label, O'Dell and Kalden

Petitioners assert that claims 1–3, 5–7, and 9–11 would have been obvious over the combined teachings of Edwards, the Rituxan Label, and O'Dell or Kalden. Pet. 8–23, 33–42; Reply 2–25. Patent Owner disagrees. PO Resp. 1–63. In particular, our analysis focuses on Patent Owner's contention that Petitioners have not established that the Rituxan Label qualifies as prior art. *Id*. at 6, 53–56.

1. Edwards

Edwards is a journal article discussing a strategy to cure RA by destroying RF-producing B-cell clones (rheumatoid factor-producing B-cell clones) using "anti-CD20 antibodies and/or other agents." Ex. 1030, 129. The article presents this strategy in the form of a hypothesis that, in some respects, "refocuses attention on the possibility that permanent interruption of autoantibody production might effectively cure the disease." *Id*. at 126. According to Edwards, local and systemic events in the pathogenesis of RA suggest that "if B cells of pathogenic RF specificity are destroyed, the chance of them reappearing may be no greater than that of *de novo* appearance on the same genetic background." *Id*. at 128.

Edwards explains that, although attempting to selectively destroy B-cell clones exhibiting RF specificity may be ineffective, a better strategy may be to kill all mature B cells. *Id*. at 128–129. According to Edwards, doing so should allow only anti-non-self-B-cell clones to re-emerge because these clones, and not pathogenic IgG RF-producing clones, develop from clones with germline sequences by sequential affinity-based selection under control of corresponding T-cell responses. *Id*. at 129. Edwards explains that it had been reported that mature B cells can be destroyed using an anti-B-cell (CD20) antibody (IDEC-C2B8), i.e., rituximab, with minimal unwanted effects. *Id*. at 129–130 n.37 (citing 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 2457–2466 (1994)).

Edwards characterizes "[t]he ultimate test of the hypothesis [as] the efficacy of destruction of RF-producing B-cell clones by anti-CD20 antibodies and/or other agents." *Id*. According to Edwards, "[t]he chance that RF B-cell clones can be abrogated permanently is uncertain," but because it may lead to curing RA, "it is worth trying." *Id*.

2. The Rituxan Label

The Rituxan Label describes rituximab as a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Ex. 1037, 1. The product is formulated for intravenous administration and is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma. *Id*. The recommended dosage of Rituxan is 375 mg/m^2 given as an IV infusion once

weekly for four doses. *Id*. at 2. As a warning, Rituxan is described as being "associated with hypersensitivity reactions." *Id*. at 1. The product label states, "[m]edications for treatment of hypersensitivity reactions, e.g., epinephrine, anti-histamines and corticosteroids should be available for immediate use in the event of a reaction during administration." *Id*.

3. O'Dell

O'Dell is a journal article discussing the importance of methotrexate in managing RA and its use in combination therapy. Ex. 1015, 779. At the time O'Dell was written, methotrexate was considered "the disease-modifying antirheumatic drug (DMARD) most commonly used to treat RA," due to its efficacy and tolerability. *Id*. However, methotrexate rarely induces remission, which is the therapeutic goal for all patients with RA. *Id*. O'Dell explains that combination therapies most commonly used in clinical practice include methotrexate, and suggests that methotrexate used in combination therapy represents a treatment approach that is "a step closer to the goal of remission." *Id*. at 790, 792. O'Dell states, "[b]ecause methotrexate is the most effective DMARD available, it should be the foundation of most combination therapies." *Id*. at 792. According to O'Dell, continued research on combination therapies that "include biologic agents and methotrexate" is necessary. *Id*.

4. Kalden

Kalden is a journal article discussing the development of different monoclonal antibodies and other biological agents to treat RA. Ex. 1051 Abstract. Kalden explains that clinical rheumatologists "have long recognized that the treatment repertoire available for patients with rheumatoid arthritis (RA) is by no means satisfactory." *Id*. at S-91.

