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 SUR-REPLY

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I. INTRODUCTION

Petitioner contends that it would have been obvious to use a dosing regimen designed for **induction** of patients who are *relapsed/refractory* (four weekly administrations of 375 mg/m^2 rituximab) as repeated courses for **maintenance** therapy for LG-NHL patients who have *responded* to CVP therapy per the patent, according to a schedule designed for the different population of IG-NHL patients (every six months for two years).

Petitioner's argument can be rejected based on the undisputed facts, which include the following: First, multiple claim limitations are not taught by any cited reference: (i) the clinical criteria that must be satisfied by "the patient [who] responds"; (ii) administering "rituximab maintenance therapy…[as] four weekly administrations of rituximab at a dose of 375 milligrams mg/m^2"; and (iii) administering "rituximab maintenance therapy…every 6 months…for 2 years" for low-grade lymphoma (LG-NHL).

Second, clinical response criteria taught in the art differed from the specific criteria required by U.S. Patent 8,329,172.

Third, therapies used for maintenance were different—namely, less intensive—than the therapies used for induction.

Fourth, success or failure of a regimen in the context of intermediate-grade NHL (IG-NHL) "says nothing" about its success or failure in the context of LG-NHL, which is a different disease.

Petitioner is unable to establish obviousness on this record. Moreover, Petitioner's expert was unable to support several of Petitioner's arguments. At deposition, he conceded that clinicians had abandoned prior-art maintenance therapies due to lack of efficacy. He also conceded that maintenance regimens were less intensive than induction regimens, and he could not identify any prior-art therapy that used the same dosing regimen for induction and maintenance. Petitioner tries to overcome these and other concessions by raising new arguments in reply. But even if these untimely arguments were allowed, they would fare no better than the originals.

The Board should find that Petitioner failed to establish that Claim 1 is unpatentable.

II. PETITIONER FAILED TO ESTABLISH THAT THE ALLEGED PRIOR ART WAS PUBLICLY ACCESSIBLE

Petitioner contends that each of Hochster I (Ex. 1005), Maloney (Ex. 1008), and McNeil (Ex. 1003) is an article that was publicly accessible in a library before the priority date. But Petitioner has not shown that any of these references, or even the alleged journal issues in which they appear, were catalogued, indexed, and shelved in a library by August 11, 1999.

Petitioner argues that "[e]ach of the journal articles" was "cataloged, indexed, and accessible to the public," citing pages 29-31 and 36-37 of the Petition and ¶¶37-40 of the Hall-Ellis declaration. Reply 2. But Hall-Ellis relies solely on MARC records as evidence of cataloging and indexing, Ex. 1016, ¶¶37-40, and as she admitted, a MARC record does not catalog or index any specific journal issue. Ex. 2053, 72:9-73:4. Nor does it catalog any individual article; it simply catalogs a serial title as a whole. *Id.*, 110:1-8. Petitioner fails to establish that any article or journal issue was cataloged and indexed before the priority date.

Petitioner also failed to establish that any article or journal issue, or the "PDR label" (Ex. 1039), had been *shelved* before the priority date. Petitioner asserts that "Hall-Ellis' testimony concerning library practices sufficiently establishes that these references would have been shelved and available within days of each reference's MARC record creation." Reply 3. But Petitioner nowhere cites the Hall-Ellis declaration or deposition for any discussion of shelving. Moreover, Hochster I, Maloney, and McNeil could not have been shelved "within days of each reference's MARC record creation" because there exist no MARC records for the articles themselves, as noted above, and Hall-Ellis testified that MARC records for the serial titles were created long before the alleged publication dates. For example, the MARC record cited in connection with Hochster I was purportedly created on February 1, 1980, which was almost two decades ***before*** the alleged publication of

Hochster I. Ex. 2053, 86:25-87:7, 88:13-89:1, 91:13-93:7; *id.,* 100:14-101:22, 104:22-106:10 (Maloney); *id.*, 64:11-65:2, 70:7-72:1 (McNeil).

The Board should reject Petitioner's attempt to distinguish the *Acceleration Bay* and *Bayer* cases. POR 10. These cases do not hold or suggest that the technical accessibility requirement—e.g., shelving at a library—does not apply to articles "in scientific journals" or arises only when there is affirmative evidence that "references were not publicly disseminated or sufficiently indexed or cataloged." Reply 3. It is Petitioner's burden to prove public accessibility, not Patent Owner's burden to disprove it. Patent Owner has never contended that Petitioner must establish "a *specific* date of cataloging and shelving," *id.*, but rather that the alleged art was catalogued, indexed, and shelved at some time before the priority date.

