UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.
Petitioner,

v.

BIOGEN, INC.
Patent Owner.

Case IPR2017-01166
U.S. Patent No. 8,329,172

PATENT OWNER PRELIMINARY RESPONSE

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I. INTRODUCTION

Petitioner Pfizer, Inc. repeats arguments already considered and rejected by the Board in an earlier petition for *inter partes* review (IPR2015-00418) of the same patent, U.S. Pat. 8,329,172 (the "'172 patent"). Two of the three references in the sole ground advanced by Petitioner here were previously considered by the Board and found inadequate to support an obviousness challenge—even under the "reasonable likelihood of prevailing" standard. And the additional reference cited by Petitioner here, Hochster I, contains teachings that are cumulative of the other art and arguments previously considered by the Board. Petitioner identifies nothing here that warrants a different outcome. The Board should again deny *inter partes* review.

Petitioner's challenge fails because none of the cited references teaches material limitations of the claim, including (i) "CVP therapy to which the patient responds," (ii) "four weekly doses of 375 mg/m^2" as maintenance therapy; and (iii) administration of rituximab "every six months for two years" for low-grade lymphoma (LG-NHL).

Attempting to fill these gaps, Petitioner merely pieces together disparate portions of different references for each claim element using impermissible hindsight, and fails to establish that a POSA would have combined such references, or would have had a reasonable expectation of success in doing so.

Petitioner asserts, for example, that a POSA would have used four weekly rituximab infusions of 375 mg/m^2 ("4 x 375 mg/m^2") as maintenance for complete or partial responders to chemotherapy with no relapsed disease because that was the only rituximab regimen that the FDA had approved. But the FDA approved that dosing regimen only for ***relapsed or refractory*** patients. The patients claimed in the '172 patent are ***neither*** relapsed nor refractory. Rather they are partial or complete responders to prior chemotherapy who have not relapsed. The Board previously held there was inadequate evidence showing that a POSA supposedly would have been encouraged to use the 4 x 375 mg/m^2 regimen in a patient population distinct from that described in the FDA-approved indication. *See* Ex. 2001, 024 ("Petitioner has not adequately explained why an ordinary artisan would have been prompted to modify McNeil's [maintenance] process according to the teachings of the Rituxan® Label [for relapsed disease] … to arrive at the process recited in claim 1 of the '172 patent."). Petitioner here offers no new evidence that warrants a different outcome.

If anything, a POSA would have used a lower dose of rituximab for the patient population claimed in the '172 patent. Rituxan® was approved for use at a specific dose to treat relapsed or refractory patients, who have higher tumor burdens because they did not achieve partial or complete responses to prior

therapy, or if they did, they subsequently relapsed.[1] The patients claimed in the '172 patent, by contrast, have lower tumor burdens because they have achieved such responses and have not relapsed. A POSA would therefore have believed that if rituximab was going to be used for maintenance as claimed in the '172 patent, then a dose of rituximab ***lower*** than the 4 x 375 mg/m^2 dose for relapsed or refractory patients should be used (either by giving fewer infusions or less drug per infusion).

Petitioner further argues that a POSA would have administered to the claimed patient population—people with low-grade lymphoma—a maintenance dosing schedule (every six months for two years) being studied in "a different patient population": elderly patients with ***intermediate-grade*** lymphoma (IG-NHL), as reported by McNeil.[2] *See* Ex. 2001, 021 (recognizing that patients with IG-NHL and LG-NHL were different populations). But that dosing schedule for intermediate-grade lymphoma was not even reported to be successful. And even if it had been, Petitioner provides no new evidence that should alter the

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[1] Refractory patients are those who had been resistant to prior chemotherapy.

[2] "[I]ntermediate- or high-grade lymphomas…[are] referred to as the aggressive lymphomas to distinguish them from the indolent or low-grade histologies." Ex. 1013, 010.

Board's prior finding that disclosures related to intermediate-grade lymphomas do not apply to low-grade lymphoma, or vice versa. *See, e.g.*, *id.* ("Petitioner does not persuade us that an ordinary artisan would have been prompted to modify McNeil's treatment of patients with intermediate grade NHL to instead treat the LG-NHL required by claim 1 of the '172 patent.").

In fact, both Petitioner and its expert admit that "the success or failure of a regimen in the context of intermediate-grade NHL ***says nothing*** about its success or failure in the context of LG-NHL, which is a different disease." Pet. 42; *see also* Ex. 1002 ¶ 103 ("[T]he success or failure of a particular regimen in the context of treating intermediate-grade NHL does not imply that the same result will occur in treating LG-NHL, which is a different disease.").[3]

The Board's prior holding, and Petitioner's admission, reflect the only plausible conclusion on this record: a POSA would not look to McNeil's dosing schedule for IG-NHL patients when addressing the LG-NHL patients studied in Hochster I. The Board should reach the same holding it did last time and deny institution.

[3] Emphasis is added to quotes unless otherwise noted.

II. BACKGROUND

A. Technical Overview Of The Invention

The sole claim of the '172 patent is narrowly directed to the treatment of low-grade non-Hodgkin's lymphoma with CVP therapy to which the patient responds, followed by rituximab maintenance therapy given as four weekly doses of 375 mg/m^2 every six months for two years. Ex. 1001, 22:57-64.[4]

1. Non-Hodgkin's Lymphomas (NHL)

Although sometimes referred to in the singular form, NHL "is not a single disease but a diverse group of diseases ranging from the very aggressive and rapidly fatal to the more indolent." Ex. 2002, 004; *see also* Ex. 1002 ¶ 33 ("[T]here is not one singular kind of lymphoma. Each lymphoma has its own distinct genetic, immunologic, and molecular characteristics."). "Low-grade lymphoma usually presents as a nodal disease, and is often indolent or slow-growing," whereas "[i]ntermediate and high-grade disease usually presents as a much more aggressive disease." Ex. 1001, 4:49-52.

As the Board previously found, teachings in the prior art related to intermediate-grade lymphoma, an aggressive lymphoma, do not necessarily apply to low-grade lymphoma, an indolent lymphoma. *See, e.g.*, Ex. 2001, 018

[4] CVP, as the Board previously recognized, "is a combination of the drugs cyclophosphamide, vincristine, and prednisone." Ex. 2001, 005.

("Petitioner does not persuade us that it has explained adequately why an ordinary artisan would have been encouraged to use rituximab maintenance therapy in a ***patient population distinct*** from that described in McNeil.") (emphasis added). This is because the type of lymphoma is "the major determinant[] for treatment outcome and prognosis" as the diseases differ "in sensitivity to…chemotherapy." *See* Ex. 2003, 001-2; *see also* Ex. 1002 ¶ 34 ("One of the central determining factors for a patient's prognosis as of August 1999 was the patient's 'grade' of lymphoma: low, intermediate, or high. Ex. 1015, Skarin at 1-3.").

Low-grade NHL is a deadly cancer that is "low-grade" in name only. The term "low-grade" in NHL refers to the speed with which the disease progresses, not its severity. At the time of the invention, a diagnosis of LG-NHL meant a very poor prognosis because the disease was (and still is) a chronic, incurable cancer. "'LG-NHL is characterized by 'a pattern of continuing relapse with RFS [i.e., relapse-free survival] of only 2 to 3 years' following chemotherapy." Ex. 1002, ¶ 39, citing Ex. 1010, 007. In contrast, patients with intermediate-grade NHL were frequently cured by first-line therapy (and therefore did not relapse). *See* Ex. 2003, 002 ("[H]igh-grade lymphomas of all stages are generally treated with curative intention, final disease eradication cannot be achieved in low-grade lymphomas."); Ex. 1013, 010 ("Most patients with intermediate- or high-grade lymphomas who achieve a complete remission with therapy may be cured.").

2. Treatment Of Low-Grade NHL And Intermediate-Grade NHL Differed

Traditionally, the type of lymphoma from which a patient suffered dictated the chemotherapeutic regimen used. Most chemotherapy regimens used for low-grade NHL were not used for intermediate-grade NHL, and vice versa. *Compare* Ex. 1013, 009, Table 111-7 (listing chemotherapy used for low-grade lymphoma) *with id.*, 011, Table 111-8 (listing chemotherapy used for intermediate-grade lymphomas).[5] Petitioner's expert similarly acknowledges that "[g]iven these important differences [between IG-NHL and LG-NHL], treatments for different types of lymphomas were markedly different." Ex. 1002 ¶ 34.

