UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.
Petitioner,

v.

BIOGEN, INC.
Patent Owner.

Case IPR2018-00285
U.S. Patent No. 8,329,172

PATENT OWNER PRELIMINARY RESPONSE

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I. INTRODUCTION

This is the fourth *inter partes* review petition filed against the sole claim of U.S. Patent 8,329,172. It is the second such petition serially filed by Petitioner Pfizer Inc. The Board has denied institution on the first three petitions, and it should deny institution on this petition, too.

The Board should deny institution under 35 U.S.C. § 325(d) because "substantially the same prior art or arguments previously were presented to the Office" in the prior three petitions. Petitioner concedes that the current petition is "substantially the same" as its prior petition (IPR2017-01166), Pet. 12, and that it "sets forth substantially the same arguments on the merits that Petitioner previously advanced." Pet. 2.

Moreover, the art and arguments in the current petition are the same or substantially the same as those that other petitioners previously presented (without success) to the Office in IPR2015-00418 and IPR2017-01093. Petitioner argues that its current petition is different than prior petitions because previous "petitioners there did not cite Hochster I, or any other prior art 'teach[ing] rituximab maintenance therapy following CVP induction therapy.'" Pet. 6. This is not true. Although Hochster I was not cited before, its disclosure is entirely cumulative of a Grossbard article (Ex. 2039) that was previously relied on by petitioner Celltrion in IPR2017-01093. The Grossbard reference also allegedly

disclosed an ongoing study using rituximab maintenance therapy in low-grade lymphoma following CVP (in fact, the disclosure in Grossbard was about the Hochster study).[1]

The Board also should deny institution under 35 U.S.C. § 314(a) because the seven *General Plastic* factors weigh against institution:

- This is the second petition against the '172 patent filed by Petitioner.
- Petitioner admits that at the time it filed its first petition, it knew of the references advanced in the current petition, as they "were cited in the text and declarations…of the first petition." Pet. 13.
- At the time it filed the second petition, Petitioner had already received Patent Owner's preliminary response to, and the Board's non-institution decision on, the first petition. Petitioner even admits that it used the Board's decision to prepare the current petition, conceding that it filed the second petition "to cure the perceived procedural deficiencies raised by the decision denying institution of the first petition." Pet. 12.

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[1] The Board found the disclosure in Grossbard insufficient to raise a reasonable likelihood of obviousness because "the reference is silent as to the rituximab dosing regimen or amount employed." Ex. 2042, 020.

- Petitioner was aware of the references asserted in the current petition at least nine months before filing, having included them in its first petition.
- Petitioner fails to provide an adequate explanation for the time that elapsed between the filings of its multiple petitions. Petitioner offers an excuse for why it did not include additional art in its first petition, but entirely fails to address the passage of time between the filing of the first and second petitions.
- The Board has already expended significant resources addressing three, staggered petitions against the '172 patent.
- Multiple, staggered petitions such as this are an inefficient use of the IPR process and the Board's resources, making it more difficult for the Board to meet the one-year deadlines imposed by 35 U.S.C. § 316(a)(11).

Therefore, the Board should deny institution of this fourth petition under either or both § 325(d) and § 314(a).

* * *

The Board should also deny institution on the merits.

The Board previously held that even assuming that the art, e.g., Grossbard, disclosed the use of rituximab maintenance following CVP induction therapy in LG-NHL, it was "silent as to the rituximab dosing regimen or amount employed." Ex. 2042, 020. The Board also previously recognized that the "best dose and

schedule of rituximab remain[ed] to be established," and that there was no evidence a POSA would have used a "rituximab dosing regimen employed in a study of a wholly different patient population—namely, elderly patients having aggressive non-Hodgkin's lymphoma that is responsive to CHOP chemotherapy"—as maintenance therapy following CVP in LG-NHL. *Id.* at 020-021.

The cited references in the current petition do not fill in any gaps left by Grossbard or other references previously considered by the Board. The Board should, therefore, again deny *inter partes* review because none of the cited references teach material limitations of the claim, including (i) "four weekly doses of 375 mg/m^2" as maintenance therapy; and (ii) administration of rituximab "every six months for two years" for low-grade lymphoma (LG-NHL).

Like prior petitioners, in 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 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, in two separate non-institution decisions, 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. 2042, 021 (holding that there is insufficient evidence "why an ordinarily skilled artisan would have used, or had a reasonable expectation of success in using, a rituximab dose of 375 mg/m^2" in the claimed regimen); Ex. 2001, 024 (same). 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.[2] The patients claimed in the '172 patent, by contrast, have lower tumor burdens because they have achieved

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

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.[3] *See* Ex. 2042, 020-021 (holding there is insufficient evidence "a relevant skilled artisan would have sought to treat LG-NHL patients with the same rituximab dosing regimen employed in a study of a wholly different patient population—namely, elderly patients having aggressive non-Hodgkin's lymphoma that is responsive to CHOP chemotherapy—and for which no results are described"); Ex. 2001, 021. But that dosing schedule for IG-NHL was not even reported to be successful. And even if it had been, Petitioner

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[3] "[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.

provides no new evidence that should alter the Board's prior finding that disclosures related to IG-NHL do not apply to LG-NHL, or vice versa. *See* Ex. 2001, 021 ("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."); Ex. 2042, 021 (same).