According to Kalden, as the knowledge in the art increases due to recent develops in the fields of clinical immunology and molecular biology, "novel avenues for treatment of this disease entity have been explored and developed." *Id*. For example, Kalden refers to a study combining methotrexate and the repeated administration of anti-TNF-α MAb cA2 as demonstrating that "combination therapy might be an important therapeutic approach for RA patients whose disease is not completely controlled by [methotrexate] alone." *Id*. at S-96. The article concludes that "biological agents such as anti-CD4 monoclonals or other anti-inflammatories might be of special value in combination with drugs such as [methotrexate] and other immunosuppressive compounds." *Id*.

5. Prior Art Status of the Rituxan Label

Before considering the combined teachings of Edwards, the Rituxan Label, O'Dell and Kalden, we address Patent Owner's contention that Petitioners fail to establish that the Rituxan Label is a "printed publication" under 35 U.S.C. §102(b). PO Resp. 6, 53–56.[11] According to Patent Owner, "[t]here is no evidence that Ex. 1037 was publicly accessible before the priority date," so as to qualify as prior art to the claimed invention. *Id*. at 6. Petitioners and Patent Owner agree that the earliest priority date is May 7, 1999. *See* Pet. 3, PO Resp. 9. Thus, as Petitioners assert, "publication prior to May 7, 1998, qualifies as prior art under 35 U.S.C. § 102(b) . . . ." Pet. 3–4.

[11] Patent Owner does not challenge the prior art status of the cited journal publications: Edwards, O'Dell, and Kalden.

"Public accessibility" is considered to be "the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. §102(b)." *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)). A determination whether a particular reference qualifies as a printed publication "is a legal determination based on underlying fact issues, and therefore must be approached on a case-by-case basis." *Hall*, 781 F.2d at 899.

Petitioners assert that Exhibit 1037 was "accessible to the public prior to May 1998." Pet. 17. Petitioners begin by noting that label bears a copyright date of 1997. *Id*. at 17 n.2. Petitioners assert also that the label and "associated Approval Letter, Ex. 1052, are available on the FDA's website as part of the November 26, 1997 approval package [Ex. 1053]." *Id*.[12] According to Petitioners, FDA regulations required Genentech to include the label with its Rituxan product as of December 1997, when Genentech began selling the product in the United States. *Id*. (citing Ex.

[12] Petitioners provide the following citation for Exhibits 1052 and 1053: "*Approval History BLA 103705*, Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.) (last visited July 6, 2016)." Pet. 18 n.2.

1054).[13] Thus, Petitioners asserts that the Exhibit 1037 was publicly available as of December 1997. *Id*.

In the Patent Owner Response, Patent Owner asserts that neither a copyright date nor the presence of the label identified as Exhibit 1037 on the FDA website currently establishes whether Exhibit 1037 was publicly accessible, on an FDA website or otherwise, as of December 1997. PO Resp. 54–55. We agree with Patent Owner. Petitioners have not identified any authority for considering a copyright date on the Rituxan Label as evidence of public accessibility of the document on that date. Nor have Petitioners shown that the Rituxan Label it retrieved from the FDA website in 2016 was available on that site prior to the critical date of the '161 patent, and in a manner such that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, could have located it.

As for Petitioners' assertion that Exhibit 1037 was "part of the November 26, 1997 approval package" from the FDA, Pet. 17 n.2, Patent Owner asserts that Petitioners have not supported that contention with any evidence. PO Resp. 55. Further, although not denying that the 1997 version of 21 C.F.R. § 201.59 applied to Genentech's sale of its Rituximab product, Patent Owner asserts that Petitioners fail to submit any evidence that such regulation prohibited Genentech from making any changes to the label before selling Rituxan, or that the FDA did not approve a revised label for Rituxan before it was sold. *Id*.

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[13] IDEC Pharms. Corp. Annual Report (Form-K/A) (Mar. 3, 1998) at 34; 21 C.F.R. § 201.59 (1997).

Insofar as Petitioners assert that Exhibit 1037 was part of an FDA "approval package" and that an FDA regulation required including a drug label with the sale of a drug product like Rituximab to demonstrate that Exhibit 1037 was disseminated to the public in December 1997 with the sale of Rituximab, that showing is inadequate. In particular, Petitioners have not submitted documentary or testimonial evidence establishing that Exhibit 1037 is, in fact, the drug label disseminated with Rituximab at any time. At most, Petitioner has shown that a drug label was disseminated with Rituximab sales beginning in 1997, while inviting us to speculate as to whether Exhibit 1037 is a copy of that disseminated label. *See* Pet. 17. However, the legal determination whether a particular reference qualifies as a printed publication is based upon underlying facts and not upon speculation. *See Hall*, 781 F.2d at 899.