As Petitioner admits, because of the differences between LG-NHL and IG-NHL, "the success or failure of a regimen in the context of intermediate-grade NHL ***says nothing*** about its success or failure in the context of LG-NHL, which is a different disease." Pet. 42. Petitioner expert similarly concedes that "the success or failure of a particular regimen in the context of treating intermediate-grade NHL does not imply that the same result will occur in treating LG-NHL, which is a different disease." Ex. 1002 ¶ 103.

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[5] CHOP chemotherapy (a chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone) was an exception, as it was used for both.

3. Maintenance Therapy For LG-NHL

At the time of the invention, there was a significant unmet medical need for effective maintenance therapy to maintain remission and prevent relapse of LG-NHL. Standard chemotherapeutic agents, such as the combination regimen BCVP,[6] that were successful as induction therapies[7] were not successful as maintenance therapies. *See* Section V.B.1. Similarly, biologic drugs, such as interferon, that had been tried as maintenance therapy were unsuccessful. ***Id.*** Petitioner attempts to argue otherwise, citing clinical studies where chemotherapy and interferon maintenance therapy were given. For a variety of reasons, discussed in Section V.B.1, these studies did not show that maintenance therapy was beneficial.

Due to failed efforts to develop successful maintenance therapy for LG-NHL, "[m]aintenance therapy [was] rarely employed in non-Hodgkin's lymphoma once a clinical complete response has been obtained." Ex. 2004, 008.

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[6] BCVP is a combination chemotherapy regimen consisting of BCNU (a.k.a, carmustine), cyclophosphamide, vincristine, and prednisone.

[7] Induction therapy is treatment given to induce an initial response. Maintenance therapy, as the Board previously recognized, is given to maintain that response and prevent relapse. *See* Ex. 2001, 006.

The result was frequent recurrence of the low-grade lymphoma, *i.e.*, "relapse," after initial responses to chemotherapy.

4. Rituximab

Rituximab, the first monoclonal antibody approved to treat cancer, binds to the CD20 antigen on B-cells, facilitating their destruction. *See* Ex. 1001, 1:47-50, 5:35-43. Most B-cell lymphomas express CD20. *Id.* at 1:27-41. A known danger of multiple treatments with rituximab, however, was antigen escape, whereby cancerous B cells would develop resistance by losing expression of CD20. *See* Section V.B.2 below.

By the priority date, the FDA had approved rituximab as monotherapy to treat relapsed or refractory, low-grade NHL. *Id.*, 1:47-50.

B. Prosecution History

During examination, the Patent Office issued a restriction requirement compelling Patent Owner "to elect a particular form of NHL" because the different types of NHL are patentably distinct. *See* Ex. 2005, 003. The Office also compelled Patent Owner to elect "a specific chemotherapy protocol" to be paired with rituximab maintenance therapy because the different chemotherapy regimens are "patentably distinct species." *Id*. Patent Owner elected LG-NHL and CVP chemotherapy. Ex. 2006, 008.

Petitioner's present attempt to challenge patentability by equating McNeil's intermediate-grade NHL with Hochster's low-grade NHL, and equating McNeil's CHOP therapy with Hochster's CVP therapy, contradicts the Office's correct view that skilled artisans viewed these cancers and chemotherapies as significantly different.

C. Previous IPR Proceedings

Boehringer Ingelheim filed an IPR petition against the '172 patent (IPR2015-00418) in December 2014. In that petition, Boehringer raised grounds for invalidity substantially similar to those now argued by Petitioner. In particular, Boehringer relied on the McNeil news article (Ex. 1003), which reported on an ongoing clinical study using rituximab maintenance following CHOP induction therapy in elderly patients with intermediate-grade NHL. Boehringer argued that McNeil, in combination with the Rituxan® label and other references, rendered the '172 patent claim obvious. Petitioner now raises a cumulative argument in the single Ground of this proceeding.

The Board denied institution of Boehringer's petition on all grounds, finding that Boehringer failed to show that skilled artisans would (1) "modify McNeil's treatment of patients with intermediate grade NHL to instead treat the LG-NHL," (2) "modify McNeil's CHOP treatment to instead use the CVP treatment," (3) apply the Rituxan Label's dosage for relapsed disease to the maintenance therapy

setting, and (4) believe that alleged success with interferon maintenance therapy indicates that rituximab maintenance therapy would be successful. Ex. 2001, 021. The Board's decision is further discussed below in the applicable sections of this preliminary response.

III. CLAIM CONSTRUCTION

A. "chemotherapy consisting of CVP therapy"

Patent owner agrees with the Board's prior construction of this term, "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. 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." Ex. 2001, 005.

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

Patent owner agrees with the Board's prior construction of this term to mean that the patient must have experienced a complete or partial response, as defined by the criteria set forth in the specification:

> [W]e 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").

Ex. 2001, 006.

C. "A method…comprising…[method steps], wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m2 every 6 months, and wherein the maintenance therapy is provided for 2 years"

Petitioner argues that Claim 1 "provides that the 'maintenance therapy comprises' certain steps, it covers methods with additional steps beyond those expressly recited." Pet. 12. Because the Petition does not argue that skilled artisans would have practiced the method encompassing the steps expressly recited in the claim plus additional steps, the Board need not decide whether the word "comprises" covers methods with additional steps beyond those expressly recited.

IV. PETITIONER FAILS TO ESTABLISH THAT EX. 1004 ("THE RITUXAN LABEL") IS A PRINTED PUBLICATION

As the Board recognized in connection with the prior petition, "[t]he Federal Circuit has held that 'public accessibility' is 'the touchstone' in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986)." Ex. 2001, 008. "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." *Id.* (citing *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008)).

To prove that a document is a printed publication, it is not enough merely to assert that the document is an FDA-approved label that was publicly available by a certain date; yet, this is what Petitioner does in its petition for Exhibit 1004.

The Board's decision in *Mylan Pharms. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01566 (Paper 15) (Feb. 3, 2017) is on point. There, the "Petitioner contend[ed] that the Glucophage® Label qualifies as prior art under 35 U.S.C. § 102(b) because it was approved and published by the FDA for treating type 2 diabetes in February 2001." *Id.* at 10. In its decision denying institution, the Board held that the purported label itself, without more, was insufficient to show it was a publicly accessible printed publication. *Id.* at 11. So too here. Exhibit 1004 contains none of the hallmarks of a document published or disseminated prior to the priority date.

Even assuming that Exhibit 1004 contains information consistent with a Rituxan® label, Petitioner has offered ***no*** evidence to show that Exhibit 1004 is a copy of a document publicly disseminated before the priority date. Indeed, Exhibit 1004 actually suggests that it was ***not*** a document that was ever disseminated with vials of Rituxan® or otherwise distributed. Exhibit 1004 bears what appears to be handwriting at the top of the document partially spelling "***Rit***uximab" in vertical orientation. Ex. 1004, 001. It is highly unlikely that a

document with half the product name written in by hand was distributed with Rituxan® drug packages.

That Exhibit 1004 bears a copyright date of 1997 says nothing about whether it was ever actually publicly accessible. Indeed, the Federal Circuit has held that even an official certificate of registration from the Copyright Office does not establish a document as a printed publication. *In re Lister*, 583 F.3d 1307, 1312-13, 1317 (Fed. Cir. 2009).

Simply put, Petitioner's assertion that Ex. 1004 is a "publicly accessible printed publication under 35 U.S.C. § 102(b)" Pet. 26, is a conclusion bereft of competent supporting evidence.

Petitioner relies on the testimony of Scott Bennett, Ph.D., "Managing Partner of the firm Prior Art Documentation LLC," in support of its printed-publication argument. *See* Pet. 24 ("As Dr. Bennett confirms, the Rituxan™ label is available ***today*** from the FDA's website, which represents that it is the original approved label for Rituxan™ as of November 26, 1997."). But all Dr. Bennett's declaration does is parrot the conclusory statements from the petition. *See* Ex. 1016 ¶ 50. Dr. Bennett does not purport to have any knowledge, direct or otherwise, of FDA practices. That Ex. 1004 may be available on the FDA's website today says nothing about whether it was publicly accessible—on an FDA website or otherwise—before the priority date.