As for "the FDA and Website labels" (Exs. 1004 and 1041), Petitioner relies on the same evidence that the Board found unpersuasive in IPR2017-01166 when it ruled that Petitioner failed to establish public accessibility, Ex. 2044, 011-15, except Petitioner has now additionally filed a declaration from Mr. Christopher Butler. The Board should give that declaration no weight, however, because Petitioner failed to produce Mr. Butler for deposition. Ex. 2063, 001.

III. PETITIONER FAILS TO CITE ANY REFERENCE THAT DISCLOSES ADMINISTERING MAINTENANCE TO A PATIENT WHO "RESPONDS" PER THE PATENT

Petitioner's cited art disclosed only rituximab dosing regimens for treating relapsed-or-refractory ("relapsed/refractory") patients. It is undisputed that the '172 patent claims a different patient population: responders. POR 18-21.

The Board construed the language "to which the patient responds" as requiring satisfaction of particular clinical criteria set forth in column 9:14-23. Paper 10, 007. Unable to dispute that no cited art articulates such criteria, Petitioner now argues that it does not matter because Hochster I allegedly discloses administering anti-CD20 to responders, and the criteria set forth in the '172 patent is supposedly "the common understanding a POSA would have of a 'responder.'" Reply 6. Petitioner's argument fails for at least two reasons. First, Hochster I nowhere discloses administering anti-CD20 maintenance to a patient who "responds." Second, Petitioner fails to establish any "common understanding" of "responders" in the art.

A. Hochster I Does Not Disclose Administering Anti-CD20 Maintenance To A Patient Who "responds" Per The Patent

Hochster I's only disclosure of maintenance therapy is of a study being conducted using "CVP ± anti-CD20 maintenance." POR 49. Hochster I nowhere discloses administering CVP to which "the patient ***responds***" per the patent.

POR 13-15; Ex. 2051, 97:1-19 (conceding that "[t]here is no disclosure of providing anti CD-20 maintenance therapy to responders").[1]

Recognizing that there is no express disclosure, Petitioner argues that Hochster I's mention of "anti-CD20 maintenance" inherently discloses "administer[ing] to responders." Reply 5. But there was no guarantee that the particular patients in the study would have any response, let alone the specific response required by the claim. Moreover, Petitioner's expert acknowledged, that maintenance is given to patients with stable disease, i.e., non-responders. Ex. 2062, 39:17-40:8 ("[i]f the document…did not clarify whether the maintenance therapy was being given to patients with complete or partial responses or stable disease, the POSA might not know what's being referred to"); POR 15. At best, Hochster I discloses only a possibility that maintenance would be administered after some sort of response to CVP therapy, and it in no way suggests that any such response would satisfy the claim. However, "it is well established that 'inherency does not follow even from a very high likelihood that a prior art method will result in the claimed invention.'" *Celltrion v. Genentech*, IPR2016-01667, Paper 15, 009 (Mar. 2, 2017).

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[1] Hochster I reports responses to CF therapy in a "phase I/II study," but that treatment was not followed by maintenance.

B. Petitioner Fails To Establish Any "Common Understanding" Of "Responders" In The Art

Petitioner would have this Board believe that the criteria for the claimed response "reflect nothing more than the common understanding a POSA would have." Reply 6. But Petitioner offers no prior-art reference—or even expert testimony—to substantiate that bold assertion. Nor does Petitioner even attempt to reconcile the assertion with the absence of any articulation of the claimed criteria anywhere in the art.

To the contrary, the prior art articulates only clinical criteria that is different from the '172 patent. *E.g.*, Ex. 1026, 004 (not requiring measurements 28 days apart for lymph-node reduction); Ex. 2015, 003 (requiring no "appearance of new locations"); Ex. 2018, 002 (requiring "amelioration of performance status"); Ex. 2062, 69:3-70:1 (conceding "there were likely different definitions of how long the response needed to be maintained" than the patent's "28 days" requirement); *id.*, 42:15-45:3.