In fact, both Petitioner and its expert admit that "the success or failure of a regimen in the context of IG-NHL ***says nothing*** about its success or failure in the context of LG-NHL, which is a different disease." Pet. 54; Ex. 1002 ¶ 113 ("[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.").[4]

In short, this Board has already considered and rejected many of the arguments made in the current petition because it merely repeats arguments found unpersuasive in IPR2015-00418 and IPR2017-01093. And the only additional art cited by Petitioner here, Hochster I, is cumulative of a Grossbard article the Board found insufficient in IPR2017-01093.

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

The Board's prior holdings, 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 conclusion it did in the prior IPRs and deny institution again.

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, 22:56-64.

1. Non-Hodgkin's Lymphomas (NHL)

Although sometimes referred to in 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; Ex. 1002 ¶ 35. "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 IG-NHL do not necessarily apply to LG-NHL lymphoma. *See* Ex. 2001, 018; Ex. 2042, 021. 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, 001-002; Ex. 1002 ¶ 34. "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, ¶ 40, citing Ex. 1010, 007. In contrast, patients with IG-NHL were frequently cured by first-line therapy (and therefore did not relapse). *See* Ex. 2003, 002; Ex. 1013, 010.

2. Treatment Of LG-NHL And IG-NHL Differed

Traditionally, the type of lymphoma from which a patient suffered dictated the chemotherapeutic regimen used. Most chemotherapy regimens used for LG-NHL were not used for IG-NHL, and vice versa. *Compare* Ex. 1013, 009, Table 111-7 *with id.*, 011, Table 111-8. 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 ¶ 35.

As Petitioner admits, "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. 54. 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 ¶ 113.

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,[5] that were successful as induction therapies[6] were not successful as maintenance therapies. *See* Section VI.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 VI.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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[5] BCVP is a combination chemotherapy regimen consisting of BCNU (a.k.a, carmustine), cyclophosphamide, vincristine, and prednisone.

[6] 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 LG-NHL, *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 VI.B.2 below.

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

B. Prior and Current IPR Petitions

1. Denial of Institution on Boehringer's Petition

Boehringer 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 article (Ex. 1003), which reported on an ongoing clinical study using rituximab maintenance following CHOP induction therapy in elderly patients with IG-NHL, and an alleged "Rituxan® label" that described treatment of relapsed LG-NHL with 375 mg/m^2. Boehringer argued that McNeil, in combination with an alleged Rituxan® label and other references, rendered the '172

patent claim obvious. Petitioner now raises a cumulative argument relying also on McNeil and an alleged Rituxan label in 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.

2. Denial of Institution on Celltrion's Petition

After the Board denied Boehringer's petition, Celltrion filed an IPR petition against the '172 patent (IPR2017-01093) in March 2017. Ex. 2043, 076. In that petition, Celltrion raised grounds for invalidity substantially similar to those now argued by Petitioner. Like Boehringer, Celltrion also relied on McNeil and an alleged "Rituxan® label." Celltrion also relied on a 1998 Grossbard article (Ex. 2039) that reported "a phase III trial of cyclophosphamide and fludarabine (Fludara) vs. CVP (cyclophosphamide, vincristine, and prednisone) followed by rituximab or observation." Ex. 2043, 048 (quoting Grossbard). Celltrion argued that Grossbard, in combination with the Rituxan® label, rendered the '172 patent

claim obvious. *Id.* at 058-59. Petitioner now raises a cumulative argument in this proceeding by relying on Hochster I (Ex. 1005), which discloses the same clinical trial that is reported in Grossbard.

The Board denied institution of Celltrion's petition on all grounds, finding that "Grossbard does not disclose or suggest the rituximab maintenance therapy dosing regimen required by claim 1 of the '172 patent." Ex. 2042, 020. The Board found that there was insufficient evidence that a POSA "would have sought to treat LG-NHL patients with the same rituximab dosing regimen employed in a study of a wholly different patient population—namely, elderly patients having aggressive non-Hodgkin's lymphoma that is responsive to CHOP chemotherapy." *Id.* at 020-21. The Board also found insufficient evidence that a POSA would have had "a reasonable expectation of success in using, a rituximab dose of 375 mg/m^2" weekly for four doses following CVP induction in LG-NHL because of the art's teaching that "doses up to 500 mg/m^2 in a weekly x 8 regimen" had been used in patients with intermediate- or high-grade lymphoma, and that "the best dose and schedule of rituximab remain to be established." *Id.*

3. Denial of Institution on Petitioner's Prior Petition

In April 2017, Petitioner filed its first petition against the '172 patent (IPR2017-01166). Petitioner raised a single ground relying on McNeil, an alleged

"Rituxan label," and Hochster I (Ex. 1005) and made arguments that were substantially similar to those made by the prior Petitioners.

The only reference not previously relied on was Hochster I, which Petitioner described as teaching "the combination of CVP chemotherapy and maintenance therapy with an anti-CD20 agent." Pet. 3. Hochster I, however, is cumulative of the Grossbard article relied on by prior petitioner Celltrion. *See* Section III.B.1 below.