Petitioner cites appendices to Dr. Bennett's declaration and Exhibit 1039 to argue that ***the information*** on Exhibit 1004 was known before the priority date. *See* Pet. 24-25.[8] But again, a printed publication is a particular document, not just information. *See* Pre-AIA 35 U.S.C. § 102(a) (distinguishing between "known or used by others" and "printed publication"). The evidence must show that a particular document was "publicly accessible." *SRI Int'l*, 511 F.3d at 1194. It is not enough to merely show that certain information was disseminated or made available in some form or another. *See* 35 U.S.C. § 311(b) ("A petitioner in an inter partes review may request to cancel as unpatentable…***only*** on the basis of prior art consisting of patents or printed publications") (emphasis added).

Petitioner has failed to establish that Exhibit 1004 is a printed publication.

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[8] Attachment 2a (a copy of Exhibit 1004) is not the same document as Attachment 2b (a webpage printout from Wayback Machine). In addition to formatting differences, Attachment 2a bears what appears to be handwriting at the top of the document partially spelling "***Rit***uximab" in vertical orientation, whereas Attachment 2b does not. Analogously, even if "a paper by third-party researchers published in November 1998 lists the Rituxan® label as a reference," as Petitioner contends at page 25 of the Petition, this does not suggest that Exhibit 1004 is a copy of the document that the third-party researchers allegedly reviewed.

V. PETITIONER FAILS TO ESTABLISH THAT THE COMBINATIONS OF REFERENCES IN GROUND 1 RENDER THE CLAIM OBVIOUS

The combination of Hochster I, McNeil, and the Rituxan Label does not render obvious Claim 1 of the '172 patent. Two out of the three documents in the Ground—McNeil and "the Rituxan Label"—were already considered and found unpersuasive in connection with the prior IPR petition. Nothing offered by Petitioner in these proceedings should change the Board's prior analysis and holding.

To prove obviousness, Petitioner must show "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012). "[I]n the unpredictable arts such as medicinal treatment, for a method to be obvious to try, there must be some suggestion in the prior art that the method would have a reasonable likelihood of success." *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016).

A. Petitioner Fails To Establish A Reason To Modify Or Combine The Cited References To Practice The Invention

Petitioner fails to establish a reason to combine the alleged teachings that it cherry-picks from Hochster I, McNeil, and the Rituxan Label to achieve Claim 1 of

the ’172 patent. Specifically, Petitioner fails to prove that a POSA would combine McNeil’s rituximab maintenance dosing scheduling for elderly patients with intermediate-grade NHL following CHOP chemotherapy with Hochster’s distinct patient population—patients with LG-NHL and an unknown age range following a different induction chemotherapy (CVP). As Petitioner concedes, McNeil’s work with intermediate grade NHL patients “says nothing about its success or failure in the context of LG-NHL, which is a different disease,” Pet. 42.

Petitioner further fails to prove that a POSA would use the Rituxan Label’s dosing regimen (4 x 375 mg/m^2) for relapsed or refractory disease as the regimen for maintenance therapy in patients claimed in the ’172 patent—partial or complete responders to prior chemotherapy who have not relapsed. A POSA would have believed that lower doses should be used in the maintenance setting, where the disease burden is lower (or even undetectable) than in the induction setting; consistent with historical practice for chemotherapy regimens.

Petitioner further fails to show that any of its cited references disclose the specific clinical response to CVP therapy required by the ’172 patent claim. As the Board previously recognized, the claim encompasses only patients who have had a complete or partial response as defined by certain clinical criteria in the specification. Neither Petitioner nor its expert explain how these claim limitation is disclosed by the cited art.

1. Hochster I Does Not Disclose Any Dosing Regimen For Using Rituximab Maintenance

Hochster I is an abstract that reports results of a small "Phase I/II" study using the combination of fludarabine and cyclophosphamide (FC) as first-line chemotherapy to treat patients with LG-NHL. Ex. 1005, 005. The results were "promising," and so, the authors proposed "conducting [a] phase III study of CF vs. CVP ± anti-CD20 maintenance with PCP & H-Z prophylaxis (E1496)." *Id.*[9]

Petitioner argues this last sentence indicates that the authors were conducting a study where LG-NHL patients would be assigned to either FC or CVP as induction therapy, followed by rituximab maintenance for a subset of patients. *See* Pet. 1-2. Even if this characterization is accurate, Hochster I fails to provide any disclosure of what dosing regimen and schedule of rituximab would be used as maintenance therapy, and therefore fails to satisfy at least the claim limitation "wherein the maintenance therapy comprises four weekly

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[9] PCP and H-Z are abbreviations for pneumocystis pneumonia and herpes zoster, respectively. The prophylaxis therapy may have been TMP/SMX, an antibiotic regimen, that was added because the FC therapy resulted in infections in Hochster's study. Ex. 1005, 005.

administrations of rituximab at a dose of 375 mg/m^2 every 6 months, and wherein the maintenance therapy is provided for 2 years."

2. The Claimed Schedule Of Giving Rituximab Every Six Month For Two Years As Maintenance Therapy For LG-NHL Was Not Obvious

a. *Skilled Artisans Would Not Have Used McNeil's Rituximab Dosing Schedule In The Patient Population Of Hochster I*

As the Board previously recognized, "McNeil describes a clinical trial for elderly patients with intermediate-grade non-Hodgkin's lymphoma (IG-NHL) in which patients who responded to CHOP chemotherapy, 'the standard chemotherapy for this form of NHL,' were 'assigned to receive [a] maintenance regimen—Rituxan every 6 months for 2 years—or observation.'" Ex. 2001, 015.

Petitioner's primary argument is that skilled artisans would have used this rituximab dosing schedule from McNeil, which treated elderly patients with IG-NHL following CHOP induction chemotherapy, in the Phase III study proposed by Hochster I, which involved a different patient population (patients with low-grade NHL and an unknown age range) following a different induction chemotherapy (CVP). *See* Pet. 39. But neither Petitioner nor its expert provides 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.

(1) ***McNeil's Dosing Schedule Would Not Be Used With The Patient Population Of Hochster Because, As the Board Found and Petitioner Acknowledges, An IG-NHL Dosing Regimen "Says Nothing" About What Would Be An Appropriate Dosing Regimen For LG-NHL Patients***

Petitioner's argument that McNeil's dosing schedule would be combined with the patient population of Hochster I ignores the Board's prior holding that skilled artisans would understand intermediate-grade lymphoma and low-grade lymphoma as different diseases that should be treated differently.

The Board previously rejected—and should reject again–an argument that "an ordinary artisan would have been prompted to modify McNeil's treatment of patients with intermediate grade NHL to instead treat the LG-NHL required by claim 1 of the '172 patent." Ex. 2001, 021; *see also id.*, 014-15 (rejecting the argument that "it would have been obvious to those of ordinary skill to use the protocol described in McNeil to treat LG-NHL"). The Board recognized, and the record shows, that intermediate-grade and low-grade NHL were known to be materially different in disease tumor growth, relapse rate, remission, prognosis, and therapies used to treat.

Significantly, Petitioner and its expert do not dispute any of this; in fact Petitioner concedes that "the success or failure of a regimen in the context of intermediate-grade NHL ***says nothing*** about its success or failure in the context of

LG-NHL, which is a different disease." Pet. 42 (citing and endorsing the Board's prior decision articulating the same). Petitioner's expert similarly states that "the success or failure of a particular regimen in the context of treating intermediate-grade NHL ***does not imply that the same result will occur*** in treating LG-NHL, which is a different disease." Ex. 1002 ¶ 103.

Petitioner's expert further acknowledges that "[o]ne of the central determining factors for a patient's prognosis as of August 1999 was the patient's 'grade' of lymphoma: low, intermediate, or high." Ex. 1002 ¶ 34. Low-grade NHL tumors grow more slowly than intermediate-grade NHL. *Id.* ("Low-grade lymphomas (also called 'indolent' lymphomas), unlike intermediate- and high-grade lymphomas, grow more slowly. Intermediate- and high-grade NHL patients were considered to have an 'aggressive' form of NHL marked by rapidly growing tumorous cells."). But IG-NHL patients, unlike LG-NHL patients, were "frequently curable." *Id.* Petitioner's expert indeed concedes that "[g]iven these important differences [between IG-NHL and LG-NHL], treatments for different types of lymphomas were ***markedly different***." Ex. 1002 ¶ 34; *see also comparison of* Ex. 1013, 009, Table 111-7 (chemotherapy regimens used with low-grade NHL) *with id.*, 031, Table 111-8 (chemotherapy regimens used with intermediate-grade NHL).