According to Petitioner, the patent demonstrates that the definition of "responder" in column 9 was the "common understanding" because the patent later "uses the term 'responder' generally without referring to the specific criteria set forth in 9:14-23." Reply 6-7. But that in no way suggests that there existed a common understanding of the term or that the inventor's definition of "responder" was the

"common understanding." If anything, it simply suggests that the inventor did not feel the need to repeat his definition of "responder" every time he used the term.

IV. PETITIONER FAILS TO ESTABLISH A REASON OR MOTIVATION TO MODIFY OR COMBINE THE CITED REFERENCES TO PRACTICE THE INVENTION

A. No Motivation To Give Rituximab Maintenance Using The Relapsed/Refractory Induction Regimen

Petitioner does not dispute, and its expert conceded, that "no prior art reference teaches administering rituximab as four weekly doses of 375 milligrams per meter squared [mg/m^2] for maintenance therapy." Ex. 2051, 191:4-20. Petitioner's expert also conceded that "as of the priority date, it was not known what treatment schedule should be used for rituximab as maintenance therapy," and rituximab dosing was a "stumbling block." POR 18.

Petitioner argues that a POSA would have used a four weekly 375 mg/m^2 regimen repeatedly for maintenance because that was the regimen used for induction of relapsed/refractory-patients in Maloney and alleged Rituxan Labels. Patent Owner's Response explained that the record cannot support such a finding. It is undisputed that induction therapy is different from maintenance therapy and that relapsed/refractory patients are different from responders. POR 18-23; Ex. 2051, 29:24-30:11. Petitioner does not dispute that art disclosing a therapy regimen for one patient population does not render obvious using the same regimen in a different patient population, absent a sufficient connection between those disparate

populations. POR 20 (citing Federal Circuit decisions *Eli Lilly* and *Am. Hospital Supply*); Ex. 2062, 31:20-33:3 (listing "information…needed before using a drug regimen from one patient population in another patient population"). Yet Petitioner never offers any evidence of such a connection here.

1. No Motivation To Use The Induction Dosing Regimen For Rituximab As Maintenance Therapy

a. There Is No Dispute That Maintenance Regimens Were Less Intensive Than Induction Regimens

Both experts agree—and the literature shows—that maintenance regimens were less intensive (e.g., fewer infusions or less drug per infusion) than induction regimens. POR 21-24. It is therefore unsurprising that Petitioner has failed to provide any example of the same dosing regimen being given for induction and maintenance. POR 27-29. Instead, the art shows that less intensive doses were given as maintenance. POR 21, 27-29.

b. Petitioner Fails To Establish That An Exception Would Have Been Made For Rituximab

Petitioner argues that the practice of using maintenance doses that were less intense than induction doses was confined to drugs like chemotherapy. Petitioner argues that for rituximab, a POSA would have made an exception to this practice because "there were no toxicity concerns with the dosage regimen recommended by Maloney." Reply 13.

As a threshold matter, Petitioner is wrong that there was no toxicity concern for rituximab induction therapy. In the Maloney trial, "[t]hirty-two of the 37 patients [87%] experience[d] adverse events," and "6 patients [16%] experienced 12 grade 3 or 4 adverse events." Ex. 1008, 008-9. Both experts agree that Grade 3 and 4 toxicities are the most severe non-fatal events (Grade 5 is death). Ex. 2062, 96:4-98:8 ("Grade 3 to 4 toxicities are…more severe."); Ex. 1061, 49:14-50:9 ("grade 4 toxicities…require serious intervention, hospitalization and could be life-threatening"). And Petitioner's expert testified that rituximab as induction therapy had significant toxicities overlapping with chemotherapy, including leukopenia, thrombocytopenia, neutropenia, nausea, and vomiting. Ex. 2062, 63:13-66:9 (identifying toxicities associated with CVP, and agreeing that Table 1 of Ex. 1039 [page 12] listed toxicities associated with rituximab).

A fundamental problem with Petitioner's toxicity argument is that the rituximab regimen in Maloney (and alleged Rituxan labels) was given as a single induction course, not repeatedly given as maintenance courses. To the extent that a course of rituximab induction therapy was tolerable, it was no different than the chemotherapy that Petitioner seeks to distinguish.

Petitioner has conceded that chemotherapy also was tolerable as a single course for induction therapy. According to Petitioner, chemotherapy, including

CVP, was "the preferred first-line treatment" and "the standard combination chemotherapy for LG-NHL" induction therapy. Pet. 3, 21. This was because, in the words of Petitioner's expert, CVP "toxicity was considered acceptable" as induction therapy. Ex. 2062, 10:14-13:20.

