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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Case IPR2018-00285
Patent 8,329,172 B2

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

Opinion of the Board filed by *Administrative Patent Judge* SNEDDEN.

Opinion Dissenting filed by *Administrative Patent Judge* HARLOW.

SNEDDEN, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Pfizer, Inc. ("Petitioner"), filed a Petition requesting an *inter partes* review of claim 1 of U.S. Patent No. 8,329,172 B2 (Ex. 1001, "the '172 patent"). Paper 2 ("Pet."). Biogen, Inc. ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp."). We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." *See also* 37 C.F.R. § 42.4 (a).

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioner has shown that there is a reasonable likelihood that it would prevail with respect to the single challenged claim. We thus institute an *inter partes* review of the challenged claims on all grounds set forth in the Petition.

A. Related Matters

Petitioner previously filed a petition against the '172 patent, however, this panel declined to institute *inter partes* review in that proceeding. *Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01166 (PTAB Nov. 13, 2017) (Paper 9) (IPR2017-01166).

The '172 patent has previously been challenged by each of Celltrion, Inc. and Boehringer Ingelheim International GmbH; however, the Board declined to institute *inter partes* review in those proceedings. Pet. 7; Paper 4; *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01093 (PTAB Oct. 6, 2017)

(Paper 12); *Boehringer Ingelheim Int'l GmbH v. Biogen, Inc.*, IPR2015-00418 (PTAB July 13, 2015) (Paper 14).

The parties indicate that the '172 patent is currently at issue in *Genentech, Inc. v. Celltrion, Inc.*, Case No. 1:18-cv-00574 (D.N.J. 2018) and *Celltrion, Inc. v. Genentech, Inc.*, Case No. 3:18-cv-00276 (N.D. Cal. 2018). Pet. 7–8; Paper 7.

B. The '172 Patent

The '172 patent is titled "Combination Therapies for B-Cell Lymphomas Comprising Administration of Anti-CD20 Antibody." Ex. 1001, [54]. The '172 patent describes treating B-cell lymphomas with anti-CD20 antibodies combined with other therapeutic regimens, such as chemotherapy. Ex. 1001, 2:7–38. The '172 patent explains that CD20 is a B-cell-restricted differentiation antigen that is usually expressed at very high levels on cancerous B-cells, and is "appealing for targeted therapy, because it does not shed, modulate, or internalize." *Id*. at 1:33–41. The '172 patent explains that a preferred anti-CD20 antibody "is C2B8 (IDEC Pharmaceuticals, Rituximab)." *Id*. at 2:59–60.

The '172 patent discloses that rituximab, also known as "RITUXAN®" has been approved for use in relapsed and previously treated low-grade non-Hodgkin's lymphoma ("LG-NHL"), but that such patients may nonetheless still be subject to disease relapse. *Id*. at 1:47–58. Therefore, the '172 patent advises, "it would be advantageous if anti-CD20 antibodies had a beneficial effect in combination with other lymphoma treatments, and if new combined therapeutic regimens could be developed to lessen the likelihood or frequency of relapse." *Id*. at 1:60–64.

In this regard, the ’172 patent describes a Phase III study conducted by the Eastern Cooperative Oncology Group (“ECOG”) of patients with LG-NHL in which a subset of patients responsive to cyclophosphamide, vincristine, and prednisone (“CVP”) chemotherapy “will undergo a second randomization to Rituximab maintenance therapy (375 mg/m^2 weekly times 4 every 6 months for 2 years (Arm C)[)].” Ex. 1001, 13:8–16.

C. Illustrative Claim

Claim 1, reproduced below, is the sole claim of the ’172 patent.

> 1. A method of treating low grade B-cell non-Hodgkin’s lymphoma in a human patient comprising administering to the patient chemotherapy consisting of CVP therapy to which the patient responds, followed by rituximab maintenance therapy, wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m^2 every 6 months, and wherein the maintenance therapy is provided for 2 years.

Ex. 1001, 22:56–63.

D. Evidence Relied Upon

Petitioner relies upon the following prior art references:

Ex. 1003, McNeil, *Non-Hodgkin’s Lymphoma Trials In Elderly Look Beyond CHOP*, 90 J. NAT. CANCER INST. 266–67 (1998) (“McNeil”).

Ex. 1004 (alternatively, Ex. 1039 or Ex. 1041), IDEC Pharmaceuticals Corporation and Genentech, Inc., Product label for Rituxan® (1997) (“Rituxan Label”).

Ex. 1005, Hochster et al., *Prolonged Time to Progression (TTP) In Patients with Low Grade Lymphoma (LGL) Treated with Cyclophosphamide (C) and Fludarabine (F) [ECOG1491]*, American Society of Clinical Oncology, Program/Proceedings, Thirty-Fourth Annual Meeting (May 1998) (“Hochster I”).