Relevant art at the time showed that POSAs knew that intermediate-grade NHL and low-grade NHL responded differently to drug treatment. *See, e.g.*, Ex. 2009, 001 ("Patients with nodular histology [usually low-grade] have a significantly better response rate . . . than those with the corresponding diffuse [usually intermediate- and high-grade] involvement[.]"); Ex. 2003, 001 ("Non-Hodgkin's lymphomas…differ…in sensitivity to currently available chemotherapy…."). A POSA knew that even with an initial response to chemotherapy, relapses occurred sooner but were exceedingly less common with intermediate-grade NHL than with low-grade NHL. *See* Ex. 2009, 001 (finding that "[p]atients with diffuse histiocytic lymphoma [*e.g.*, IG-NHL lymphoma] demonstrated the highest rate of relapse during the first year of follow up, but late recurrence was uncommon;" "[i]n contrast, the combined nodular histologic groups [*i.e.*, low-grade lymphoma]...demonstrated a pattern of continued relapse from remission over a 6-year period of follow up").

Most patients with intermediate-grade NHL were cured with chemotherapy and therefore did not relapse. *See, e.g.,* Ex. 1013, 010 ("Most patients with intermediate- or high-grade lymphomas who achieve a complete remission with therapy may be cured."); Ex. 2010, 001 (finding that 76% of "patients with diffuse intermediate-grade lymphoma" achieve CR and "overall risk of late relapse of those who attained CR was 6.8%."). In contrast, almost all patients with low-grade

NHL continuously relapsed until succumbing to the disease. *See, e.g.*, Ex. 2003, 002 ("[F]inal disease eradication cannot be achieved in low-grade lymphomas…."); Ex. 2027, 002 ("Relapse [] is the rule" for low-grade lymphoma.); Ex. 2002, 004 ("[R]elapse rate remains high" for "low-grade lymphoma.").

Federal Circuit precedent makes clear that absent a sufficient connection between disparate patient populations, prior art disclosing a drug regimen in one patient population does not render obvious a patent claiming the same regimen in a different patient population. In *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329 (Fed. Cir. 2010), for example, the infringer argued that because the prior art suggested that the drug at issue could be used in one setting, autoimmune disorders, it would have been obvious to use it in another setting, osteoporosis. *Id.* at 1338. The court rejected this argument because the infringer "was not able to show a credible connection between the" two different settings. *Id.* Similarly, in *American Hospital Supply Corp. v. Travenol Labs., Inc.*, 745 F.2d 1 (Fed. Cir. 1984), the prior art was "directed to providing adequate nutritional support [using an amino acid product] to patients." *Id.* at 7. The claimed method at issue, however, was limited to a narrower subset of patients: those with liver disease. The court held that the claim was not obvious because it was "directed to a different class of users with specific unique nutritional problems." *Id.*

So too here.

Hochster I proposes treating patients with low-grade NHL, a type of lymphoma that is not curable and is characterized by constant relapse. McNeil discloses a rituximab dosing schedule for a different set of patients, elderly patients with intermediate-grade NHL (a curable disease). These are different diseases in different patient populations understood to require different treatments. The above evidence, the Board's prior holding, and Petitioner's admission lead to the only plausible conclusion supported by the record: a POSA would not have combined McNeil with Hochster I, or otherwise looked to McNeil's disclosure of a maintenance regimen, when addressing LG-NHL.

(2) ***McNeil's Rituximab Dosing Regimen Was Designed For Elderly Patients, Not The General Population In Hochster I***

In arguing that McNeil's dosing regimen would have been used in Hochster I's patients, Petitioner also fails to consider that the patient population in the McNeil article was distinct—it enrolled only elderly patients with IG-NHL. Hochster I, on the other hand, does not restrict its study to any particular age group, and therefore would have used a maintenance regimen that could be applied to the general population with LG-NHL.

Skilled artisans knew that cancer regimens were frequently different for elderly patients, such as those studied in McNeil, as compared with the general

population. Elderly patients are more susceptible to the toxicities associated with therapy, Ex. 1003, 003 ("CHOP…[and] some other chemotherapy regimens [are known to be] more toxic in this age group."), and as a result, usually were treated with fewer cycles of therapy than younger patients. *Id.*

Elderly patients also "have changes in liver and kidney functions that may alter drug metabolism; moreover, they have a reduced bone marrow reserve and may have metabolic and cardiovascular diseases." Ex. 2031, 010. "As a consequence, because toxicity may be enhanced, many physicians believe that elderly patients are unable to withstand intensive chemotherapy." *Id.* Consequently, physicians devised treatment regimens where "drug doses are reduced or scheduled less frequently." Ex. 2032, 003.

Elderly patients with lymphoma who responded to induction therapy were also known to "have a higher relapse rate" than younger patients for unknown reasons. Ex. 1003, 002. This too would impact how maintenance therapy would be scheduled.

But neither Petitioner nor its expert provides any underlying scientific or clinical rationale why skilled artisans would use McNeil's rituximab dosing regimen for the Hochster I study despite differences in lymphoma type and patient age. Petitioner's ground for challenge therefore fails.

(3) *McNeil's Rituximab Dosing Schedule Was Used With CHOP Induction, Not With The CVP and FC Induction Used In Hochster I*

Petitioner's conclusory assumption that McNeil's rituximab dosing schedule would be used in Hochster I's study also ignores the fact that different induction chemotherapies were used. CHOP was used in McNeil, while FC or CVP were used in Hochster I. *See* Ex. 1003, 001; Ex. 1005, 005. Neither Petitioner nor its expert offer any analysis concerning how the difference in chemotherapy induction would impact what dosing regimen for rituximab should be given.

This is especially troublesome considering that rituximab was known to be synergistic with doxorubicin, which is a component of CHOP but not of FC or CVP. *See* Ex. 2025, 002 ("The rationale[s] for combination of IDEC-C2B8 [rituximab] with CHOP" was "known synergy with doxorubicin."); Ex. 2023, 001 ("The standard CHOP regimen...was chosen for combination therapy with rituximab because...there is evidence of in vitro synergy between the antibody and doxorubicin."). In the context of chemotherapy combinations, synergy between agents can lead to reduced drug doses. *See, e.g.*, Ex. 2040, 002 (explaining that "synergistic combination[s] . . . could result in reduced drug doses compared with the doses for each drug alone."); Ex. 2036, 001 (explaining that because "[s]orafenib and metformin synergistically decreased the proliferation of [thyroid cancer] cell lines…, [a] combined treatment enabled a significant dose reduction of

sorafenib"); Ex. 2037, 001 (explaining that "[t]riptolide prodrug synergizes with reduced dose standard of care (gemcitabine and nab-paclitaxel) and helps in reducing the doses of these [standard of care] toxic drugs").

Because of this known synergy between rituximab and CHOP (but not CVP), skilled artisans may not have used the same rituximab dosing regimen for CHOP induction (McNeil) and CVP induction (Hochster I).

b. *It Was Not Obvious To Give Rituximab Every Six Months As Maintenance Therapy To LG-NHL Patients*

Petitioner also argues that even without McNeil, skilled artisans would have known that rituximab maintenance should be given every six months for two years, as required by the '172 patent claim. This argument, as the prior Board decision recognized, is based on pure hindsight and post-priority-date explanations of how the claimed dosing regimen was designed.

Petitioner argues that skilled artisans would have known to give rituximab every six months because it was "known that 'B-cell recovery began at approximately six months following completion of treatment.'" Pet. 18-19 (citing Ex. 1006, McLaughlin). But this argument does not withstand scrutiny. First, the 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. Moreover, the claimed six-month interval between doses of rituximab refers to the spacing between repeated maintenance doses, not the spacing between induction therapy and maintenance therapy.

Second, Petitioner's citation relies on the B-cell recovery data for ***normal*** B cells, not cancerous ones. Ex. 1004, 1 (reporting also that "Median B-cell levels returned to normal by twelve months following completion of treatment."). In this study, cancerous B cells did not repopulate until ***13 months*** after treatment with rituximab. Ex. 1006, 001 ("[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.