Indeed, there is nothing in the record suggesting that chemotherapy (or interferon for that matter) was intolerable as induction therapy. Despite the tolerability of these drugs as single courses for induction, they were not tolerated when given as repeated courses for maintenance. POR 51-52; Ex. 2051, 70:20-71:25. Thus, the tolerability of four weekly 375 mg/m^2 rituximab doses as induction therapy would not have suggested to a POSA that it would be tolerable as repeated courses for maintenance.

Tellingly, Petitioner argues that four weekly 375 mg/m^2 doses "was known to be safe and efficacious," but relies only on safety data from a single course for induction. Reply 12-13. Petitioner's expert conceded that "[t]here was no safety…data for rituximab as a maintenance therapy." Ex. 2062, 66:3-9.

Petitioner even mischaracterizes Dr. Oleksowicz's testimony as suggesting that rituximab was "a tolerable drug" even for maintenance. Reply 9. But Petitioner's omits her complete answer, which made clear that her tolerability comment was limited to "induction [use] for relapse/refractory disease," not as repeated maintenance for responders. Ex. 1061, 49:25-50:9. Dr. Oleksowicz

explained there were serious toxicity concerns with giving repeated courses as maintenance, including fatal infections due to B-cell suppression for two or more years. Ex. 2054 ¶¶148-50.

In Reply, Petitioner cites Van Oers (Ex. 2013), a non-prior-art publication, to argue that others tested rituximab maintenance near the priority date. Critically, Van Oers used a rituximab regimen for maintenance that was less intensive than the four weekly doses used for induction: a single dose every course. Ex. 2013, 001. Apart from the inventor's own study (ECOG 1496), POR 59-60, no other clinician used four weekly doses every six months as maintenance for LG-NHL.

2. A POSA Would Have Understood McNeil To Teach Using Only One Dose Every Six Months

Patent Owner explained, based on testimony from experts on both sides, that a POSA would have read McNeil to teach giving a single dose, not four weekly doses, of an undisclosed amount of rituximab every six months for two years in IG-NHL patients. POR 17-18. Petitioner does not dispute this. Rather, it simply argues that because the amount of drug per infusion (dose) is not disclosed in McNeil (e.g., 125 mg/m^2, 375 mg/m^2, or 500 mg/m^2), "McNeil therefore does not motivate or teach changing the dosing amount." Reply 14-15. But whatever the amount, McNeil teaches administering a single dose every six months. That is different from the claimed invention, which requires ***four weekly*** doses every six months.

3. No Motivation To Treat Responders With The Dosing Regimen For Relapsed/Refractory Patients, Who Are More Resistant To Therapy

Patent Owner's Response explained that another reason a POSA would have used a less intensive rituximab regimen as maintenance is because the regimen of four weekly 375 mg/m^2 doses was specifically designed for relapsed/refractory patients, who were known to be "more resistant to therapy." POR 24-25 (quoting Petitioner's expert). Patent Owner explained that for maintenance treatment of responders, who have less resistant (if any) disease, a POSA would have used a less intensive dosing regimen. *Id.*

Petitioner acknowledges that "relapsed or refractory patients…may have been more resistant," but then simply asserts that it would not matter because "there were no toxicity concerns with the dosage regimen recommended by Maloney." Reply 13. The Board should reject this *non sequitur*. Moreover, as discussed in Section IV.A.1.b, Maloney's dosing regimen resulted in severe toxicity; which a POSA would want to reduce.

4. The Claimed Dosing Regimen Does Not Fall Within A "Range" Disclosed By The Art

Petitioner argues that, "Maloney disclosed a range of possible dosage regimens, including four weekly doses of 125 to 375 mg/m^2," and there is therefore a burden shift to Patent Owner. These regimens, however, were all used as induction therapy of relapsed/refractory patients, not as maintenance therapy. Ex. 2051,

154:16-155:8 (agreement by Petitioner's expert). The claimed rituximab regimen of 375 mg/m^2 weekly for four weeks every six months for two years as maintenance, therefore, does not fall within any disclosed range.

