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Paper 12
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Case IPR2016-01614
Patent 7,820,161 B1

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

FRANKLIN, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

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. ("Patent Owner") did not file a Preliminary Response to the Petition.

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the Petition, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–3, 5–7, and 9–11. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

Petitioner and Patent Owner identify two previous proceedings challenging 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); Case IPR2015-01744 (terminated on Oct. 6, 2015, pursuant to a Motion to Dismiss filed by petitioner Celltrion, Inc).

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, or Rituxan®, refers to the genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen. *Id*. at 2:29–31. Rituximab is also known as "C2B8." *Id*. at 2:31–32. Studies have shown that rituximab binds human

complement and lyses lymphoid B cell lines through complement-dependent cytotoxicity. *Id.* at 2:35–39. Methotrexate is an anti-metabolite, immunosuppressive, and chemotherapeutic agent. *Id*. at 10:7, 30–31; 27:48–49.

C. Illustrative Claim

Claim 1 of the '161 patent is illustrative of the challenged claims and is 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.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–12 of the '161 patent on the following grounds:

Claims	Basis	References
1–12	§ 103(a)	Edwards,[1] FDA Conversation,[2] and the Rituxan® Label[3]
1–12	§ 103(a)	Edwards, O'Dell,[4] and the Rituxan® Label
1–12	§ 103(a)	Edwards, Kalden,[5] and the Rituxan® Label

Petitioner also relies upon the Declarations of Maarten M. Boers, M.D. (Ex. 1002) and Jack Goldberg, M.D. (Ex. 1028).

II. 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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[1] 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).
[2] Schwieterman, *Immunosuppression in Combination with Monoclonal Antibodies,* BIOLOGIC AGENTS IN AUTOIMMUNE DISEASE 291–298 (1995) (Ex. 1030).
[3] IDEC Pharmaceuticals Corporation and Genentech, Inc., Product label for Rituxan® (1997) (Ex. 1037).
[4] O'Dell, *Methotrexate Use In Rheumatoid Arthritis,* 23 RHEUMATIC DISEASE CLINICS OF NORTH AMERICA 779–796 (1997) (Ex. 1015).
[5] 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).

Petitioner asserts that no terms of the challenged claims require construction. Pet. 22. In view of our analysis, we agree that construction of claim terms is not necessary for purpose of this Decision. *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).

B. Obviousness over Edwards, the Rituxan® Label, O'Dell and Kalden

Petitioner asserts that claims 1–12 would have been obvious over Edwards, the Rituxan® Label, and O'Dell or Kalden. Pet. 33–42.

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*. 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 Rituxan® (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. Analysis

a. Claims 1–3, 5–7, and 9–11

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 methotrexate. Petitioner asserts that a person of ordinary skill in the art would have found that method of treating RA obvious based on the teachings of Edwards, the Rituxan® Label, and either O'Dell or Kalden. Pet. 33. Petitioner, however, has not set forth separate arguments with respect to the alternative grounds

involving O'Dell or Kalden. Rather, Petitioner has relied upon both of those references together in its argument. Thus, we consider the ground as involving Edwards, the Rituxan® Label, O'Dell *and* Kalden.

Petitioner asserts that a person of skill in the art would have understood from Edwards that rituximab (a) 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. Petitioner explains further that the skilled artisan would have known the recommended dosage amount of rituximab from the Rituxan® Label, and that such dosage is administered via intravenous infusion once weekly for four doses. *Id*.

According to Petitioner, the suggestion to administer rituximab in combination with methotrexate to treat RA is provided by O'Dell and Kalden. *Id*. at 36–38. Petitioner asserts 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). Petitioner asserts 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).

Regarding dependent claims 2, 6, and 10, Petitioner asserts that the recommended dosage of 375 mg/m^2 for rituximab disclosed in the Rituxan® Label falls within the range recited by the claims, i.e., "from about 250 mg/m^2 to about 1000 mg/m^2." *Id*. at 40. Regarding dependent claims 3, 7, and 11, requiring additionally administering a glucocorticosteroid, Petitioner

asserts that the Rituxan® Label meets that limitation by teaching the use of corticosteroids to treat hypersensitivity reactions known to occur with infusions of rituximab. *Id*. at 41.