Petitioner fails to provide an adequate explanation because it is relying on improper hindsight. As Petitioner implicitly concedes in a footnote, its argument is based on a later publication in 2009 explaining why "Patent Owner selected a six-month frequency of rituximab maintenance" Pet. 40, fn. 4, citing Ex. 1029, 006 (a 2009 publication explaining that "[t]he maintenance schedule devised for E1496 was based on the observed time to B-cell recovery with rituximab monotherapy."). In the prior IPR petition, the Board rejected this very argument about B-cell recovery time, holding that Section "103(a) states expressly that '[p]atentability

shall not be negatived by the manner in which the invention was made' and that the argument based on "B-cell depletion observed….appears to be based on improper hindsight." Ex. 2001, 031-32.

Petitioner also argues skilled artisans would have given rituximab maintenance every six months because "it was known that '[r]ituximab was detectable in the serum of patients three to six months after completion of treatment.'" Pet. 18 (citing Ex. 1004, 1). But this argument also lacks merit. If the range of detectability is "three to six months," and assuming a POSA would use drug detectability to design a maintenance schedule, then a POSA would have chosen to administer rituximab every ***three*** months, not every ***six*** months, so that the maintenance dosing regimen could benefit everyone, including patients whose rituximab blood levels drop more quickly. 1-2, 7-9, 13-18,

In any event, a POSA would ***not*** have designed a maintenance schedule based on drug detectability. For example, in Petitioner's own reference Ex. 1010, the drug chlorambucil was given as maintenance therapy "daily for 14 days ***every 4 weeks***." Ex. 1010, 004. But chlorambucil has a "terminal half-life" of "1.5 hours," Ex. 2041, 006, meaning that the drug level drops to nearly undetectable (less than

half of a percent) after only half a day.[10] If Petitioner's drug detectability logic were correct, chlorambucil maintenance therapy would have to be administered twice a day. Similarly, in another reference cited by Petitioner, the drug combination CVP was given as maintenance therapy "every 3 months." Ex. 1025, 002. Again, based on terminal half-lives of the drugs in CVP, even the one drug with the longest half-life (vincristine), levels drop to nearly undetectable levels after less than a month.[11] Petitioner and its expert provide no reason why skilled artisans would be motivated to design a rituximab maintenance schedule of every

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[10] Terminal half-life refers to the time by which one-half of the prior plasma level of drug remains as a result of metabolism and excretion. Thus, for chlorambucil one-half the level of drug remains 1.5 hours after dosing. After another 1.5 hours, that amount drops by half again (i.e., to a quarter of the original level. And so on. In a 12-hour half day there are thus eight half-lives (1.5-hour periods) for chlorambucil. Accordingly, the percent of a chlorambucil dose remaining in the body after half a day is calculated as follows: 100% x 0.5 ^ (8) = 0.4%

[11] Cyclophosphamide has a "half-life of 3 to 12 hours." Ex. 2041, 003. Vincristine has a terminal half-life of "85 hours." *Id.* at 10. Prednisone has a half-life of 3.4 to 3.8 hours. Ex. 2030, 001.

six months based on drug detectability when the only evidence suggests the contrary.

c. *It Was Not Obvious To Give Rituximab For Two Years As Maintenance Therapy*

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. *Id.* ¶¶ 93–99." Pet 3. 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.

Petitioner alleges that skilled artisans would have believed that giving rituximab every six months would prevent any normal "B-cell recovery." *See* Pet. 18-19 (alleging that it was "known that 'B-cell recovery began at approximately six months following completion of [rituximab] treatment"). If that is true, then Petitioner is alleging that skill artisans would have thought that giving 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. Petitioner fails to explain why a POSA would be motivated to give rituximab every six months for two years given the safety risks involved.

The risk of infection would have been especially concerning in the context of chemotherapy induction followed by maintenance therapy, as most chemotherapy regimens, including FC and CVP, have risk of fatal infections. Hochster I, for example, reported that half of the first eight patients treated in its phase I/II study developed infections. Ex. 1005, 005. Petitioner never even addresses this issue, much less offers an explanation why, prior to the invention, POSAs would have believed it safe or advisable to deplete a patient's B-cells for more than two years.

3. Petitioner Fails To Establish That A POSA Would Have Used Four Weekly Doses Of 375 mg/m^2 As Maintenance Therapy

a. *A POSA Would Not Have Used A Dose Of Rituximab Approved For Relapsed Or Refractory Patients, Who Have Higher Tumor Burdens, As Maintenance Therapy For Patients With Lower Tumor Burdens.*

As discussed, Hochster I fails to provide any dosing regimen for rituximab. McNeil states that the maintenance regimen studied in elderly patients with IG-NHL was "Rituxan every 6 months for 2 years," Ex. 1003, 001, but there is no disclosure that each dosing regimen given every 6 months should be ***four weekly doses of 375 mg/m^2***, as required by the '172 patent claim. Indeed, the natural

reading of "Rituxan every 6 months for 2 years" would suggest that a single dose of Rituxan is given every 6 months, not four weekly doses.

With little analysis, Petitioner cites Exhibit 1004 (the "Rituxan Label") in an effort to fill the holes in Hochster I and McNeil. Petitioner argues that "the claimed dosing regimen—four weekly doses of 375 mg/m^2—was likewise the only approved dosing regimen for rituximab at the time, and was specifically 'recommended' for treating LG-NHL in the Rituxan™ label." Pet. at 2.

But even if Exhibit 1004 were a prior art printed publication, it recommended the regimen of four weekly doses of 375 mg/m^2 only for induction therapy, not maintenance therapy. Indeed, the word "maintenance" appears nowhere in Exhibit 1004. Petitioner fails to establish that a POSA would have believed that the dosing regimen for ***induction*** therapy would have been appropriate for ***maintenance*** therapy.

Petitioner's reliance on Exhibit 1004 as teaching that four weekly doses of 375 mg/m^2 was "specifically 'recommended' for treating LG-NHL" is misplaced. Pet. 2. Exhibit 1004 describes treatment of only "patients with ***relapsed or refractory"*** LG-NHL. The patients referred to in the claims of the '172 patent are ***neither relapsed nor refractory***. Rather, as the Board previously found, they are complete or partial responders to prior therapy (meaning they were not refractory to such therapy) with no intervening relapse. *See* Section III.B above;

see also Ex. 2001, 018 (holding that "relapsed patients…are beyond the scope of claim 1"). The Board previously denied institution because there was insufficient evidence that a POSA supposedly would have been encouraged to use the 4 x 375 mg/m^2 dosing in a patient population distinct from that described in the FDA-approved indication. *See* Ex. 2001, 024 ("Petitioner has not adequately explained why an ordinary artisan would have been prompted to modify McNeil's process according to the teachings of the Rituxan® Label…to arrive at the process recited in claim 1 of the '172 patent."). Petitioner provides no new evidence that warrants a different outcome here.

At the time of the invention, dosing monoclonal antibodies such as rituximab was a "stumbling block[]" for skilled artisans, and "the best dose and schedule of rituximab remain[ed] to be established," even for existing uses (much less untried uses such as maintenance). Ex. 2039, 010. And even three years ***after*** the priority date, skilled artisans still held the view that "[f]urther study is needed to establish treatment schedules [for rituximab], such as maintenance therapy after remission induction." Ex. 2026, 005. This belies Petitioner's assertion that a POSA would have found four weekly doses of 375 mg/m^2 for maintenance therapy to have been obvious at the time of the invention.

If anything, a POSA would have been motivated to treat the patients claimed in the '172 patent with ***less*** than the 4 x 375 mg/m^2 dose for relapsed or refractory

patients. Relapsed or refractory patients have higher tumor burdens because they fail to achieve responses to prior therapy, or if they do achieve such responses, they relapse before maintenance therapy is given. The patients claimed in the '172 patent, by contrast, have lower tumor burdens because they have achieved complete or partial responses and have not relapsed.[12] *See also* Ex. 1018, 003 (describing complete and partial responses, or remissions, as reductions in tumor lesions). A POSA would have understood that patients who have lower tumor burdens would naturally require less rituximab to attack their fewer tumors—particularly given that rituximab causes tumor cells to be destroyed by binding to them directly. *See* Pet. 18 ("Rituximab…is an antibody that binds to 'CD20,' a protein that is only expressed on the surface of B-cells…. By targeting this specific protein, rituximab can selectively activate the immune system to kill only B cells…."). In other words, a POSA would have appreciated that the total amount of rituximab needed to bind to tumors is proportional to the total number of tumors that need to be destroyed.