Ex. 1008, Maloney et al., *IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma*, 90(6) BLOOD 2188–2195 (Sept. 15, 1997) ("Maloney")

Petitioner also relies upon the Declarations of Howard Ozer, M.D., Ph.D. (Ex. 1002) and Sylvia D. Hall-Ellis, Ph.D. (Ex. 1016) to support its contentions.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following ground of unpatentability (Pet. 10):

Ground	Claim	Basis	Reference(s)
I	1	§ 103(a)	Hochster I, Maloney, and McNeil
II	1	§ 103(a)	Hochster I, Rituxan Label, and McNeil

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 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 the context of the entire disclosure. *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 Sections II.A.1. and II.A.2 below, we construe the certain claim terms. We determine that no explicit construction of any other claim term is necessary to determine whether to institute a trial in this case. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

1. "chemotherapy consisting of CVP therapy"

Although the Specification of the '172 patent refers to "standard CVP therapy" (Ex. 1001, 13:10), the patent does not explain precisely what CVP therapy is. Both parties agree, however, that CVP therapy is a combination of the drugs cyclophosphamide, vincristine, and prednisone, which is sometimes referred to as "COP" because the drug vincristine is also known as oncovin. Pet. 17–18; Prelim. Resp. 30.

The "consisting of" language used in connection with the CVP therapy limits the chemotherapeutic portion of the claimed regimen to only the CVP treatment, to the exclusion of other agents. *See AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001) ("'[C]losed' transition phrases such as 'consisting of' are understood to exclude any elements, steps, or ingredients not specified in the claim.").

2. "CVP therapy to which the patient responds, followed by rituximab maintenance therapy"

We construe claim 1 as requiring administration of CVP therapy, to which the patient responds according to the criteria set forth in the '172 patent. *See* Ex. 1001, 9:14–23 (the '172 patent providing specific criteria for a complete response (CR) and a partial response (PR) and distinguishing such patients from "non-responders"). The CVP must be followed at some time by the rituximab maintenance therapy, with no disease relapse occurring between the patient's response to the CVP therapy and the maintenance therapy. Both parties agree with this construction. Pet. 18; Prelim. Resp. 30.

B. Priority Date of the '172 Patent

The '172 patent issued from U.S. Patent Application No. 11/840,956, filed on August 18, 2007. Ex. 1001, [21], [22]. The '172 patent is a continuation of U.S. Patent Application No. 10/196,732, filed on July 17, 2002, now abandoned, which is a continuation of U.S. Patent Application No. 09/372,202, filed on August 11, 1999, now U.S. Patent No. 6,455,043. *Id*. at [63]. The '172 patent claims priority to U.S .Provisional Patent Application No. 60/096,180, filed on August 11, 1998. *Id*. at [60].

Petitioner contends that the subject matter of claim 1 does not find support in the provisional application to which the '172 patent claims priority. Pet. 13–15. Rather, Petitioner argues, the effective filing date of the claimed subject matter at issue here is August 11, 1999. *Id*. at 14. Patent Owner does not dispute Petitioner's contention. Therefore, for purposes of

this decision, we accord the subject matter of claim 1 of the '172 patent an effective filing date of August 11, 1999.

C. 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); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

According to Petitioner, a person of ordinary skill in the art at the time of the invention would have been "a practicing oncologist with at least an M.D. degree and several years of experience treating patients with NHL and/or researching treatments for NHL, including with chemotherapeutic drugs." Pet. 17 (citing Ex. 1002 ¶ 15). Patent Owner does not address Petitioner's position on this matter and does not propose its own description for a person of ordinary skill in the art at the time of the invention.

At this stage in the proceeding, we determine that Petitioner's description of the level of ordinary skill in the art is supported by the current record. Moreover, we have reviewed the credentials of Dr. Ozer (Ex. 1002, Attachment A), and, at this stage in the proceeding, we consider him to be qualified to opine on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. 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).

D. Asserted Prior Art

1. Hochster I

Hochster I describes the results of a phase I/II study examining the combination of fludarabine ("F") and cyclophosphamide ("C") as a first-line chemotherapy to treat LG-NHL patients. Ex. 1005, *66. Hochster I states that based on the "promising" results of that study, "we are conducting phase III study of CF vs. CVP ± anti-CD20 maintenance with PCP & H-Z prophylaxis (E1496)."[1] *Id*.

2. 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. 1004, 1; Ex. 1039, 10; Ex. 1041, 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 NHL. *Id*. The reference reports results from various clinical trials in which 375 mg/m^2 of Rituxan was administered intravenously weekly for four doses to patients having relapsed or refractory NHL, including relapsed or refractory LG-NHL. *Id*.