Contrary to Petitioner's argument, *Galderma Labs. v. Tolmar*, 737 F.3d 731 (Fed. Cir. 2013) does not stand for the proposition that a disclosed range of values in an entirely different context than the claimed invention shifts burden. In *Galderma*, the context for the art and invention was the same—treatment of acne—and the only difference was the dosage regimen. *Id.* at 738. Here, treatments in the art and invention are different: a single course as induction for relapsed/refractory patients versus repeated courses as maintenance for responders.

5. Petitioner Abandoned Dosing Arguments Based On Its Obvious-To-Try Theory And On The Prosecution History

Patent Owner's Response explained why it was not "obvious to try" the rituximab induction regimen as maintenance therapy, POR 30, and why statements in the prosecution history did not indicate that maintenance dosing had been "optimized." POR 31; Ex. 1022, 011 ("maintenance schedule…did not consist of 'mere optimization'"). Petitioner has not rebutted Patent Owner's argument.

B. No Motivation To Give Maintenance Rituximab Every Six Months For Two Years To LG-NHL Patients

Petitioner does not dispute, and its expert conceded, that "no prior art reference teaches…administration of rituximab every six months for two years for low-grade lymphoma." Ex. 2051, 191:4-20; POR 2.

1. No Motivation To Use A Maintenance Schedule For IG-NHL Patients Following CHOP Induction As The Schedule For LG-NHL Patients Following CVP Induction

McNeil disclosed a rituximab maintenance schedule for elderly ***IG-NHL*** patients following CHOP induction.

a. It Is Undisputed That A Dosing Regimen For IG-NHL "says nothing" About A Dosing Regimen For LG-NHL

In its Petition, Petitioner took the position 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. 54 (endorsing the Board's prior decision holding the same).[2] Petitioner did so to argue that the failure of rituximab every-six-months-for-two-years maintenance in IG-NHL would not have suggested that it would also fail in LG-NHL. *Id.*

Petitioner now attempts to change positions to argue that, "[a] POSA would nevertheless have found information from an IG-NHL study relevant to a

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

maintenance regimen for LG-NHL patients." Reply 18. But Petitioner's "says nothing" position necessarily means that a POSA would not have applied disclosures about an untested regimen in IG-NHL to the wholly distinct disease of LG-NHL. As Petitioner's expert conceded, "[t]he success or failure of a regimen encompasses both efficacy and toxicity considerations." Ex. 2062, 33:4-7. If the success or failure of one "says nothing" about the other, then it is by definition not relevant to obviousness.

McNeil cannot provide any motivation or reason to use its (untested) every-six-months-for-two-years schedule in LG-NHL.

b. Petitioner Concedes That Synergies Between Rituximab And Doxorubicin Permitted Using Less Rituximab Following CHOP Versus CVP

The Board previously recognized that a POSA would not have used a rituximab maintenance schedule following CHOP (McNeil) as the schedule following CVP (Hochster I and the '172 claim) because the "H" of C**H**OP—doxorubicin—was synergistic with rituximab. POR 37-39. A POSA would have known that when synergy exists, drug dosing would be different. *Id.*

Petitioner and its expert concede this in Reply, explaining that synergy "would have permitted the organizers of the trial disclosed by McNeil to use ***either a lower dose or a lower frequency*** of rituximab for maintenance" following CHOP as compared to what they would have used for maintenance following CVP, as claimed.

Ex. 1062 ¶14; Reply 17 ("CHOP includes doxorubicin, which has synergies with rituximab…."). In other words, even if a POSA looked to McNeil for guidance on treating LG-NHL, McNeil would have encouraged a POSA to use a lower-frequency dosing than McNeil's every-six-months frequency.

c. A POSA Would Have Dosed The General Population Differently Than McNeil's Elderly Population

Petitioner argues that McNeil's treatment of elderly patients suggests that its maintenance schedule would be appropriate for the general population. Reply 17-18. Not so.

McNeil expressly teaches that, "[o]ften elderly people respond to therapy initially but do not maintain remissions as long as younger people. 'The elderly have a higher relapse rate.'" Ex. 1003, 006. Petitioner never explains why a POSA supposedly would have used McNeil's maintenance schedule for elderly patients to treat a general population who takes longer to relapse.

2. No Motivation To Administer Rituximab Every Six Months To Keep Normal B-Cell Levels Depleted

a. Maintenance Is Designed To Prevent Emergence of Tumor Cells, Not Normal B-Cells

Petitioner argues that a POSA would have administered rituximab every six months because the art showed that median recovery time of ***normal*** B-cells was six months after rituximab therapy for relapsed/refractory patients. Reply 19 (citing Maloney [Ex. 1008, 9] and the alleged Rituxan labels).