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[12] As discussed in Sections III.B and V.A.2.b, the '172 patent is limited to treatment of complete or partial responders, who are defined by the specification as having regression of all lymph nodes to less than 1×1 cm^2 or a fifty percent reduction, respectively.

This is reflected by pharmacokinetic data in Petitioner's own cited reference (assuming *arguendo* that it could qualify as printed publication), which shows that serum levels of rituximab in patients after any given dose are inversely proportional to their tumor burdens. This is because the higher the tumor burden, the more rituximab drops out of circulation by binding to and destroy those tumor cells—i.e., the tumors act as "sinks," sequestering rituximab from the blood and reducing its serum concentration. *See* Ex. 1004, 001 ("The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden.").

A POSA would therefore have believed that if rituximab was going to be used as maintenance for complete or partial responders to chemotherapy with no disease relapse, then a dose of rituximab ***lower*** than the 4 x 375 mg/m^2 dose for relapsed or refractory patients should be used (e.g., less than 375 mg/m^2 for each infusion and/or fewer than four weekly infusions).[13]

Petitioner nowhere disputes that the pharmacokinetic data disclosed by Exhibit 1004 (if it were prior art), would have suggested, to any POSA inclined to use rituximab for maintenance therapy, using a dose of rituximab that is ***lower*** than

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[13] Single infusions of 10, 50, 100, and 250 mg/m^2, for example, had been successfully used in the art for relapsed disease. Ex. 2034, 001.

the dose for relapsed or refractory disease. Instead, Petitioner asserts that such data "does not amount to teaching away" because it supposedly points to such lower dosing only as an "alternative" to the dose that the FDA approved for relapsed or refractory patients. Pet. 37. Petitioner tries to justify that assertion by arguing that Exhibit 1004 teaches that "'[t]here has been no experience with overdosage in human clinical trials,' even at a higher '500 mg/m^2' dose." *Id.* at 38. But all of the human clinical trials discussed in Exhibit 1004 were trials in relapsed or refractory patients. Ex. 1004, 001 ("Clinical Studies"). Moreover, the "500 mg/m^2" dose Petitioner relies on was in "single doses," not four weekly doses, in patients with relapsed or refractory disease. Exhibit 1004 does not report any study evaluating the safety of doses greater than four weekly doses of 375 mg/m^2 even for patients with relapsed or refractory disease.

As discussed above, patients who experienced complete or partial responses with no disease relapse, as claimed in the '172 patent, have lower tumor burdens than patients who are refractory to prior therapy or have relapsed. And lower tumor burdens result in higher serum rituximab levels because of the tumor sink phenomenon, as also discussed above. Petitioner fails even to assert, let alone cite evidence, that a POSA would have believed that at a dose of 4 x 375 mg/m^2, the serum rituximab levels in patients with low tumor burdens would be just as safe as the levels observed in relapsed or refractory patients with higher tumor burdens.

Accordingly, the Board should reject Petitioner's argument that Exhibit 1004 taught that a rituximab dose of 4 x 375 mg/m^2 would be a safe option for maintenance therapy.

Petitioner's conclusion that it would have been obvious to use the relapsed-or-refractory dose for maintenance therapy instead, without any analysis or any discussion of the differences between the treatment of relapsed or refractory patients and the complete and partial responders claimed in the '172 patent, is indicative of the petition's impermissible hindsight-driven approach to obviousness. Obviousness "cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013).

Petitioner also argues that the rituximab induction regimen for relapsed or refractory patients (4 x 375 mg/m^2) would have been used by a POSA as repeating maintenance therapy for complete or partial responders with no disease relapse because "prior maintenance therapies (e.g., CVP) had likewise been given 'at the same drug dosages' that were used for first-line induction therapy." Pet. 38. As alleged support, Petitioner and Dr. Ozer cite only a single reference: Portlock (Ex. 1025). But Portlock did not use its first-line induction regimen as repeating maintenance therapy. In Portlock, the first-line induction regimen comprised

administering "6-17 cycles" of CVP "every 21-28 days" followed by "four consolidation cycles . . . at 21-28 day intervals," for a total of about 10 to 21 cycles (over 7 to 20 months) of CVP therapy. Ex. 1025, 002. The maintenance regimen, by contrast, involved only a ***single*** cycle of CVP "repeated every 3 months." *See id.* Thus, Portlock administered ***less*** CVP to patients as recurring maintenance therapy than it did as first-line induction therapy. The reference in Portlock to "maintenance CVP (at the same drug dosages)" simply indicates that CVP was repeatedly administered as maintenance in amounts that were the same as those used in ***each*** of the multiple cycles of the induction regimen—e.g., "cyclophosphamide 400 mg/m^2 p.o.q.d. x 5 . . . vincristine 1.4 mg/m^2 i.v. on day 1 . . . and prednisone 100 mg/m^2 p.o.q.d. x 5 days"—not that the induction regimen as a whole was repeatedly administered as maintenance. *Id.*

Other references likewise disclosed maintenance therapies that used ***less*** of an agent than was used for induction. *See e.g.,* Ex. 2018, 002, Fig. 1 (studying interferon dose of 5 MU/m^2 as first-line induction therapy, and a dose of 2 MU/m^2 as maintenance). As the website created by the American Society of Clinical Oncology (ASCO), Cancer.net, explains to patients: "Maintenance therapy often uses traditional chemotherapy drugs[,] [b]ut doctors give lower doses than when you first have treatment." Ex. 2038, 001. Thus, using an induction regimen as recurring maintenance therapy, as claimed in the '172 patent, was not obvious.

b. *Petitioner's Obvious-To-Try Argument Fails.*

Petitioner argues that the "four weekly doses of 375 mg/m^2" limitation "would have been at least obvious to try." Pet. 34. But the obvious-to-try doctrine does not apply to individual claim limitations; it applies to claimed inventions as a whole. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416, 421 (2007) (finding that "a patent claim" can be proved obvious "by showing that the combination of elements was '[o]bvious to try'"); *see also Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479–80 (Fed. Cir. 1998) (explaining that the obviousness analysis must be done for the "invention…as a whole and the claims must be considered in their entirety.").. Even Petitioner's own obvious-to-try case makes this clear. *See Bayer Schering Pharma AG v. Barr Labs, Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (addressing criteria for evaluating when only "an invention" would or would not have been obvious to try). Petitioner cites no case finding an individual limitation "obvious to try." Such a case does not exist because controlling authority has long held that inventions are not necessary obvious even if all the elements are individually known or unpatentable. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 959 (Fed. Cir. 1986) (holding "[t]hat each element in a claimed invention is old or unpatentable does not determine the nonobviousness of the claimed invention as a whole" and reversing lower court's "improper[]… analysis of the claimed invention by the parts, not by the whole").

Even if the obvious-to-try doctrine was applicable to an individual limitation, Petitioner fails to establish that the elements of the doctrine—as articulated by Petitioner itself—would be satisfied here. Pet. 35. For example, Petitioner fails to establish that "the prior art provides direction about 'which parameters were critical'" in developing a maintenance therapy for LG-NHL using rituximab, or "'which of many possible choices is likely to be successful'" such that it could be said that the prior art "reduces the options to a set that is 'small [and] easily traversed.'" *Id.* (quoting Petitioner's cited authority, *Bayer Schering Pharma AG v. Barr Labs, Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009)).