[1] As Dr. Ozer explains, "the phrase 'PCP & H-Z prophylaxis' referred to standard treatments to prevent infections associated with chemotherapy and drugs that affect the immune system (e.g., rituximab)." Ex. 1002 ¶ 56.

3. McNeil

McNeil describes a randomized trial for elderly patients with intermediate-grade NHL involving a combination treatment of CHOP and Rituxan (IDEC-C2B8). Ex. 1003, 266. McNeil explains that the trial, organized by the ECOG, "will recruit 630 patients age 60 and over" to receive the combination therapy. *Id*. McNeil additionally discloses that the trial will test the efficacy of CHOP plus rituxan maintenance therapy. *Id*. McNeil states that "[a]fter initial therapy, patients who responded will be again randomly assigned to receive the maintenance regimen — Rituxan every 6 months for 2 years — or observation." *Id*. McNeil further observes that "[t]his is the first randomized trial to address maintenance therapy in any kind of NHL." *Id*.

4. Maloney

Maloney describes a "phase II, multicenter study evaluating four weekly infusions of 375 mg/m^2 IDEC-C2B8 in patients with relapsed low-grade or follicular NHL." Ex. 1004, 1. In that study, 17 of the 37 patients enrolled exhibited clinical responses, i.e., partial or complete remission, to rituximab treatment. *Id.* at 5, Table 3.

Notably, however, "none of the 4 patients with small lymphocytic lymphoma (WF group A) responded." *Id.* at 6; *see also id.* at 5. Maloney reasons that the absence of response in SLL patients may result from the decreased expression of CD20 on the B-cells of SLL patients relative to the B-cells of NHL patients. *Id.* at 6.

> Although patients with chronic lymphocytic leukemia (CLL) were excluded from this trial (based on the presence of

> >5,000 lymphocytes/μL for this histologic subgroup), it is possible that the decreased response rate in this [SLL] subgroup was due to a lower expression of the CD20 surface antigen that has been observed in cases of CLL.

Id. at 6.

E. Asserted Grounds

1. Petitioner's Ground 1: Obviousness over Hochster I, Maloney, and McNeil

Petitioner asserts that claim 1 is unpatentable under § 103 as obvious in view of the combination of Hochster I, Maloney, and McNeil. Pet. 38–52. Petitioner contends that Hochster I discloses that the investigators of the study were "conducting [a] phase III study of CF vs. CVP ± anti-CD20 maintenance . . . ." *Id.* at 39. Relying on the testimony of Dr. Ozer, Petitioner contends that

> a [person of ordinary skill in the art] as of August 1999 would have understood that Hochster I's disclosure of "CVP ± anti-CD20 maintenance" referred to induction chemotherapy consisting of CVP followed by maintenance therapy—i.e., therapy used to maintain and prolong the remission obtained after a patient responded to CVP induction—using an anti-CD20 agent. Ex. 1002 ¶ 79. Specifically, a [person of ordinary skill in the art] would have understood that the "±" symbol, which is used in clinical trial abstracts to mean "with or without" as a comparison of two treatment arms, denoted that one patient group in the clinical trial would receive only CVP induction chemotherapy, whereas another group would receive CVP induction chemotherapy followed by anti-CD20 maintenance therapy. *Id.* ¶ 80.

Pet. 39–40.

Citing McNeil, Petitioner further contends that a person of ordinary skill in the art would have understood "anti-CD20 maintenance" therapy to

directly refer to rituximab, a known, commercially-approved anti-CD20 monoclonal antibody. *Id.* at 41 (citing Ex. 1003, 5; Ex. 1002 ¶ 85).

Citing Maloney, Petitioner contends that a person of ordinary skill in the art would have had reason to select the claimed dosing regimen for rituximab of four weekly administrations of rituximab at a dose of 375 mg/m^2 because that is the dose that had been proven effective in depleting CD20+ B-cells. *Id.* at 44 (citing Ex. 1008, 6–7). In particular, Petitioner notes that Maloney discloses "four weekly infusions of 375 mg/m^2 [rituximab] in patients with relapsed low-grade or follicular NHL" and concluded that this regimen had a favorable "safety profile" and led to "antitumor activity in patients with relapsed low-grade or follicular NHL." *Id.* at 44–45 (quoting Ex. 1008, 6).

Finally, Petitioner contends that a person of ordinary skill in the art would have selected a rituximab maintenance therapy regimen of every six months for 2 years, as recited in claim 1, because this was the only schedule of frequency and duration for rituximab maintenance described in the art as of August 1999. Pet. 49. Here, Petitioner directs our attention to McNeil, which discloses that a phase III clinical trial was evaluating "the maintenance regimen [of] Rituxan *every 6 months for 2 years*." *Id.* (citing Ex. 1003, 5 (emphasis added)). Furthermore, with regard to the two-year period, Petitioner notes that

> McNeil followed previous studies on maintenance therapy following CVP to treat LG-NHL, including the regimen in Portlock, where patients "receive[d] 2 years of planned maintenance CVP" (Ex. 1025, 2), and the regimen in Steward,

> where patients received "'maintenance' chemotherapy with 2 years of intermittent chlorambucil" (Ex. 1010, 3).