But Petitioner's own expert could not support this argument at deposition. The experts from both sides agree that the goal of maintenance is to "prevent the emergence of new ***tumor*** cells." Ex. 2062, 49:21-50:5; Ex. 2051, 142:10-13 (agreeing, "a POSA would have designed a Rituximab maintenance dosing regimen predominantly based on progression time"); Ex. 2054 ¶135. They agree that, in the art, the median time for emergence of new tumor cells was thirteen months, not six months. POR 41-42; Ex. 2051, 125:15-21 (agreeing that "McLaughlin [Ex. 1006] showed a median progression…of 13 months") and Ex. 2051, 30:21-31:18 (agreeing that "progression…is the emergence of new tumor cells").

Indeed, a POSA would have been concerned that preventing any recovery of normal B-cells carries with it a risk of fatal infections (especially when combined with chemotherapy inductions that also "have risk of fatal infections"). POR 46-47; Ex. 2051, 150:10-19.

Patent Owner's Response noted that Petitioner's argument appears to be based on hindsight and the inventor's post-priority-date publication. POR 40-41. This Board rejected this same argument in a prior IPR, holding that the "B-cell depletion observed" argument "appears to be based on improper hindsight." Ex. 2001, 031-32. Petitioner does not rebut this in its Reply.

b. Maintenance Would Not Have Been Designed Based On A Median Recovery Time

Even if Petitioner were correct that a POSA would design a maintenance schedule based on normal B-cell recovery time, the POSA would not have used the median value as the dosing interval. Petitioner's expert acknowledged that six months was a "median" value. Ex. 2051, 131:4-24 ("median [B-cell] count was zero at six months"); Ex. 2062, 51:23-52:20 (acknowledging that normal B-cell recovery values in the alleged Rituxan Labels were "median levels").

Because six months is a median value, it means that approximately 50% of patients would be dosed too late if the maintenance dosing interval was six months. A POSA would not do this; as both experts agree, the POSA would design a dosing interval that covered the vast majority, if not all, of the patients. Ex. 2051, 126:25-127:7 (testifying that "maintenance dosing interval" should be designed for "[m]ore than just the majority, more than 51 percent…but something like 70, 80, 90 percent."); Ex. 2054 ¶¶142-43.

c. Petitioner Does Not Dispute That Time To Relapse In Relapsed/Refractory Patients Is Different Than In Responders

Patent Owner's Response explained that a POSA would not use unadjusted "B-cell recovery" values from relapsed/refractory patients when designing a dosing interval for maintenance of responders. POR 41. This was because, as both experts agree, responders have "generally more durable" responses than relapsed/refractory

patients. *Id.*, quoting Ex. 2051, 207:11-18; Ex. 2062, 52:25-53:4 (testifying that "more durable" means a "longer time to relapse or progression"). Petitioner does not rebut this in its Reply.

d. Petitioner Would Not Have Given Maintenance Therapy Every Six Months To Maintain Serum Levels

Petitioner argues that a POSA would have given maintenance therapy every six months to "maintain[] rituximab serum levels." Reply 15. This argument fails for several reasons.

First, Petitioner identifies no serum level that a POSA would want to maintain for maintenance therapy. Its own expert testified that he did not know "what serum level of Rituximab is required for it to be effective." Ex. 2051, 123:7-9; Ex. 2062, 22:13-26:12. Second, Petitioner's expert acknowledged that rituximab would be out of the body before six months. He testified that, a six-month maintenance interval would "not really [be] based on drug levels per se, because it was established that the drug levels were basically gone." Ex. 2051, 124:3-6. Third, as explained in Patent Owner's Response, no "drug in the prior art…was tested for maintenance therapy in low grade lymphoma and dosed based on drug detectability levels." Ex. 2051, 146:17-21; POR 42. Petitioner's Reply fails to rebut any of these arguments.

3. Petitioner's New Relapse-Free-Survival Theory Fails

Patent Owner's Response explained that a POSA would not have given maintenance therapy for "as long as possible," including at least two years. POR 45-48. Instead of rebutting these arguments, Petitioner now raises a new theory that maintenance therapy should last two years because "LG-NHL patients generally have only two to three years of relapse-free survival following induction." Reply 19.