The Board denied institution because "Petitioner has failed to establish sufficiently in the Petition that the Rituxan Label was publically accessible as of the critical date of August 11, 1998." Ex. 2044, 017.

4. Petitioner's Current, Substantially Similar Petition

This current petition is, as Petitioner concedes, "substantially the same" as its prior petition. Pet. 12. The only difference is that the prior petition relied on Exhibit 1004, an alleged print-out from an FDA website, as the "Rituxan label," whereas in the current petition, Petitioner relies on Exhibits 1004, 1041, and 1039 in the alternative as the "Rituxan label" for one Ground and for another Ground, Petitioner substitutes in Maloney 1997 (Ex. 1008) for the "Rituxan label" for the teaching of using 375 mg/m^2 for treating relapsed or refractory LG-NHL. Pet. 13.

III. THE PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 325(d)

In determining whether to institute *inter partes* review, "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). Here, 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.

A. The Petition Presents To The Office Substantially The Same Art And Arguments As *Petitioner's* Previous Petition

As discussed in Section II.B.3, Petitioner previously challenged the '172 patent in IPR2017-01166, where institution was denied. Ex. 2044; Pet. 7. Petitioner concedes that its current petition is "substantially the same" as its prior petition. Pet. 12.

1. Petitioner Does Not Dispute That The Art In The Petition Is The Same Or Substantially The Same As The Art That *Petitioner* Previously Presented To The Office.

Petitioner's prior petition advanced a single ground based on three references: "Hochster I [Ex. 1005], Rituxan™ label [Ex. 1004], and McNeil [Ex. 1003]." Ex. 2044, 005. Likewise, the current petition advances a ground based on "Hochster I (Ex. 1005); Rituxan™ label (Ex. 1004 or Ex. 1039 or Ex. 1041); and McNeil (Ex. 1003)." Pet. 10.

The current petition also advances a substantially similar ground, likewise based on Hochster I (Ex. 1005) and McNeil (Ex. 1003), but with Maloney (Ex. 1008) substituted for "Rituxan™ label." Petitioner does not contend that the substitution of Maloney makes the ground substantially different from the ground

in its first petition. To the contrary, Petitioner asserts that Maloney "contains the same relevant information as the Rituxan™ label." Pet. 1.

Accordingly, the art in this petition is the same or substantially the same as the art that Petitioner itself previously presented to the Office, and the Board should deny institution under § 325(d). *See Arista Networks v. Cisco Sys.*, IPR2015-01710, Paper 7, at 8 (Feb. 16, 2016) (denying institution under § 325(d) in part because "[o]ther than the substitution [of one reference for another], the art cited in the present Petitioner's obviousness grounds overlaps completely with that asserted against the claims in the [prior petition]").

2. Petitioner Admits That The Arguments In The Petition Are Substantially The Same As The Arguments That *Petitioner* Previously Presented To The Office.

Petitioner itself concedes that its second petition "sets forth substantially the same arguments on the merits that Petitioner previously advanced." Pet. 2. This independently warrants denial of institution under § 325(d). *Travelocity.com L.P. v. Cronos Tech., LLC*, CBM2015-00047, Paper 7, at 10 (June 15, 2015) ("[A]ccording to 35 U.S.C. § 325(d), we may reject the present petition because 'the same or substantially the same prior art ***or*** arguments previously were presented to the Office' in the earlier Petition.") (emphasis in original).

3. There Is No Exception In § 325(d) For Correcting Procedural Deficiencies In A Prior Petition.

Petitioner argues that the Board should not deny institution because "Petitioner is filing a petition that is substantially the same solely to cure the perceived procedural deficiencies raised by the decision denying institution of the first petition." Pet. 12. But "35 U.S.C. § 325(d) is concerned only with whether a petition presents 'the same or substantially the same prior art or arguments,'" *Ford Motor Co. v. Paice LLC et al.*, IPR2015-00767, Paper 14, at 7 (Aug. 18, 2015) (emphasis removed), and there is no dispute that the present petition relies on such prior art and arguments, as discussed above.

Petitioner tries to justify its duplicative petition by citing *Panduit Corp. v. CCS Tech.*, but *Panduit* did not involve petitions with substantially the same prior art or arguments. *See* IPR2017-01323, Paper 8 (Nov. 8, 2017), at 6 (showing that the second petition against the challenged claims was based on Eichenberger and Bennett); *Panduit Corp. v. CCS Tech., Inc.*, IPR2016-01647, Paper 8, at 5 (Feb. 8, 2017) (showing that the first petition against the challenged claims was based on Toyooka and "TIA Technical"). The patent owner's arguments in *Panduit* were "directed to factors addressing discretionary denial under 37 C.F.R. § 42.108 and 35 U.S.C. § 314(a)," and the Board's decision analyzed discretionary denial under the same regulation and statute. IPR2017-01323, Paper 8, at 6-9.

Petitioner fails to cite a single case where the Board ignored the language of § 325(d) and instituted trial on a subsequent petition that presented "substantially the same prior art or arguments" on the ground that the second petition was an attempt to cure procedural deficiencies. There is no exception in § 325(d) for correcting such deficiencies with respect to an earlier petition. The waste of resources and potential harassment associated with multiple, substantially similar petitions are no less problematic when the later petitions are filed to allegedly cure procedural deficiencies. Accordingly, the Board has denied petitions under § 325(d) in circumstances similar to those here.