Petitioner argues that the "four weekly doses of 375 mg/m^2" limitation "would have been at least obvious to try" because "Patent Owner acknowledged that the prior art 'showed that the dosing [of rituximab] had been optimized as 4 doses.' Ex. 1022, 16." Pet. 35-36. But that "acknowledgement" was made with respect to induction therapy, not maintenance therapy. Indeed, the pending claim at issue, claim 49, was "[a] method of treating low grade or follicular non-Hodgkin's lymphoma," not a method of treating complete or partial responders with no disease relapse. Ex. 1022, 015 (citing a study by Grillo-Lopez et al., Ex. 2029, in which 4 doses "were found to be effective" in ***relapsed*** patients); Ex. 1022, 010 ("Grillo-Lopez et al. refer to treatment of relapsed NHL in patients….").

c. *Petitioner's Argument That "The Claimed Dose Falls Within A Range Disclosed In the Prior Art, And Is Thus* Prima Facie *Obvious" Fails.*

Petitioner characterizes the disclosure in Exhibit 1004 of "rituximab 'doses [of] 10, 50, 100, 250 [and] 500 mg/m^2'" as disclosure of "a range" in which "[t]he claimed dose falls." Pet. 36. But Exhibit 1004 makes clear that those discrete values were all "single doses," not "four weekly doses," as claimed in the '172 patent. Ex. 1004, 001. Thus, Exhibit 1004 does not disclose a range in which the claim limitation of ***four weekly doses*** of 375 mg/m^2 falls.

Moreover, Petitioner is again improperly arguing that a claim ***element***, *i.e.,* "the claimed dose," can be rendered *prima facie* obvious. But, of course, the obviousness analysis must be done for the "invention…as a whole and the claims must be considered in their entirety." *Kahn*, 135 F.3d at 1479–80. Petitioner does not—and could not—contend that Exhibit 1004 discloses a range of maintenance therapies for LG-NHL patients who had complete or partial responses to CVP therapy without disease relapse, let alone that within any such range falls the claimed dosing regimen of four weekly doses of 375 mg/m^2 every 6 months for two years. Put simply, Petitioner's piecemeal analysis of whether an individual claim element was "*prima facie* obvious" is emblematic of its hindsight-based obviousness argument.

4. None Of The References Disclose Or Suggest Administering Maintenance Therapy Following "CVP Therapy To Which The Patient Responds," As Required By The Claim

In the prior IPR, the Board correctly construed the term "CVP therapy to which the patient responds" to mean that the patient who has received CVP must have experienced a complete or partial response, as defined by the criteria set forth in the specification. *See* Section III.B (citing Ex. 2001, 006).

First, none of the references in Petitioner's Ground discloses any clinical response ***to CVP*** chemotherapy. Exhibit 1004, the alleged Rituxan Label, does not mentioned CVP chemotherapy and Petitioner does not contend otherwise. McNeil, as discussed in Section V.A.2.a(3), teaches the use of CHOP, not CVP, with rituximab maintenance therapy. Hochster I, as discussed in Section V.A.1, reports results from using FC chemotherapy and but no results from CVP chemotherapy.

Second, none of the references disclose the "to which a patient responds" limitation. The cited portion of the '172 patent defines the clinical criteria for complete and partial responses as: "***Complete response*** required the regression of all lymph nodes to $<1\times1$ cm^2 demonstrated on two occasions at least 28 days apart on neck, chest abdomen, and pelvic CT scans, resolution of all symptoms and signs of lymphoma, and normalization of bone marrow, liver, and spleen. ***Partial response*** required a $\geqq$50% decrease in the sum of the products of perpendicular

measurements of lesions without any evidence of progressive disease for at least 28 days." Ex. 1001, 9:14-23.

Neither Petitioner nor its expert addresses whether the prior art references teach the limitation of, "to which a patient responds," which is defined by specific clinical criteria of CR and PR in the patent specification. And indeed, neither Hochster I nor McNeil provide any specific clinical criteria for assessing whether there was a PR or CR to chemotherapy, and if so, whether such a response was required before rituximab maintenance therapy.

Petitioner's failure to address this claim limitation is fatal to its Ground. *See Apple Inc. v. Smartflash LLC*, CBM2014-00105 (Paper 9) at 14 (Sept. 30, 2014) (denying institution because "Petitioner does not provide adequate argument or explanation as to why [the prior art disclosure] satisfies the claimed [limitation].").

At one point, Petitioner alleges that "[b]y definition, the 'maintenance' disclosed in Hochster I necessarily requires that patients responded to the CVP induction therapy." Pet. 29. Not so. It was known in the art that "maintenance" therapy can be given even where the patient has ***not*** had a complete or partial response. For example, Petitioner's own reference taught that study patients were given rituximab "maintenance" therapy even if they had "***stable disease***," which is neither partial nor complete response. Ex. 1029, 002. The use of the word "maintenance" in Hochster I, therefore, does not necessarily disclose the claim

limitation of "CVP therapy to which a patient responds," which is defined by specific clinical criteria of CR and PR in the patent specification.

B. Petitioner Fails To Establish A Reasonable Expectation Of Success For Using The Claimed Rituximab Maintenance Regimen

Hochster I also fails to provide any support for Petitioner's assertion that there was a reasonable expectation of success for using rituximab as maintenance therapy for low-grade lymphoma. First, Hochster I reports only that the authors proposed "conducting phase III study of CF vs. CVP ± anti-CD20 maintenance"; it provides no results or data of any kind. Ex. 1005, 005.

Hochster I's mere plan to study rituximab maintenance in LG-NHL cannot provide a reasonable expectation of success. As the Board held in connection with the previous IPR petition, the fact that prior art "suggest[s] that rituximab maintenance therapy might warrant further study" does not mean that skilled artisans would have viewed that art "as encouraging rituximab maintenance therapy in LG-NHL." Ex. 2001, 024; *see also id.*, 026-27 (same).[14]

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[14] Petitioner argues that the '172 patent specification "'adds nothing beyond the teachings of' Hochster I." Pet. 33. But this relies on Petitioner's mischaracterization that the "Hochster I's disclosure '[as] identical to the ['172] patent itself.'" *Id.* This is demonstrably false. The specification discloses the rituximab maintenance regimen claimed, "Rituximab maintenance therapy (375

Like Hochster I, McNeil reported only on the commencement of the study; it provided no results or data of any kind. Rather, it simply speculated that rituximab maintenance in that particular setting—following CHOP-based induction in patients with IG-NHL, *i.e.*, aggressive NHL—would be a "***possible*** improvement." Ex. 1003, 001. Petitioner never explains why, much less offers evidence that, a POSA reviewing McNeil would have had any reasonable basis to believe rituximab maintenance therapy would work even in the reported study following CHOP-based induction in IG-NHL patients. *See Eli Lilly*, 619 F.3d at 1338 (explaining that a prior art reference disclosing a "bare proposal to use" the drug raloxifene in one clinical setting "is insufficient to require a finding that an ordinary skilled artisan would have expected that a compound with known bioavailability issues—and known clinical failures—would successfully treat any human condition").

As discussed in Section V.B.1, the field was replete with other maintenance-therapy failures, rebutting Petitioner's contention that a POSA would have had a reasonable expectation of success in developing an efficacious maintenance treatment. Given the unpredictability in the field and the fact that McNeil fails to provide any reasoning for its proposed rituximab maintenance

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mg/m^2 weekly times 4 every 6 months for 2 years," Ex. 1001, 13:7–16, whereas, Hochster I does not disclose ***any*** dosing regimen.

regimen for IG-NHL, much less any results, McNeil would not have provided a reasonable expectation of success in a different disease: low-grade NHL.

Even if McNeil showed that IG-NHL patients were responsive to the disclosed maintenance therapy, a POSA would have recognized that any responsiveness in IG-NHL could not presumptively be applied to LG-NHL. As Petitioner and its expert conceded, "the success or failure of a regimen in the context of intermediate-grade NHL ***says nothing*** about its success or failure in the context of LG-NHL, which is a different disease." Pet. 42, citing the Board's prior decision; *see also* Ex. 1002 ¶ 103 ("Petitioner expert similarly states that "the success or failure of a particular regimen in the context of treating intermediate-grade NHL ***does not imply that the same result will occur*** in treating LG-NHL, which is a different disease.").

As discussed in Section V.A, the proposed study disclosed by McNeil not only treated a different patient population than Hochster I, but also used a different induction chemotherapy, than the claim limitation. Whatever alleged suggestion of success Petitioner draws from McNeil, there is nothing in McNeil (or elsewhere in the record) to suggest that a POSA would believe that one could change the patient population ***and*** the induction therapy and still retain any alleged expectation of success. Petitioner simply resorts to unsubstantiated speculation, and McNeil

cannot support the weight of Petitioner's claims. This is precisely what the Board found in the last IPR.