But when Petitioner's own expert was asked whether a POSA would have used "median relapse-free survival after induction therapy" as "the total duration of maintenance therapy," he replied, "[p]robably not." Ex. 2062, 57:12-15. Indeed, Petitioner provides no reasoned analysis why maintenance therapy should end (i.e., total duration time of maintenance) when patients are expected to relapse.

V. NO REASONABLE EXPECTATION OF SUCCESS

Patent Owner's Response noted that Petitioner's expert applied an incorrect standard for his opinion on reasonable expectation of success. POR 48; Ex. 2051, 246:23–247:6 (testifying that he presumed there is a reasonable expectation of success even when there is "not a likelihood necessarily, but a ***possibility*** that maintenance Rituxan would provide a better outcome than observations and that it would be safe."). Petitioner has not rebutted this.

A. Petitioner Fails To Establish That There Was A Reasonable Expectation Of Success For Rituximab Maintenance In LG-NHL

Whereas Petitioner had argued that maintenance therapy in the art was successful, Petitioner now concedes that maintenance was abandoned (after its expert repeatedly testified to such). POR 51-52. Because of this concession, Petitioner now argues that rituximab would have been expected to defy the field's failures because "it was well known that rituximab lacked those same toxicities [as chemotherapeutic agents and interferon]." Reply 1. This argument should be rejected for several reasons.

First, it was not true that rituximab "lacked those same toxicities." As discussed above in Section IV.A.1.b, many of the toxicities for rituximab as induction therapy overlapped with those for chemotherapy and interferon.

Second, Petitioner's toxicity argument relies on a false comparison of chemotherapy and interferon toxicity in the ***maintenance*** setting to rituximab toxicity in the ***induction*** setting. Reply 9. As discussed in Section IV.A.1.b, "toxicity was considered acceptable" for a course of chemotherapy induction.

Third, Petitioner's argument that rituximab would have defied prior failures because of toxicity ignores the issue of efficacy. Prior attempts at developing maintenance therapy failed not only because of toxicity, but also, as both experts agree, because they did not show efficacy, i.e., an ability to prevent relapse. Ex. 2054 ¶¶158-71; Ex. 2051, 69:1-70:2 (testifying that maintenance with chemotherapy

"wasn't being done" because of "an essential belief that this regimen did not prevent people from relapsing….The ***efficacy was the major reason*** that this was abandoned."); *id*., 104:17–105:4 ("there was no convincing evidence that Interferon was ***beneficial***"); *id.*, 74:4-11.

B. Knowledge That Investigators Added Anti-CD20 Maintenance To A Phase III Study Of Induction Therapy Would Not Have Created A Reasonable Expectation Of Success For A POSA

Hochster I abstract's single sentence about conducting a clinical trial with an "anti-CD20 maintenance" arm does not provide a reasonable expectation of success for the claimed invention. The abstract provides no data of any kind concerning maintenance or anti-CD20 therapy. It does not identify the anti-CD20 drug (Petitioner's expert acknowledged there were over a dozen anti-CD20 antibodies available at the time),[3] the patient population (e.g., responders or non-responders with stable disease), or any dosing schedule. A bare, non-specific proposal of "anti-CD20 maintenance" cannot provide a reasonable expectation of success. POR 48-49.

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[3] There were "approximately sixteen anti-CD20 antibodies available by 1996." Ex. 2062, 79:23-82:2; Ex. 1061, 39:15-21 (testifying that "there were several antibodies targeting CD20, ***including*** rituximab, Bexxar, and Zevalin.").

Petitioner's entire argument is that Hochster I's use of the word, "Phase III," means that there were "promising results in humans." Reply 20. Even if true, the "promising results" in the Hochster abstract are from its results in a "phase I/II data study of CF" induction, not from data of anti-CD20 maintenance. Ex. 2051, 92:2-7 ("[t]his abstract describes the results with FC as 'promising'"); *id.*, 100:13-101:19; Ex. 2054 ¶¶53-54. A POSA would have known there were no results of any kind with any anti-CD20 maintenance. Ex. 2051, 99:2-8; Ex. 2062, 66:3-9. So the clinical trial referred to at the end of Hochster I was not "Phase III" with respect to "promising results" using anti-CD20 maintenance.