In *NetApp Inc. v. Crossroads Sys.*, for example, the Board denied institution on a ground in the first petition because it "circumvent[ed] the page limits." IPR2014-01197, Paper 13, at 7 (Jan. 29, 2015) ("declin[ing] to consider the information found only in the [declaration]."). The petitioner filed a second petition—substantially the same as the first but without circumventing the page limits—seeking to cure its procedural deficiency. IPR2015-00777, Paper 12, at 7 (Sept. 3, 2015). The Board found that the second petition "presents the same prior art and substantially the same arguments previously presented in the [prior] proceeding" and declined to institute trial under § 325(d). *Id.* at 6, 8. The Board should reach the same result here, where Petitioner admits that its petition presents substantially the same art or arguments as its first petition.

B. The Petition Should Be Denied For Relying On Substantially The Same Art And Arguments Already Rejected By The Board In Previous IPR Proceedings Brought By *Other* Petitioners

The Board has denied institution under § 325(d) based on prior petitions by different petitioners when the "same reference[s] [were] being asserted" to challenge the same claims. *Unified Patents v. Personal Web Techs. LLC*, IPR2014-00702, Paper 13, at 7-8 (July 24, 2014).

Petitioner acknowledges that the '172 was "previously challenged by [two] other petitioners" and that "[b]oth petitions were denied." Pet. 7. Those prior petitions presented art and arguments that are substantially the same as those presented by the current petition.

1. The Art In The Petition Is The Same Or Substantially The Same As The Art That *Other* Petitioners Previously Presented To The Office.

Three of the four pieces of alleged prior art in the Grounds advanced by Petitioner here were previously presented to the Office in the petitions filed by Boehringer and Celltrion. Indeed, like both of the grounds here, three grounds in Boehringer's petition, Ex. 2001, 003, and one ground in Celltrion's petition, Ex. 2042, 006, were based on McNeil (Ex. 1003) and the alleged "Rituxan label." Moreover, the Maloney reference (Ex. 1008) was cited in both the Boehringer and Celltrion Petitions, as well as in Petitioner's prior petition. *See* Ex. 2045, 031, 037; Ex. 2046, 040; Ex. 2043, 027.

As Petitioner acknowledges, the only art that was not already considered by the Board is Hochster I (Ex. 1005). Pet. 6. But Petitioner relies on that reference for a teaching that is cumulative of art previously considered and rejected by the Board—namely Grossbard. *Compare* Pet. 3 (arguing that Hochster I teaches "[t]he combination of CVP chemotherapy and maintenance therapy with an anti-CD20 agent") *with* Ex. 2043, 059 (citing Ex. 2039) (arguing that Grossbard taught that "[t]he value of rituximab maintenance therapy in low-grade lymphoma is the subject of two other cooperative group trials," including "a phase III trial of…CVP…followed by rituximab").[7] The current petition merely substitutes Hochster I for Grossbard; the references have cumulative disclosures, and both suffer from the same deficiencies previously identified by the Board in denying institution.

2. The Petition's Arguments Are Substantially The Same As The Arguments That *Other* Petitioners Previously Presented To The Office.

The current petition asserts 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

[7] Petitioner inaccurately states that Celltrion "did not cite Hochster I or any other prior art 'teach[ing] rituximab maintenance therapy following CVP induction therapy'" in IPR2017-01093. Pet. 6.

the only rituximab regimen that the FDA had approved. Pet. 53-54. Boehringer and Celltrion presented the same argument (unsuccessfully) to the Office in the prior petitions challenging the '172 patent. *See* Ex. 2001, 020 (describing Boehringer's contention that a POSA would understand "that each course of the rituximab maintenance therapy…[is] four weekly doses of 375 mg/m^2" because that was "the precise regimen described in the 1997 FDA label"); Ex. 2043, 061 (Celltrion's contention that "[a] POSA seeking a dosage for rituximab maintenance therapy would be guided by the Rituxan label's dosage").

The current petition further argues that a POSA would have administered to the claimed patient population—people with LG-NHL—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. Pet. 49-52. Again, Boehringer and Celltion presented the same argument (unsuccessfully) to the Office in the prior petitions challenging the '172 patent. Ex. 2042, 023-024 (describing Celltrion's contention that "McNeil's disclosure of…rituximab maintenance therapy for intermediate-grade NHL" would have encouraged a POSA "to use rituximab maintenance therapy…for low-grade NHL"); Ex. 2001, 014 (describing Boehringer's contention that "it would have been obvious to [a POSA] to use the protocol described in McNeil to treat LG-NHL").

Thus, the arguments in the petition are substantially the same as the arguments that were rejected on the merits twice by the Office when previously presented by other petitioners.

* * *

In sum, the current petition is the fourth in a series of petitions against the '172 patent that present substantially the same prior art or arguments previously presented to the Office. It is the second such petition that Petitioner has filed against the '172 patent. The Board should therefore deny institution under § 325(d).