Id. at 51.

Petitioner further contends that Maloney teaches the importance of a 6 month treatment interval. *Id.* at 45. In particular, Maloney teaches that "[t]reatment with the chimeric anti-CD20 antibody rapidly and effectively depleted B cells from the peripheral blood circulation . . . until approximately 6 months post treatment, followed by slow gradual recovery." *Id.* (quoting Ex. 1008, 6, 9); *see also*, *Id.* at 50; Ex. 1002 ¶ 102. "That is, the cancerous B-cells began to reappear after six months, suggesting the need for renewed treatment" every 6 months. *Id.* at 50.

2. Petitioner's Ground 2: Obviousness over Hochster I, Rituxan Labely, and McNeil

For substantially similar reasons, Petitioner contends that claim 1 is unpatentable under § 103 as obvious in view of the combination of Hochster I, Rituxan Label, and McNeil. Pet. 52–54. For this ground, Petitioner substitutes Maloney for Rituxan Label for, *inter alia*, its disclosure of the FDA-approved prescribing information for rituximab. *Id.*; *see also id.* at 24–27. First, Petitioner notes that Rituxan Label demonstrates that rituximab was known to be "a genetically engineered chimeric murine/human monoclonal antibody *directed against the CD20 antigen* found on the surface of normal and malignant B lymphocytes." *Id.* at 52 (quoting Ex. 1004, 1; Ex. 1039, 10; Ex. 1041, 1). The label further explains that "[r]ituximab binds specifically to the antigen CD20," which is

"expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL)." *Id.* at 53 (quoting Ex. 1004, 1; Ex. 1039, 10; Ex. 1041, 1).

Regarding the dosing of rituximab, Petitioner contends as follows:

> [Rituxan Label] further confirmed that 375 mg/m^2 was the only dosing regimen approved by the FDA for rituximab: "[t]he recommended dosage of RITUXAN is 375 mg/m^2 given as an IV infusion once weekly for four doses." Ex. 1004, 2 (emphases added); Ex. 1039, 12; Ex. 1041, 3. The label also taught rituximab was detectable in the blood for up to six months that B-cells regenerated after six months: "[r]ituximab was detectable in the serum of [LG-NHL] patients [who took that dose] three to six months after completion of treatment," and "B-cell recovery began at approximately six months following completion of treatment." Ex. 1004, 1; Ex. 1039, 11; Ex. 1041, 1.
>
> The fact that other hypothetical dosing regimens were also conceivable, or that this dosing regimen was not yet specifically approved for maintenance, is beside the point. Here, similar to other cases, "one skilled in the art" would first look to regimens "previously approved by the FDA and used successfully." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365–66 (Fed. Cir. 2007). A new regimen "can always be made or attempted," but "a skilled [artisan] at the time would simply [use] known" regimens first before attempting others. *Id*. at 1362.

Pet. 53.

Furthermore, according to Petitioner, Rituxan Label confirms that "[t]here has been no experience with overdosage in human clinical trials." *Id.* at 26 (quoting Ex. 1004, 2; Ex. 1039, 12; Ex. 1041, 3). With regard to toxicity, Petitioner contends that

> clinical studies by 1998 had shown that rituximab's "[t]oxicity was mild." Ex. 1006, McLaughlin at 3.[2] "After the first infusion, most patients [ ] had no toxicity for the remainder of treatment," and "[a]dverse events were typically brief." *Id*. at 6; *see id*. at 8 ("The toxicity of the current program was notably mild."). "By virtue of the modest toxicities of this agent, which do not overlap with the toxicities of standard chemotherapy," researchers concluded that rituximab—which has a mechanism of action that is different than and complementary to that of chemotherapies like CVP—"lends itself to integration with chemotherapy programs." *Id*. at 9; Ex. 1002 ¶ 52.

Pet. 26–27.

Regarding the recited 2 year duration for maintenance therapy, Petitioner contends that "a [person of ordinary skill in the art] would have been motivated to use this regimen for at least two years, as disclosed in McNeil." *Id.* at 54.