C. No Reasonable Expectation Of Success For Every-Six-Months-For-Two-Years Administration in LG-NHL

Petitioner does not deny that it relies solely on McNeil to argue that there would have been a reasonable expectation of success using "a six-month frequency and two-year duration" for LG-NHL. POR 53. Nor does Petitioner deny that McNeil provided only "speculat[ion]" that rituximab maintenance in that particular setting—following CHOP-based induction in patients with IG-NHL—would be a "possible improvement." *Id.*, quoting Ex. 2051, 106:19–107:2.

Given Petitioner's concession 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," Pet. 54, McNeil does not support even analogous speculation that this rituximab maintenance schedule in LG-NHL would be a possible improvement.

VI. OBJECTIVE INDICIA SHOW NON-OBVIOUSNESS

As Patent Owner's Response explained, the Patent Office found that the claimed invention demonstrated unexpected results based on the results of the ECOG 1496 clinical trial, which studied the claimed dosing regimen. POR 59-64. In Reply, Petitioner no longer disputes that there was long-felt need for maintenance that was effective and had tolerable toxicity, or that ECOG 1496 showed unexpected results.

Instead of attempting to defend its prior arguments, Petitioner takes the untimely position in Reply that there is insufficient nexus with the results of ECOG 1496. But even Petitioner's own expert has not disputed nexus in his declarations; indeed, he agreed there was nexus at deposition. Ex. 2051, 101:20-102:6 ("Q. So you believe that the effectiveness of the claimed method was studied in the ECOG 1496 clinical trial, correct? A. I believe so.").

A. Both Experts Agree There Is Nexus Between The Claimed Invention And The Improvement in PFS Found In ECOG 1496 and OS Found In The Vidal Meta-Analysis

Both experts agree that the results of ECOG 1496 (published in Exhibit 1029) showed "the effectiveness of the claimed method." POR 59-64.

Petitioner now raises a new argument that ECOG 1496 results are not informative because it "used different criteria for responders than that specified by the '172 patent." Reply 23. But Petitioner's expert admitted that "the majority of

responders in the Hochster article [Ex. 1029] follow the patent," that "the partial response definition in Hochster is the ***same*** as the partial response definition in the patent," and that "the definition of complete response in Exhibit 1029 requires the ***same*** reduction in lymph node as the patent." Ex. 2062, 66:13-73:25.

As both experts agree, any alleged minor differences between the claimed invention and ECOG 1496 do not detract from their opinion that results of ECOG 1496 results showed "the effectiveness of the claimed method." Ex. 2051, 101:20-102:6; Ex. 2054 ¶190. The only plausible conclusion on this record is that there is sufficient nexus; Petitioner's unsupported attorney arguments do not prove otherwise. *Genetics Inst. v. Novartis Vaccines and Diagnostics*, 655 F.3d 1291, 1308-1309 (Fed. Cir. 2011) (holding that "absolute identity of scope" is not necessary to show unexpected results).

Petitioner also argues that there is no nexus with the Vidal meta-analysis (published in Exhibit 2050) because the meta-analysis included clinical trials other than ECOG 1496. Reply 23-24. Again, however, both experts agree that these results, which showed that "maintenance Rituximab improves overall survival," "applies to the different dose and dosing regimens used for Rituximab maintenance ***including the ECOG 1496 regimen***." Ex. 2051, 229:8-17; POR 61-62. As Petitioner's expert testified, even though "oftentimes meta-analyses will include

studies with different dosing regimens," a POSA can find meta-analysis to be "informative." Ex. 2062, 74:2-77:9.

B. Unexpected Results Are Not Due To Any Prior-Art Method

Petitioner argues that there is no nexus because unclaimed treatment regimens can achieve similar results to the claimed invention. Reply 24. Even if true, Petitioner's argument fails because none of these alleged unclaimed treatment regimens were disclosed in the art. *Id.* (citing only post-priority-date publications). Unexpected results are not undermined by post-priority-date publications. *In re Huai-Hung Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011) (focusing on "unclaimed ***prior-art***").

Dated: February 15, 2019

Respectfully submitted,

/s/Michael R. Fleming

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on February 15, 2019, a copy of the foregoing documents **BIOGEN, INC.'S PATENT OWNER SUR-REPLY, PATENT OWNER'S EXHIBIT LIST** and **EXHIBITS 2062-64** 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 5,598 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, signature block, certificate of service, or this certificate of word count.

Dated: February 15, 2019

Respectfully submitted,

/s/ *Alaina Bird*
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