IV. THE PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 314(a)

Alternatively, or additionally, the Board should deny institution under 35 U.S.C. § 314(a) to avoid the "potential inequity of Petitioner filing multiple attacks, adjusting along the way based on Patent Owner's contentions and the Board's decision responding to a prior challenge." *Akamai Techs., Inc. v. Limelight Networks, Inc.*, IPR2017-00358, Paper 9, at 8 (May 2, 2017).

When determining whether to exercise its discretion to decline institution under § 314(a), the Board considers seven non-exhaustive factors. *Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, at 16 (Sept. 6, 2017). Although "not all the factors need to weigh against institution for [the Board] to exercise discretion under § 314(a)," *Apple Inc. v. Immersion Corp.*,

IPR2017-01310, Paper 8, at 9 (Nov. 2, 2017), all seven of the *General Plastic* factors compel denial of institution here, as explained below.

A. Factor One: Same Petitioner

Petitioner concedes that it previously filed a petition directed to the single claim of the '172 patent. Pet. 7. This factor weighs in favor of denying institution.

B. Factor Two: Knowledge of Prior Art

Petitioner concedes that the three references it added to the grounds of this current petition—Ex. 1008, Ex. 1039, and Ex. 1041—were not only known, but in fact "were cited in the text and declarations…of the first petition," Pet. 13, which was filed nearly eight months earlier. *See* Ex. 2045. This factor weighs in favor of denying institution.

C. Factor Three: Availability of Information From Prior Proceedings

Petitioner does not dispute that at the time it filed its second petition, it had already received both Patent Owner's preliminary response to and the Board's non-institution decision in the first petition.

The Board issued its decision denying institution of Petitioner's first petition on November 13, 2017, Ex. 2044, and Petitioner filed this petition a month later. Petitioner thus had the "benefit of seeing" the analysis conducted by the Board in the prior IPR. *Alere Inc. v. Rembrandt Diagnostics*, IPR2017-01130, Paper 10, at 9 (Sept. 28, 2017). For example, Petitioner's prior petition raised multiple arguments

concerning public accessibility. *See* Ex. 2045, 036-038. In its decision denying institution, the Board thoroughly explained why Petitioner's arguments concerning public accessibility were not persuasive. Ex. 2044, 009-017. The Board also discussed why the three references that Petitioner now attempts to rely on in this subsequent petition were insufficient to support the public accessibility of the alleged Rituxan® label. *Id.* The Board further explained why a receive-date stamp from the National Library of Medicine was insufficient "to support the conclusion that the 1999 PDR was publicly accessible prior to the August 11, 1998 critical date for the '172 patent." *Id.* at 016.

One month after the Board denied institution, Petitioner filed the current petition, which attempts to (1) re-argue why Exhibit 1004 is a printed publication based on a different librarian declaration and (2) add more grounds based on three references "that were cited in the text and declaration…of the first petition," and addressed by the Board. Petitioner has used the Board's prior non-institution decision as a roadmap in trying to convince the Board, with more evidence and argument than in its prior petition, that these three references—including the PDR—were publicly accessible. Pet. 31-36 (referring back to the Board's prior non-institution decision and adding new arguments why alleged "Rituxan label" references should be considered printed publications).

Petitioner even admits that it used the Board's denial of institution as a roadmap in preparing the current petition. According to Petitioner, "the present Petition cures the perceived procedural defects identified in the decision denying institution in IPR2017-01166." Pet. 1.

Petitioner argues that the Board did not reach the merits in denying the first petition, and therefore it is permitted to employ the Board's decision as a guide in preparing a serial petition. Pet. 11-12. Petitioner tries to justify that argument by citing *Panduit*, but *Panduit* does not support Petitioner's position.

In *Panduit*, as here, the Board denied institution on certain claims in a first petition "because one of the asserted references was not shown to have been a printed publication." *Panduit Corp. v. CCS Tech., Inc.*, IPR2017-01323, Paper 8, at 8 (Nov. 8, 2017). But unlike Petitioner here, the petitioner in *Panduit* did not then file a second petition seeking to cure the printed publication problem—e.g., by addressing the articulated deficiencies in its printed-publication argument or substituting a different reference in the corresponding ground. *See id.*, Paper 2. Instead, the petitioner in *Panduit* asserted all new prior art in the second petition. *Id*. Thus, the reason "the particular facts of [that] case [did] not present a situation in which Petitioner [was] 'using [the Board's] decisions as a roadmap'" was because the second petition took an entirely different tack—not because the first decision did not reach the merits. *Id.*, Paper 8 at 9. Unlike the petitioner in *Panduit*,

Petitioner here has clearly used the Board's previous decision as a roadmap for its arguments on the public accessibility of alleged "Rituxan label" references.

In any event, Petitioner does not deny that it used earlier IPRs against the '172 patent as roadmaps. For example, throughout its Petition, the Petitioner uses Patent Owner's prior arguments and statements as a roadmap to contrive new arguments of unpatentability. *See, e.g.*, Pet. 40 (attempting to use statements in Patent Owner's prior POPR as admissions); Pet. 48 (arguing that Patent Owner's POPR statements did not suggest that a prior art taught away); Pet. 54-55 (attempting to rebut Patent Owner's prior POPR arguments). Therefore, this factor weighs in favor of denying institution. *See Samsung Electronics Co. v. Elm 3DS Innovations, LLC*, IPR2017-01305, Paper 11, at 8-12, (Oct. 17, 2017) (denying institution on the basis that the new petitioner relied on three of the four references, as well as evidence and rulings, from prior proceedings).