3. Patent Owner's contentions

Patent Owner sets forth several arguments to support its position that Petitioner fails to establish a reasonable likelihood that challenged claim 1 of the '172 patent would have been obvious over the either the combination of Hochster I, Maloney, and McNeil or the combination of Hochster I, Rituxan Label, and McNeil. Prelim. Resp. 31–64. First, Patent Owner contends that "Hochster I fails to provide any disclosure of what dosing regimen and schedule of rituximab would be used as maintenance therapy" (*id.* at 33),

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[2] Ex. 1006, McLaughlin et al., *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program*, 16 J. CLIN. ONCOL. 2825–33 (Aug. 7, 1998) ("McLaughlin").

that McNeil concerns treating elderly patients with intermediate-grade non-Hodgkin's lymphoma ("IG-NHL"), not LG-NHL (*id.* at 34–35), and that "neither Petitioner nor its expert provide[] any sound scientific or clinical rationale why skilled artisans would use the same rituximab dosing schedule despite substantial differences in patient population and induction chemotherapy regimens" (*id.* at 34). *See also id.* at 35–41.

Regarding the recited frequency and duration of rituximab maintenance therapy regimen of every six months for 2 years, Patent Owner argues as follows:

> First, the [McLaughlin] study on which Petitioner relies for "B-cell recovery" data reports the use of rituximab as induction therapy for relapsed or refractory patients, not administration of rituximab as maintenance therapy. Petitioner fails to explain why B-cell recovery time would have been expected to be the same for patients receiving rituximab for relapsed disease as for those receiving rituximab for maintenance therapy.
>
> Second, Petitioner's citation relies on the B-cell recovery data for ***normal*** B cells, not cancerous ones. Ex. 1004, 001. In this study, cancerous B cells did not repopulate until ***13 months*** after treatment with rituximab. Ex. 1006, 003 ("[T]he projected median time to progression for responders is 13.0 months."). Petitioner fails to explain why skilled artisans would use the time to return of normal B cells, as opposed to cancerous B cells, as the schedule for rituximab maintenance dosing.

Prelim. Resp. 42.

Patent Owner further argues as follows:

> Petitioner further argues that "it would have been obvious to administer rituximab maintenance [therapy] as long as possible to maintain remission, including for at least two years." Pet. 5 (citing Ex. 1002 ¶¶ 103–104). But this conclusory argument fails to account for safety risks with such prolonged B-cell depletion.

> B cells are a critical and necessary component of an entire branch of our body's immune system—humoral immunity, which "involve[d] the production of antibody by plasma cells derived from B lymphocytes, the binding of this antibody to the pathogen, and the elimination of the pathogen by accessory cells and molecules of the humoral [bodily fluid, e.g., blood] immune system." Ex. 2033, 004. . . .
>
> [G]iving rituximab every six months for two years would have resulted in no B-cell presence for at least two years. There was simply no safety data at the time of the invention about possible toxicities, such as infections, with complete B-cell depletion for two years.

Prelim. Resp. 44–45.

With regard to the recited dose, Patent Owner argues that "Petitioner fails to establish that a POSA would have believed that the dosing regimen for ***induction*** therapy would have been appropriate for ***maintenance*** therapy." *Id.* at 47. Patent Owner contends that neither Maloney nor Rituxan Label disclose "a range of maintenance therapies for LG-NHL patients who had complete or partial responses to CVP therapy without disease relapse" (*id.* at 56) and that a person of ordinary skill in the art would have selected a lower dose of rituximab for maintenance therapy, as compared to the disclosed induction therapy (*id.* at 48–55).

Patent Owner further contends that "[t]he many failures of trying maintenance therapy in LG-NHL in the art underscore the unpredictability in this field." *Id.* at 62. Patent Owner contends that Hochster I and McNeil "provide no results of any kind" (*id.* at 58), and that, at the time of the invention, "no maintenance therapy had been shown to effectively maintain remission and prevent relapse of low-grade NHL" (*id.* at 59). Thus,

according to Patent Owner, a person of ordinary skill in the art would not have had a reasonable expectation of success in developing a successful rituximab maintenance treatment. *Id.* at 56–62.

4. Analysis

Upon consideration of the arguments presented and evidence of record, we find that Petitioner has offered sufficient evidence to institute trial, and Patent Owner's arguments do not persuade us that we should decline to go forward with a trial.

First, we note that a reasonable expectation of success does not require absolute predictability. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The fact that a safe and effective maintenance dosing regimen had not been conclusively identified in the prior art does not demand a conclusion of nonobviousness. Petitioner provides sufficient information to establish a reasonable likelihood of success in showing that a person of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to use rituximab as the anti-CD20 agent for the maintenance therapy disclosed in the method of Hochster I. Furthermore, Petitioner provides sufficient information to establish a reasonable likelihood of success in showing that a person of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to use the known, FDA-approved dosing regimen for rituximab (disclosed in Maloney or Rituxan Label), at the frequency and duration suggested for rituximab maintenance therapy as disclosed in McNeil.

While we recognize that there would have been some degree of unpredictability for establishing a maintenance therapy to effectively

maintain remission and prevent relapse of low-grade NHL, we determine, on the present record, that the information set forth by Petitioner provides sufficient specific guidance directing a person of ordinary skill in the art to the claimed invention. Thus, the facts on the current record do not suggest that this is a case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d at 903; *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1167 (Fed. Cir. 2006).