We authorized Petitioners to propound Requests for Admission upon Patent Owner relating to Petitioners' contention that Exhibit 1037 is a copy of the Rituxan Label that was included with the sales of Rituxan before May 7, 1999. Paper 31, 7. In Response to the Requests for Admission, Patent Owner Genentech "denies that Exhibit 1037 is a true and correct copy of a document that Genentech enclosed with a vial of Rituxan® that was then sold in the U.S. prior to May 7, 1999." Ex. 1081, 9–10 (Response to Requests for Admission 5).[14] Thus, Patent Owner denies that Exhibit 1037

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[14] Patent Owner Biogen "denies the Request on the ground that Biogen lacks sufficient information or knowledge," as its predecessor, IDEC, was "not responsible for labeling or packaging vials of rituximab for sale to the public under the brand name Rituxan®" during the relevant time period. Ex. 1082, 10–11 (Response to Request for Admission 5).

was disseminated with the sale of the Rituxan product prior to the critical date.[15]

Petitioners assert that even if Genentech did not market Rituxan with Exhibit 1037, a "copy of the label . . . was posted on Genentech's website, www.gene.com, as least as early as January 23, 1998." Pet. 18 n.2. In support of that assertion, Petitioners refer to Exhibit 1055, a webpage copy of the "Full Prescribing Information" for Rituxan with a www.gene.com footer including a January 23, 1998 date, along with Exhibit 1056, a declaration from the Office Manager from Internet Archives explaining that a webpage copy of the Rituxan Label attached as Exhibit A is a true and accurate copy of printouts from www.gene.com on the date specified in the footer of the printout, i.e., January 23, 1998. *Id*. According to Petitioners, "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." *Id*. Petitioners assert, "for this additional reason, it is a printed publication and prior art under section 102(b)." *Id*. 18–19 n.2 (citing *Suffolk Techs, LLC v. AOL Inc.*, 752 F.3d 1358, 1364–65 (Fed. Cir. 2014); *Voter Verified, Inc. v. Premier Election Sols., Inc.* 698 F.3d 1374, 1380–81 (Fed. Cir. 2012)). Petitioners punctuate that argument with a statement that "[a]ll 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

[15] We note, however, that Patent Owner Genentech's denial is unaccompanied with an explanation regarding how Exhibit 1037 differs from the labeling included with the Rituxan product distributed for sale.

Ex. 1055; both versions reflect the same content." *Id*.

Patent Owner does not address Exhibit 1055 in the Patent Owner Response. However, in the context of a contention that the exhibit is not authenticated, Patent Owner asserts in its Motion to Exclude that the declaration from the Internet Archive Office Manager attesting to the veracity of the post from that date, as reflected in Exhibit A of Exhibit 1056, does not suffice as it "makes no reference to Ex. 1055." Paper 51, 11–12. Further, Patent Owner asserts that a comparison of the webpage printout in Exhibit 1055 and that in Exhibit A of Exhibit 1056 shows that the two documents are different. *Id*.

Thus, we next consider whether Exhibit 1055 is a printed publication under 35 U.S.C. § 102(b). Even assuming that Exhibit 1056 authenticates Exhibit 1055 and establishes that the reference was online on January 23, 1998, our determination whether Exhibit 1055 was publicly accessible prior to the critical date requires further inquiry. That is, we must determine whether Petitioners made a satisfactory showing that the reference was "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc.*, 511 F.3d at 1194. For example, the Federal Circuit has explained "evidence that a query of a search engine before the critical date, using any combination of search words, would have led to the [reference] appearing in the search results" is probative of public accessibility. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350 (Fed. Cir. 2016).