This is an improper follow-on petition that seeks to "unveil strategically their best prior art and arguments in serial petitions, using [the Board's] decisions on institution as a roadmap." *Conopco, Inc. dba Unilever v. The Procter & Gamble Co.*, IPR2014-00628, Paper 23, at 5 (Mar. 20, 2015).

D. Factor Four: Length Of Time Between When Petitioner Learned Of The Prior Art Asserted In The Second Petition And The Filing Of The Second Petition

As noted above in the discussion of Factor Two, Petitioner concedes that it was long aware of the three references it now relies on in its Grounds. Pet. 13. This factor weighs in favor of denying institution.

E. Factor Five: Petitioner's Explanation

Petitioner fails to provide an adequate explanation for the time elapsed between the filings of its multiple petitions directed against claim 1 of the '172 patent. Petitioner argues that "when the first petition was filed, Petitioner reasonably relied on the fact that, at the time, the Board already had instituted trial on a related patent in which the Rituxan™ label (Ex. 1004) had been used in the grounds (and Patent Owner had not challenged the public accessibility of that exhibit)." Pet. 12. The Board should reject Petitioner's explanation for multiple reasons.

First, Petitioner did not show that it actually relied on the proceedings concerning the "related patent." Pet. 12. And the content of its first petition points away from such reliance. Petitioner did not simply assume in the first petition that "the Rituxan label" was a prior art printed publication. Rather, as noted above, Petitioner raised multiple arguments concerning the public accessibility of "the Rituxan label." *See* Ex. 2045, 036-038.

Second, Petitioner did not—and could not—show that any such reliance was reasonable. A petitioner bears the burden of proving that the references it relies on qualify as printed publications. *See, e.g., Actavis, Inc. v. Research Corp. Techs., Inc.*, IPR2014-01126, Paper 22, at 9 (Jan. 9, 2015) (denying institution, in part, because Petitioner has "not satisfied its burden to prove that [a reference] is a printed publication"). That burden is not contingent. It is absolute. Petitioner cannot excuse its failure to carry that burden because in a ***different*** proceeding involving a ***different*** patent, the Board had instituted trial on a ground that included the "Rituxan label" reference and "Patent Owner had not challenged the public accessibility" of the reference yet, having elected not to file any Preliminary Response. Pet. 12. Petitioner knew that Patent Owner could still challenge the public accessibility of the reference in its Patent Owner Response—which it did.

Third, Petitioner's explanation, at best, only addresses why Petitioner did not prove that "the Rituxan label" was a prior art printed publication in its first petition. The explanation entirely fails to address the time that elapsed between the filing of the first petition and the second petition, which is the focus of Factor Five. Here, Petitioner filed its first petition on April 21, 2017. *See* Ex. 2045. Six weeks later, on June 2, 2017, Patent Owner filed its Patent Owner Response challenging the public accessibility of "the Rituxan label" in the proceeding on which Petitioner allegedly relied. *See* Ex. 2047. Yet Petitioner then waited more than ***six***

months to file the current petition on December 14, 2017. Petitioner never even tries to explain this passage of time. It appears that Petitioner was simply waiting until the Board issued its decision on whether to institute trial on the first petition. The Board issued that decision on November 13, 2017, Ex. 2044, and Petitioner filed the current petition four weeks later. Pet. 64. Such serial filings are precisely what § 314(a) is designed to combat. This factor weighs against institution.

F. Factor Six: Board Considerations Of Finite Resources

"[M]ultiple, staggered petition filings" are, in general, "an inefficient use of the *inter partes* review process and the Board's resources." *Alere*, IPR2017-01130, Paper 10, at 10 (quoting *General Plastic*, IPR2016-01357, Paper 19, at 21). This current petition is the fourth petition filed against the '172 patent, and the second filed by Petitioner. Each of the petitions were staggered filings. Pet. 7. Because the Board already has expended significant resources on challenges to the '172 patent, this factor weighs against institution.

G. Factor Seven: One-Year Timeline

Multiple, staggered petition filings such as this are an inefficient use of the Board's resources, impairing the Board's ability to meet the one-year deadlines imposed by 35 U.S.C. § 316(a)(11).

* * *

In sum, the *General Plastic* factors weigh in favor of denying institution under 35 U.S.C. § 314(a).

V. CLAIM CONSTRUCTION

A. "chemotherapy consisting of CVP therapy"

Patent Owner agrees with the Board's prior construction of this term. 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. *Id.*, 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. 19. Because the petition does not rely on this proposed construction, the Board need not decide whether the word "comprises" covers methods with additional steps beyond those expressly recited.