As noted by Patent Owner, however, there are certain differences between the scope and content of the prior art that a person of ordinary skill in the art would have to contemplate prior to combining the teachings to arrive at the claimed subject matter. For example, Patent Owner notes that McNeil discloses a clinical study involving elderly patients with IG-NHL, which Patent Owner contends a person of ordinary skill in the art would have understood to be a distinct disease with a distinct patient population, thereby suggesting that a person of ordinary skill in the art would not have understood the maintenance therapy disclosed for IG-NHL to be immediately applicable to maintenance therapy for LG-NHL. Prelim. Resp. 34–46. While we appreciate Patent Owner's several cogent arguments, we determine that Petitioner has offered sufficient evidence to institute trial and Patent Owner's argument alone is insufficient to persuade us that Petitioner's argument supported by declarant testimony does not meet the standard for institution. That being said, we will evaluate both parties' arguments once the record is developed further during trial.

In view of the above, we determine that Petitioner has demonstrated a reasonable likelihood in showing that claim 1 of the '172 patent would have been obvious over the either the combination of Hochster I, Maloney, and McNeil or the combination of Hochster I, Rituxan Label, and McNeil.

F. Discretionary Denial under 35 U.S.C. § 325(d)

Patent Owner asserts that we should exercise our discretion to deny the Petition under 35 U.S.C. § 325(d) because "the same or substantially the same prior art and arguments challenging the '172 patent have already been unsuccessfully presented to the Office multiple times—by Petitioner and by others." Prelim. Resp. 14.

We have discretion under 35 U.S.C. § 325(d) to reject a petition when the same or substantially the same prior art or arguments were presented previously to the Office. The relevant portions of that statute are reproduced below:

> In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

35 U.S.C. § 325(d). In exercising our discretion under § 325(d), we take into account numerous factors, including the facts of each case, and the burden on the parties and the Board. *See Conopco, Inc. v. Proctor & Gamble Co*., Case IPR2014–00506, slip op. at 4, 6 (PTAB Dec. 10, 2014) (Paper 25) (Informative), slip op. at 6 (PTAB July 7, 2014) (Paper 17), cited in *NVIDIA Corp. v. Samsung Elec. Co*., Case IPR2016–00134, slip op. at 6–

7 (PTAB May 4, 2016) (Paper 9); *see also* Amendments to the Rules of Practice for Trials Before the Patent Trial and Appeal Board, 77 Fed. Reg. 18750, 18759 (Apr. 1, 2016) ("[T]he current rules provide sufficient flexibility to address the unique factual scenarios presented to handle efficiently and fairly related proceedings before the Office on a case-by-case basis, and that the Office will continue to take into account the interests of justice and fairness to both petitioners and patent owners where multiple proceedings involving the same patent claims are before the Office."). We note that while we have the authority to decline to institute review on the basis that the same or substantially the same prior art or arguments were presented previously to the Office, the statute does not require that result.

Although we have discretion to reject a petition when the same or substantially the same prior art or arguments previously were presented to the Office (35 U.S.C. § 325(d)), we decline to exercise that discretion here. Petitioner brings the same challenge presented in IPR2017-01166, but supports the challenge with additional evidence sufficient to demonstrate a reasonable likelihood that it would prevail with respect to the challenged claim. That is, while the panel in IPR2017-01166 was divided on the issue as to whether Petitioner presented sufficient information to demonstrate that the FDA approved drug label for Patent Owner's drug Rituxan was publically accessible as of the effective filing date of August 11, 1999, no such division exists here in view of the present record.

With regard to the petitions previously filed by Boehringer and Celltrion, we agree with Patent Owner that McNeil, Rituxan Label, and Maloney have been previously presented, and therefore similarities exists

among the respective petitions. Prelim. Resp. 19. As Patent Owner recognizes, however, Hochster I has not been previously presented and we are not persuaded by Patent Owner's argument that "Petitioner relies on [Hochster I] for a teaching that is cumulative of art previously considered and rejected by the Board." *Id.* at 20. Petitioner presents a distinct combination of references and supporting arguments. As we discuss in Section II.E., above, we find that argument persuasive on the current record and, thus, determine that Petitioner has established a reasonable likelihood of prevailing in showing the unpatentability of claim 1.

As Petitioner has presented a new arguments regarding the patentability of the challenged claim, and such argument contributes to our determination that Petitioner in this proceeding has established a reasonable likelihood of prevailing in showing the unpatentability of that claim, we decline to exercise our discretion to deny the Petition.