1. No Successful Maintenance Therapy Had Been Established In The Prior Art

At the time of the invention, despite the efforts of many, no maintenance therapy had been shown to effectively maintain remission and prevent relapse of low-grade NHL. That is why "[m]aintenance therapy [was] ***rarely employed*** in non-Hodgkin's lymphoma once a clinical complete response has been obtained." Ex. 2004, 008 (emphasis added).

Petitioner presents no evidence of genuine success with either biologics maintenance or chemotherapy maintenance. Petitioner cites Exhibits 1025, 1026, and 1010 to argue that chemotherapy maintenance therapy had been successful. *See* Pet. 15-16. This mischaracterizes these studies. Exhibits 1025 and 1026, which reports results of clinical studies from 1976 and 1981, respectively, do not compare groups of patients who received versus those who did not receive maintenance therapy; and offers no results or discussion on whether maintenance therapy is beneficial. *See* Exs. 1025 and 1026, generally. Exhibit 1010, a study from 1988, similarly does not evidence successful chemotherapy maintenance. The study reports that only "38%" of patients were able to finish the planned duration of maintenance therapy. Ex. 1010, 006-7. The "main reasons for their early discontinuation of therapy were disease progression…persistent bone marrow

suppression," and other toxicities. *Id.*, 007. The authors concluded that "maintenance chlorambucil did not affect overall survival" and did not prevent "a continuously relapsing pattern of disease." *Id.*, 008. This does not evidence success.

A subsequent 1994 review article summarized the understanding of chemotherapy maintenance as not altering "the pattern of continuous relapse and the duration of median survival," and where any "benefit in time to failure was offset by time on treatment." Ex. 2035, 003. As an example, maintenance therapy with the chemotherapy regimen BCVP "did not translate into any appreciable survival advantage." Ex. 2012, 004. Skilled artisans were also aware that using chemotherapy as maintenance was associated with "increased toxicity, reduced patient well-being, and increased risk of secondary malignancies." Ex. 2013, 001.

Petitioner cites Exhibits 1009, 1012, 1017, and 1034 to argue that interferon maintenance therapy had been successful. *See* Pet. 16-17. This mischaracterizes these studies. Exhibit 1034, for example, reported giving interferon as induction therapy (and maintenance); and does not compare groups of patients who received versus those who did not receive maintenance therapy. *See* Ex. 1034, 002 (explaining that the interferon group "received chemotherapy plus concomitant subcutaneous IFN-alpha"). The study, therefore, offers no results or discussion on whether maintenance therapy is beneficial. *Id.* Exhibit 1012 reports that "the effect

on overall survival cannot be assessed." Ex. 1012, 003. Exhibit 1017 reports that "the difference between the IFN-alpha arm and the observation-only arm ***has not reached statistical significance***." Ex. 1017, 005. These studies do not evidence success.

On the other hand, there were many studies at the time of the invention, not cited by Petitioner, showing interferon (IFN) to be unsuccessful as maintenance therapy in LG-NHL. *See, e.g.*, Ex. 2015, 002 ("To date, no additional benefit has been seen from the administration of IFN for maintenance."); Ex. 2016, 003 ("We conclude that alpha-interferon consolidation after intensive induction chemotherapy does not prolong progression-free survival or overall survival in patients with low-grade malignant lymphoma."); Ex. 2017, 003 ("The use of IFNa as maintenance may have a slight effect on response duration, but does not have an impact on survival."); Ex. 2018, 001 ("During maintenance therapy with interferon alfa-2b, no significant differences in the occurrence of relapse have yet been seen compared to patients on no maintenance therapy."); Ex. 2019, 007 (Meta-analysis of pre- and post-filing-date clinical studies finding that "no significant effect [was seen] in studies in which [interferon] was given only as maintenance.").

Contrary to Petitioner's assertion, skilled artisans did not view interferon maintenance therapy as having showed success, which is why, "[m]aintenance therapy [was] rarely employed in non-Hodgkin's lymphoma once a clinical

complete response has been obtained." Ex. 2004, 008. Petitioner's reference, Ex. 1029 (published in 2009), for example states that, "IFN [for maintenance] was not widely adopted due to the need for continuous administration, poor tolerance, and modest benefit." Ex. 1029, 001; *see also* Ex. 2012, 005 ("A majority of the investigators have concluded that there is no role for maintenance therapy in favorable lymphoma management.").

Even assuming that one or two clinical studies showed a possible benefit of interferon or chemotherapy maintenance therapy, neither Petitioner nor its expert explain how skilled artisans would have weighed those results against the multiple failures, let alone how the results would have led to a reasonable expectation of success using ***rituximab*** in maintenance therapy.

As the Board held in the prior IPR, a POSA would not have thought that allegedly successful interferon maintenance therapy indicated that rituximab maintenance therapy would be successful:

> As Patent Owner argues (Prelim. Resp. 44), interferons were thought to boost the patient's immune system, including stimulating B-cells….In contrast, rituximab inhibits the immune system by killing B-cells. See Ex. 1008, 1 (Rituximab administration "resulted in a rapid and sustained depletion of circulating and tissue-based B-cells."). Given the significant differences in their biological activities, Petitioner does not persuade us, on

> this record, that interferon and rituximab would have been considered functionally equivalent biologics, such that an ordinary artisan would have been prompted to substitute one for the other.

Ex. 2001, 020; *see also id.*, 024 and 026-27 (accord). Similarly, Petitioner has not explained why skilled artisans would have been prompted to substitute rituximab maintenance for maintenance with traditional chemotherapy.

The many failures of trying maintenance therapy in low-grade NHL in the art underscore the unpredictability in this field, and rebut Petitioner's contention that skilled artisans would have had a reasonable expectation of success in developing a successful rituximab maintenance treatment. *See Cyclobenzaprine*, 676 F.3d at 1081 ("[T]here can be little better evidence negating an expectation of success than actual reports of failure."). Particularly in light of this background of other failures, short abstracts and review articles, such as Hochster I and McNeil, announcing the start of another study cannot support an expectation of success.

2. The Prior Art Discouraged Using Rituximab As Maintenance Therapy In LG-NHL Because Of Antigen Escape

Petitioner fails to address another reason why a POSA would have been skeptical about successfully using rituximab as maintenance therapy in low-grade NHL: reported antigen escape with repeated rituximab treatments in low-grade NHL. Ex. 2020, 002.

Antigen escape is a phenomenon whereby repeated use of rituximab causes cancerous cells to lose expression of CD20 thereby becoming treatment resistant. It was first observed before the filing date of the '172 patent that the "potential for tumor transformation with loss of CD20 expression ***may prevent recurrent treatment***." Ex. 2020, 002 (emphasis added). Others similarly published their doubts that rituximab could be successfully used as maintenance therapy because of the antigen escape problem: "Maintenance therapy [with rituximab] is also being explored, ***although antigen escape may limit its use***." Ex. 2021, 006 (emphasis added). This risk of antigen escape would have caused a POSA to be skeptical about the prospects of success of rituximab as maintenance therapy.

VI. UNCONSTITUTIONALITY OF *INTER PARTES* REVIEW

In *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, 639 F. App'x 639 (Fed. Cir. 2016), *cert. granted in part*, 2017 U.S. LEXIS 3727 (June 12, 2017), the Supreme Court will consider the constitutionality of *inter partes* review proceedings. Patent Owner preserves the position that this *inter partes* review proceeding and the challenge to Patent Owner's duly issued and existing '244 patent violates the Constitution by allowing for private property rights to be extinguished through an adversarial process in the Patent and Trademark Office, a non-Article III forum, without a jury. *See McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898) (once a patent is granted, "[i]t has

become the property of the patentee, and as such is entitled to the same legal protection as other property.").

VII. CONCLUSION

For the reasons set forth above, Biogen respectfully submits that the Board should deny the Petition for *inter partes* review in its entirety.

Dated: August 15, 2017

Respectfully submitted,

/s/Michael R. Fleming

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on August 15, 2017, a copy of the foregoing documents **BIOGEN, INC.'S PATENT OWNER PRELIMINARY RESPONSE, Patent Owner's Exhibit List,** and **Exhibits 2001-2006, 2009-2010, 2012-2013, 2015-2021, 2023, 2025-2027,** and **2029-2042** have been served in their entireties via e-mail, as agreed, on counsel of record for petitioners at the following address:

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24(d), I certify that the present paper contains 11,750 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, certificate of service, or this certificate of word count.

Dated: August 15, 2017

Respectfully submitted,

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