VI. PETITIONER FAILS TO ESTABLISH THAT THE COMBINATIONS OF REFERENCES IN ITS GROUNDS RENDER THE CLAIM OBVIOUS

The combination of Hochster I, McNeil, and Maloney / the alleged "Rituxan Label" references[8] does not render obvious claim 1 of the '172 patent. This combination of references is cumulative of the references presented in IPR2015-00418 and IPR2017-01093, both of which were denied, in part, on the merits. The only additional reference cited by Petitioner here, Hochster I, contains teachings that are cumulative of a Grossbard article the Board found insufficient in IPR2017-01093. The Board held that, even assuming that Grossbard discloses the use of rituximab maintenance following CVP induction therapy in LG-NHL, "the reference is silent as to the rituximab dosing regimen or amount employed." Ex. 2042, 020. The Board also recognized that the "best dose and schedule of rituximab remain to be established," and that there is no evidence a POSA would have used a "rituximab dosing regimen employed in a study of a wholly different patient population—namely, *elderly patients* having *aggressive* non-Hodgkin's lymphoma that is responsive to CHOP chemotherapy." *Id.* at 021 (emphasis in

[8] Petitioner describes the alleged "Rituxan label" references—Ex. 1004, Ex. 1039, and Ex. 1041—as "substantively identical," Pet. 2, and Maloney "contains the same relevant information as the Rituxan™ label." Pet. 1. This section, therefore, addresses these references together.

original). Nothing offered by Petitioner in its current petition changes 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); *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016) ("[U]npredictable arts such as medicinal treatment").

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 Maloney / the alleged "Rituxan Label" references 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 IG-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. 54.

Petitioner further fails to prove that a POSA would use the Maloney / the alleged "Rituxan Label" references' 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. *See* Section VI.A.3.a *supra*.

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, 009. The results were "promising," and so the authors proposed "conducting [a] phase III study of CF vs. CVP ± anti-CD20 maintenance…." *Id.*

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. 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 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. 2042, 020 (holding that even if Grossbard discloses use of rituximab maintenance following CVP induction therapy in LG-NHL, "the reference is silent as to the rituximab dosing regimen or amount employed.").

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 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 LG-NHL and an unknown age range) following a different induction chemotherapy

(CVP). 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. *See* Ex. 2042, 020-021 (holding that there was no evidence a POSA would have used a "rituximab dosing regimen employed in a study of a wholly different patient population—namely, elderly patients having aggressive non-Hodgkin's lymphoma that is responsive to CHOP chemotherapy" as maintenance therapy following CVP induction for LG-NHL).

(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 IG-NHL and LG-NHL as different diseases that should be treated differently.

The Board twice previously rejected—and should reject again–an argument that "an ordinary artisan would have been prompted to modify McNeil's treatment of patients with IG-NHL to instead treat the LG-NHL required by claim 1 of the '172 patent." Ex. 2001, 021; Ex. 2042, 020-021 (same). The Board recognized, and

the record shows, that IG-NHL and LG-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 ¶ 113.

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 ¶ 35. LG-NHL tumors "grow more slowly" than IG-NHL and HG-NHL. *Id.* 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 ¶ 35; *compare* Ex. 1013, 009, Table 111-7 (chemotherapy regimens used

with LG-NHL) *with id.*, 11, Table 111-8 (chemotherapy regimens used with IG-NHL).

Relevant art at the time showed that POSAs knew that IG-NHL and LG-NHL responded differently to drug treatment. *See, e.g.*, Ex. 2009, 001 ("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 IG-NHL than with LG-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. In 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 IG-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 LG-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."); Ex. 2002, 004 (same).

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. *See, e.g.*, *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1338 (Fed. Cir. 2010) (holding that it was not obvious to use the drug in another patient population because infringer "was not able to show a credible connection between the" two different settings); *Am. Hospital Supply Corp. v. Travenol Labs.*, 745 F.2d 1, 7 (Fed. Cir. 1984) (holding it was not obvious to use the therapy for "a different class of users with specific unique nutritional problems."). So too here.

Hochster I proposes treating patients with LG-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 IG-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 in its distinct patient population, 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, 005 ("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, 006. 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, 005; Ex. 1005, 009. 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 have] synergy with doxorubicin," which is a component of CHOP but not of FC or CVP. Ex. 2025, 002; Ex. 2023, 001. In the context of chemotherapy combinations, "synergistic combination[s] [between agents]…could result in reduced drug doses." Ex. 2040, 002; *see* 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. 26 (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.

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.

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. 50, fn. 7, citing Ex. 1029, 006 (a 2009 publication). 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 [LG-NHL] 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.

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.[9] 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.[10] Petitioner and its expert provide no reason why skilled artisans would be motivated to design a rituximab maintenance schedule of every 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." Pet. 5 (citing Ex. 1002 ¶¶ 103-104). But this

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[9] 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%

[10] 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, 003.

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." Pet. 50. 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, 009. 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, 005, 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 Maloney / the alleged "Rituxan Label" references in an effort to fill the holes in Hochster I and McNeil. Petitioner argues that "The Rituxan™ label disclosed that rituximab was approved at a single 'recommended' dosing regimen of 375 mg/m2 in four weekly doses—the same dosing schedule tested and disclosed in Maloney." Pet. 26.