On the current record, we discern no deficiency in Petitioner's characterization of the cited references, or in Petitioner's assertions as to the reasonable inferences an ordinary artisan would make from those references. Thus, based on the information presented at this stage of the proceeding, Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–3, 5–7, and 9–11 over Edwards, the Rituxan® Label, O'Dell and Kalden.

b. Claims 4, 8, and 12

Dependent claims 4, 8, and 12, require "administering an initial dose of the rituximab followed by a subsequent dose, where the mg/m^2 dose of the rituximab in the subsequent dose exceeds the mg/m^2 dose of the rituximab in the initial dose." Ex. 1001. Petitioner asserts that a person of ordinary skill in the art would have been motivated to administer a subsequent dose of rituximab that exceeds the initial dose "in accordance with the general medical principle that patients should be titrated slowly up on medications to minimize unwanted side effects." *Id*. at 42. In particular, Petitioner relies upon paragraph 38 of Dr. Boers' declaration. Pet. 42 (citing Ex. 1002 ¶ 38). Dr. Boers does not address titrating rituximab in that paragraph. In another section of the declaration, Dr. Boers states that "[i]t would have been obvious to a person of skill in the art to slowly titrate patients onto rituximab by administering a first dose that is lower than subsequent doses." Ex. 1002, ¶ 88. According to Dr. Boers, that method was commonly practiced for drugs that may have unwanted side effects. *Id*.

In support of that testimony, Dr. Boers cites references "discussing titrating patients onto methotrexate." *Id*.

We are not persuaded by Petitioner's argument or Dr. Boers' testimony that a person of ordinary skill in the art would have had a reason to administer a subsequent dose of rituximab that exceeds an initial dose. Although Petitioner and Dr. Boers provide some evidence that a person of ordinary skill in the art would have had a reason to escalate the dose of methotrexate, they have not explained adequately that a skilled artisan would have had a reason to practice such a method with rituximab. In particular, Dr. Boers has not provided objective support demonstrating that a person of skill in the art would have found it necessary or useful to gradually increasing the dose of rituximab to avoid unwanted side effects. Rather, as Petitioner has noted, Edwards describes rituximab therapy as advantageously involving "minimal unwanted effects." Pet. 20–21; Ex. 1030, 129–30. Moreover, the Rituxan® Label describes addressing an unwanted effect, i.e., hypersensitivity, by either administering a drug to treat that reaction, or by adjusting the infusion rate. Ex. 1037, 1–2. Because Dr. Boers has not provided adequate support for his position on this issue, we do not accord it persuasive weight. *See* 37 C.F.R. § 42.65(a) (stating opinion testimony that does not disclose underlying facts or data "is entitled to little or no weight"); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc*., 776 F.2d 281, 294 (Fed. Cir. 1985) (stating a lack of objective support for expert opinion "may render the testimony of little probative value in a validity determination").

Thus, based on the information presented at this stage of the proceeding, we determine that Petitioner has not shown sufficiently that there is a reasonable likelihood that it would prevail in showing the

unpatentability of claims 4, 8, and 12 over Edwards, the Rituxan® Label, O'Dell and Kalden.

C. Remaining Ground

The remaining ground involving the FDA Conversation challenges the same claims in the same manner as the ground previously discussed. Accordingly, we exercise our discretion by declining to proceed on the remaining obviousness ground of unpatentability. *See* 37 C.F.R. § 42.108(a).

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that claims 1–3, 5–7, and 9–11 of the '161 patent are unpatentable.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. §314 (a), an *inter partes* review is instituted as to claims 1–3, 5–7, and 9–11 of the '161 patent under 35 U.S.C. § 103(a) as unpatentable over Edwards, the Rituxan® Label, O'Dell, and Kalden;

FURTHER ORDERED that no other proposed ground of unpatentability are authorized.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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