In this regard, Petitioners assert only that "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." Pet. 18 n.2. That assertion is not further explained or accompanied by citation to any evidence supporting Petitioners' contention about Genentech's website. Nor have Petitioners offered evidence indicating that persons interested and ordinarily skilled in treating rheumatoid arthritis would have identified and visited Genentech's website before the critical date, and in doing so, would have searched for rituximab drug information, a product newly manufactured and indicated for the treatment of non-Hodgkin's lymphoma. Ex. 1055, 3.

Insofar as Petitioners characterize *Suffolk Techs* and *Voter Verified* as "finding that an online document constitutes a printed publication," Pet 19 n.2, we are unpersuaded. In each of those cases, the Federal Circuit considered the evidence submitted regarding the public accessibility of an online publication, and determined, based on the submitted evidence, whether the online publication was sufficiently publicly accessible to be considered a printed publication. *Suffolk Techs*, 752 F.3d at 1364–65; *Voter Verified*, 698 F.3d at 1380–81. We recognize that those cases were decided using a different evidentiary standard, specifically, a clear and convincing standard. Petitioners in this case, however, have not submitted any supporting evidence for us to consider regarding the issue of whether Ex. 1055 would have been, for example, "indexed and thereby findable by an internet search engine." *Blue Calypso*, 815 F.3d at 1349 (citing *Voter Verified*, 698 F.3d at 1381). Rather, Petitioners submit only attorney argument that "Genentech's website was organized such that the label could be easily located." Pet. 18 n.2.

In an *inter partes* review, a petitioner bears the burden of establishing unpatentability of the challenged claims by a preponderance of the evidence. 35 U.S.C. § 316(e). That burden includes establishing that references relied upon as prior art are printed publications. Furthermore, as the Federal Circuit has explained, "'if the fact trier of the issue is left uncertain, the party with the burden loses.'" *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378–79 (Fed. Cir. 2015) (*quoting Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326–27 (Fed. Cir. 2008)). In this case, we determine that evidence merely demonstrating publication to the internet is not "a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l*, 511 F.3d at 1194 (Fed. Cir. 2008).

In view of the foregoing, we determine that the Petitioners have not supported adequately their contention that the Rituxan Label, as set forth in Exhibit 1037 or 1055, was publicly accessible prior to the critical date so as to render it a "printed publication" under 35 U.S.C. §102(b). Thus, Petitioners have not shown that the Rituxan Label qualifies as prior art.[16] Accordingly, we analyze the instituted ground without reference to the Rituxan Label.

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[16] In the Reply, Petitioners assert also that "[d]espite the differences in formatting between the [Exhibits 1037 and 1055], they disclose the same information, and therefore, if one is a printed publication, then the other is also a printed publication." Pet. 24 (citing *In re Klopfenstein*, 380 F.3d 1345 (Fed. Cir. 2004)). We disagree with that contention; moreover, it is moot as we have determined that Petitioners have not established that either exhibit is a printed publication.

6. The Combination of Edwards, Kalden, and O'Dell

A conclusion that claimed subject matter is obvious must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

Independent claims 1, 5, and 9, each require treating RA in a human comprising administering more than one intravenous dose of a therapeutically effective amount of rituximab, and administering methotrexate. Ex. 1001, 29:43–46; 30:10–17, 27–34. Petitioners assert that a person of ordinary skill in the art would have found that method of treating RA obvious. Pet. 33. Petitioners assert that a person of skill in the art would have understood from Edwards that (a) rituximab has an ability to destroy mature B-cells without being toxic to human patients, and (b) B-cells are involved in the pathophysiology of RA. *Id*. at 34.

According to Petitioners, the suggestion to treat RA by administering rituximab and methotrexate is provided by O'Dell and Kalden. *Id*. at 36–38. Petitioners assert that O'Dell describes methotrexate as the most commonly prescribed disease-modifying antirheumatic drug in the United States for the treatment of RA, and the "foundation" for combination therapies to treat RA. *Id*. at 36 (citing Ex. 1015, 790–792). Petitioners assert that Kalden explains that combination therapies involving methotrexate would be an "important therapeutic approach for RA patients," and that biological agents, such as a monoclonal antibody, might be of "special value" in combination with methotrexate. *Id*. at 36–38 (citing Ex. 1051, S-96).