G. Discretionary Denial under 35 U.S.C. § 314(a)

Patent Owner requests that we deny institution of trial under 35 U.S.C. § 314(a), pursuant to the doctrine of *General Plastic Industries Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential), in view of the previously filed petition by the same petitioner, identified in Section I.A hereinabove. Prelim. Resp. 22–30.

In *General Plastic*, the Board identified seven nonexclusive factors that bear on the issue of whether the Board should invoke its discretion to deny institution of an *inter partes* review, based on a follow-on petition on the same patent, under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(a):

1. Whether the same petitioner previously filed a petition directed to

the same claims of the same patent;

2. Whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;

3. Whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;

4. The length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;

5. Whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;

6. The finite resources of the Board; and

7. The requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

General Plastic, slip. op. at 15–16 (citing *NVIDIA Corp. v. Samsung Elec.* Co., IPR2016-00134, slip op. 6–7 (PTAB May 4, 2016) (Paper 9)). In applying these factors, we consider not only the congressional intent that *inter partes* review proceedings provide an effective and efficient alternative to district court litigation, but also the potential for abuse of the review process through repeated attacks by the same petitioner with respect to the same patent. *See Gen. Plastic*, slip. op. at 17–18n.14 (citing H.R. Rep. No. 112-98, pt. 1, at 48 (2011) ("Allowing similar, serial challenges to the same patent, by the same petitioner, risks harassment of patent owners and frustration of Congress's intent in enacting the Leahy-Smith America Invents Act"). As *General Plastic* recognizes, however, "there may be

circumstances where multiple petitions by the same petitioner against the same claims of a patent should be permitted, and that such a determination is dependent on the facts at issue in the case." *General Plastic*, slip op. at 18. In particular, the factors outlined in *General Plastic* are "a non-exhaustive list of factors," and "additional factors may arise in other cases for consideration, where appropriate." *Id.* at 16, 18.

Patent Owner contends the *General Plastic* factors support denial of the Petition. Prelim. Resp. 19–22. For example, Patent Owner argues that "Petitioner has used the Board's prior non-institution decision as a roadmap" to provide the Board with additional evidence to support Petitioner's contention that the Rituxan Label was publicly accessible so as to qualify as a printed publication in this *inter partes* review. *Id.* at 24.

Petitioner argues that the present Petition should not be rejected as an improper "follow-on" petition "[b]ecause the previous decision had not reached the merits of the petitioner's challenge" and because this second petition is filed "solely to cure the perceived procedural deficiencies raised by the decision denying institution of the first petition." Pet. 11–12 (citing *Panduit Corp. v. CCS Tech., Inc.*, IPR2017-01323, Paper 8 at 8–9 (Nov. 8, 2017)).

Having considered the factors outlined above in light of the particular circumstances of this case, we are not persuaded that we should exercise our discretion to deny the petition. The petition in IPR2017-01166 sets forth a single obviousness ground that relied in part on a 1997 version of the Rituxan label obtained from a government website close in time to when that petition was filed. IPR2017-01166, Paper 2, 6. As Petitioner correctly

notes, the Decision on Institution in IPR2017-01166 denied institution because the majority, in a divided panel, determined that Petitioner "failed to establish sufficiently in the Petition that the Rituxan Label was publically accessible." IPR2017-01166, Paper 9, 17. Because the Rituxan Label was not shown to have been a printed publication, institution was denied. *Id.* In reaching that decision, however, the sole claim of the'172 Patent was not construed and there was no discussion regarding the application of the asserted prior art to claim 1—that is, the majority in IPR2017-01166 did not reach those issues. Therefore, the particular facts of this case do not present a situation in which Petitioner is "using our decisions as a roadmap" regarding those issues. *See General Plastic*, slip op. at 17. Insofar, as Petitioner may be viewed as using our prior decision as a roadmap regarding an issue with the printed publication status of the Rituxan Label, we determine that such use was limited and in a manner that does not prompt us to deny the Petition based upon our consideration of the facts at issue in this case, as a whole.

III. CONCLUSION

After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that claim 1 of the '172 patent is unpatentable.

At this preliminary stage in the proceeding, we have not made a final determination with respect to the patentability of any challenged claim or the construction of any claim term. Any findings of fact and conclusions of law made herein are not final, but are made for the sole purpose of determining

whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner. Any arguments not raised by Patent Owner in a timely-filed response shall be deemed waived, even if they were presented in the Preliminary Response.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claim 1 of U.S. Patent No. 8,329,172 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '172 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Case IPR2018-00285
Patent 8,329,172 B2

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge, dissenting.*

I agree with the majority's analysis of the challenged claim and asserted grounds of unpatentability. I also recognize that the application of 35 U.S.C. § 314(a) to deny institution of *inter partes* review is discretionary, and appreciate the majority's thoughtful reasoning in declining to exercise that discretion. In my view, however, Petitioner's use of our decision denying institution of its original challenge to the '172 patent as a roadmap

in formulating the current Petition warrants the exercise of our discretion under § 314(a) not to institute *inter partes* review. Accordingly, I respectfully dissent.