But Maloney / the alleged "Rituxan label" references 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 Maloney or the alleged "Rituxan label" references. 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 the alleged "Rituxan label" references as teaching that four weekly doses of 375 mg/m^2 was specifically "recommended" for treating LG-NHL is misplaced. Pet. 26. These references describe 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 V.B; 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. 2042, 021 (holding that there is insufficient evidence "why an ordinarily skilled artisan would have used, or had a reasonable expectation of success in using, a rituximab dose of 375 mg/m^2" in the claimed

regimen); Ex. 2001, 024 (same). 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. *See* 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. Pet. 4 ("'IDEC-C2B8 (Rituximab)'…'binds [to] the CD20 antigen with high affinity' and 'efficiently kills CD20+ 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.

This is reflected by pharmacokinetic data in Petitioner's own cited reference, 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).[11]

Petitioner nowhere disputes that the pharmacokinetic data disclosed by the alleged "Rituxan label" references, would have suggested, to any POSA inclined to use rituximab for maintenance therapy, using a dose of rituximab that is ***lower*** than 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. 48. Petitioner tries to justify that assertion by arguing that the alleged "Rituxan label" references teach that "'[t]here has been no experience with overdosage in human clinical trials,' even at a higher '500 mg/m^2' dose." *Id.* at 26, 48. But all of the human clinical trials discussed in the alleged "Rituxan label" references 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. The alleged "Rituxan label" references do not report any study evaluating

[11] 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 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 the Maloney / alleged "Rituxan label" references 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. v. Tetra Pak Cheese & Powder Sys.*, 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. 48. 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. 45. 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'"); *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479 (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. *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. 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.'" Pet. 45-46 (quoting *Bayer*, 575 F.3d at 1347).

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, 016." Pet. 45-46. 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, 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 Obvious" Fails.*

Petitioner argues that Maloney "disclosed that rituximab had been tested in at least doses of 100, 125, 250, and 500 mg/m^2," which was a disclosure of "a range that includes the claimed dose." Pet. 47. But Maloney discloses only "single doses up to 500 mg/m^2," not "four weekly doses," as claimed in the '172 patent. Ex. 1008, 001. Thus, the Maloney / alleged "Rituxan label" references do 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. Petitioner does not—and could not—contend that the Maloney / alleged "Rituxan label" references disclose 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.

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 LG-NHL. 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, 009.

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 id.*, 026-27 (same).[12]

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

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[12] Petitioner argues that the '172 patent specification "'adds nothing beyond the teachings of' Hochster I." Pet. 44. But this relies on Petitioner's mischaracterization that the "Hochster I's disclosure 'is identical to the ['172] patent itself.'" *Id.* at 43. This is demonstrably false. The specification discloses the rituximab maintenance regimen claimed, "Rituximab maintenance therapy (375 mg/m^2 weekly times 4 every 6 months for 2 years," Ex. 1001, 13:14–16, whereas, Hochster I does not disclose ***any*** dosing regimen.

ordinary skilled artisan would have expected that a compound with known bioavailability issues—and known clinical failures—would successfully treat any human condition"). Indeed, McNeil's hope for a "possible improvement" turned out to be misplaced. The clinical study referenced by McNeil would ultimately show that the proposed rituximab maintenance therapy regimen was not effective after R-CHOP induction therapy in IG-NHL. *See* Ex. 1037, 001 ("After R-CHOP, no benefit was provided by MR [maintenance rituximab].").

As discussed in Section VI.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 regimen for IG-NHL, much less any results, McNeil would not have provided a reasonable expectation of success in a different disease: LG-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. 54, citing the Board's prior

decision; *see* Ex. 1002 ¶ 113 ("[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.").

As discussed in Section VI.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.

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. Pet. 22. 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. Pet. 23-24. 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; Ex. 2016, 003; Ex. 2017, 003; Ex. 2018, 001; Ex. 2019, 007.

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* Ex. 2012, 005 ("A majority of the investigators have concluded that there is no role for maintenance therapy in favorable lymphoma management.").

In any event, 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 previously held, a POSA would not have thought that allegedly successful interferon maintenance therapy indicated that rituximab maintenance therapy would be successful. Ex. 2001, 020 (rejecting argument that "interferon and rituximab would have been considered functionally equivalent biologics" in the maintenance setting); *see 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 LG-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 LG-NHL: reported antigen escape with repeated rituximab treatments in LG-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. 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. This risk of antigen escape

would have caused a POSA to be skeptical about the prospects of success of rituximab as maintenance therapy.

VII. UNCONSTITUTIONALITY OF *INTER PARTES* REVIEW

In *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, 137 S. Ct. 2239 (June 12, 2017), the Supreme Court will consider the constitutionality of *inter partes* review proceedings. Patent Owner preserves the position that this IPR challenge violates the Constitution. *See McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898).

VIII. CONCLUSION

Biogen respectfully submits that the Board should deny the Petition for *inter partes* review in its entirety.

Dated: April 11, 2018

Respectfully submitted,

/s/Michael R. Fleming

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Attorney for Patent Owner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on April 11, 2018, 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 **2029-2048** have been served in their entireties via electronic mail, as agreed, on counsel of record for petitioner 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 13,991 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: April 11, 2018

Respectfully submitted,

/s/ *Sharon Song*
Sharon Song