Petitioners do not rely on Edwards, O'Dell, or Kalden as teaching or suggesting "administering more than one intravenous dose of a therapeutically effective amount of" rituximab. *See* Pet. 34–35.

Claims 2, 6, and 10 depend from claims 1, 5, and 9, respectively, and recite specific ranges for the dosage of rituximab. Ex. 1001, 30:1–3, 18–20, 35–37. Petitioners do not rely on Edwards, O'Dell, or Kalden as teaching or suggesting that limitation. Pet. 40–41.

Claims 3, 7, and 11 also depend from claims 1, 5, and 9, respectively, and recite methods further comprising administering a glucocorticosteroid. Ex. 1001, 30:4–5, 21–22, 38–39. Petitioners do not rely on Edwards, O'Dell, or Kalden as teaching or suggesting that limitation. Pet. 41.

In the Reply, Petitioners assert that "the dose of Rituxan that was approved by FDA to treat NHL, and [the] proposition that steroids effectively treat hypersensitivity reactions . . . were common knowledge in 1999 (Boers2 at ¶¶ 23–24)." Reply 24. This assertion is inadequate to supply the claim limitations not asserted to be taught or suggested by the combined prior art. Significantly, Petitioners have not shown that its assertion in the Reply was presented in the Petition. Further, the referenced testimony of Dr. Boers relates only to the use of glucocorticosteroids and not to the dose of Rituxan. Ex. 1064 ¶¶ 23–24. Moreover, Dr. Boers' opinions relating to the use of glucocorticosteroids is unaccompanied by citation to any evidence. *Id*. Thus, those opinions are not entitled to persuasive weight.

A petition for *inter partes* review "must specify where each element of the claim is found in the prior art patents or printed publications relied upon." 37 C.F.R. § 42.104(b)(4). Because Petitioners have not explained with adequate specificity how some objective teachings in the prior art, or

knowledge generally available to one of ordinary skill in the art, would have led that individual to combine the relevant teachings to arrive at the claimed invention, based upon a combination of Edwards, O'Dell and Kalden, we conclude that Petitioners have not shown by a preponderance of the evidence that the challenged claims would have been obvious over the combination of those references.

D. Motions to Exclude

Petitioners move to exclude Patent Owner's Exhibits 2015, 2029, 2038, 2048, 2049, 2063, and 2080. Paper 48. Because our Decision does not rely on any of those exhibits, we dismiss Petitioners' Motion to Exclude those items as moot.

Patent Owner moves to exclude Exhibits 1005,–1010, 1013, 1033–1035, 1039, 1041, 1053–1054, 1060, 1062, 1065, 1070–1073, and part of 2093. Paper 51. Because our Decision does not rely on any of those exhibits, we dismiss Patent Owner's Motion to Exclude with respect to items as moot. Additionally, in view of our analysis in the Decision, Patent Owner's Motion to Exclude with respect to Exhibits 1037, 1052, and 1055 is also dismissed as moot.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioners have not established by a preponderance of the evidence that claims 1–3, 5–7, and 9–11 of the '161 patent are unpatentable. Additionally, we dismiss the motions to exclude evidence by Petitioners and Patent Owner as moot.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–3, 5–7, and 9–11 of the ’161 patent have not been shown by a preponderance of the evidence to be unpatentable;

FURTHER ORDERED the motions to exclude evidence by Petitioners and Patent Owner are dismissed as moot; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

PETITIONER:

Elizabeth J. Holland
Huiya Wu
Cynthia Lambert Hardman
Robert V. Cerwinski
Elaine H. Blais
GOODWIN PROCTER LLP
eholland@goodwinlaw.com
hwu@goodwinlaw.com
chardman@goodwinlaw.com
rcerwinski@goodwinlaw.com
eblais@goodwinlaw.com

Jovial Wong
Charles Klein
Eimeric Reig-Plessis
WINSTON & STRAWN LLP
rituximabIPR@winston.com

PATENT OWNER:

Michael R. Fleming
Gary N. Frischling
Keith A. Orso
Yite John Lu
David Gindler
IRELL & MANELLA LLP
Genentech/RituxanIPR@irell.com