This marks the fourth petition for *inter partes* review of the '172 patent filed with the Board, and the second brought by Petitioner. Pet. 7–8. Petitioner indicates that it filed the instant Petition, which is "substantially the same" as its original petition, "solely to cure the perceived procedural deficiencies raised by the decision denying institution of the first petition." Pet. 12. Petitioner also grants that it was aware of the references added to the asserted grounds of unpatentability in the second petition prior to filing its original petition. *Id.* at 13.

In essence, Petitioner acknowledges that it used our decision denying institution of its first petition as a guide in formulating its second. Pet. 12–13. According to Petitioner, however, such reliance is justified by the fact that the decision denying institution of the first petition addressed only the purportedly "procedural" issue of the prior art status of an asserted reference, and, thus, cannot be said to have provided a "roadmap" to our thinking on the merits of the case. *Id.* at 11–12. I do not agree.

Whether a reference qualifies as a printed publication is a statutory requirement that goes to the heart of our patentability analysis. *See* 35 U.S.C. § 311(b) ("A petitioner in an inter partes review may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications."); pre-AIA 35 U.S.C. § 102(b) ("[a] person shall be entitled to a patent unless . . . the invention was

patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States"). This "involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004).

Because a reference cannot render the challenged claims unpatentable unless it is truly prior art, we have often required a petitioner to make a threshold showing that the reference relied upon was publicly accessible as a printed publication prior to the effective filing date of the challenged patent. *See, e.g.*, *Mylan Pharms. v. Boehringer Ingelheim Int'l GmbH*, Case IPR2016-01566, slip op. at 10–12 (PTAB Feb. 3, 2017) (Paper 15) (finding that purported "printed package insert" was not a printed publication); *Frontier Therapeutics, LLC v. Medac Gesellschaft Fur Klinische Spezialpraparate MBH*, Case IPR2016-00649, slip op. at 22 (PTAB Sept. 1, 2016) (Paper 10) (same). Our analysis of the printed publication status of a reference at institution will often require substantive consideration of the facts concerning dissemination and public accessibility of that reference—as it did here. In this vein, I do not find persuasive Petitioner's contention that the arguments modified, and the alternative versions of the previously rejected reference now proffered, constitute fixes of mere "procedural deficiencies" from one petition to the next. To the contrary, these changes go directly to the merits of whether Petitioner has carried its burden to demonstrate a reasonable likelihood of success in establishing that the challenged claim is obvious over the prior art of record.

Irrespective of how the analysis is classified, where, as here, a petitioner takes a second bite at the apple by using our prior decision as a roadmap to remedy its deficient printed publication arguments through refining its contentions and incorporating substitute references long in its possession, the exercise of 314(a) discretion is, in my view, appropriate. *See Butamax Advanced Biofuels LLC v. Gevo*, Case IPR2014–00581, slip op. at 12–13 (PTAB Oct. 14, 2014) (Paper 8) ("[T]he four obviousness grounds are 'second bites at the apple,' which use our prior decision as a roadmap to remedy Butamax's prior, deficient challenge. Allowing similar, serial challenges to the same patent, by the same petitioner, risks harassment of patent owners and frustration of Congress's intent in enacting the Leahy-Smith America Invents Act.").

General Plastic expressly recognizes that follow-on petitions have the potential to inflict "undue inequities and prejudices" on Patent Owners, and flags "shifts in the prior art asserted and related arguments in follow-on petitions" as being of particular concern. *Gen. Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha*, Case IPR2016–01357, slip op. at 17 (PTAB Sept. 6, 2017) (Paper 19) (precedential-in-part). Given the centrality of the printed publication analysis to the ultimate success of its patentability challenges, in my view, Petitioner's use of our decision denying institution of its original petition as a guide for shifting the prior art asserted and related arguments concerning public accessibility implicates the very concerns the *General Plastic* factors were designed to address.

Accordingly, because Petitioner: (a) had previously filed a petition directed to the sole claim of the '172 patent; (b) knew of each of the

instantly asserted references at the time that original petition was filed; (c) had the benefit of both Patent Owner's preliminary response and our decision denying institution in IPR2017-01166 prior to filing in the instant Petition; and (d) has not, to my mind, provided adequate explanation for its failure to marshal support in its original petition sufficient to make a threshold showing that the Rituxan label qualifies as a printed publication, I would have exercised discretion under § 314(a) not to institute *inter partes* review. *See Gen. Plastic*, Case IPR2016-01357, slip op. at 16 (Paper 19) (setting forth a "non-exhaustive list of factors . . . in evaluating follow-on petitions"). As such, I respectfully dissent.

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