UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.
Petitioner

v.

BIOGEN INC.
Patent Owner.

CASE IPR2017-01095
Patent 9,296,821

BIOGEN'S PATENT OWNER PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107

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I. INTRODUCTION

The Board should decline to institute IPR2017-01095 because Petitioner has failed to establish a reasonable likelihood that it would carry its burden to show that any claim of U.S. Patent No. 9,296,821 ("'821 patent") is not patentable.

Each of the first two grounds on which Petitioner challenges the '821 patent is based on a document dated more than five years ***after*** the patent's priority date. Petitioner tries to transform the document into prior art by attacking the patent's priority date, but Petitioner simply recycles the same written description arguments that the Office considered extensively during prosecution before allowing the claims in the first place. As the Office determined, the priority document discloses—not merely renders obvious—the claimed inventions. It is Petitioner's burden to establish that the '821 patent is not entitled to its priority date, and Petitioner fails to carry that burden. Grounds 1 and 2 therefore fail.

Even if they were based on prior art, Grounds 1 and 2 would fail because Petitioner never establishes that certain claim limitations are met. For example, claims 1 and 4 require a "beneficial synergistic effect." Petitioner does not even attempt to identify disclosure of this limitation, as properly construed, in the alleged prior art. Instead, Petitioner impermissibly reads "synergistic" out of the claims.

Petitioner also fails to establish a reasonable likelihood of prevailing on any of the other grounds in its petition. The methods claimed in the ’821 patent were counterintuitive. Before the priority date, the prior art focused on combining rituximab with a different chemotherapy regimen—one that included a drug called “doxorubicin.” A POSA would have known from in vitro studies that rituximab worked synergistically with doxorubicin to kill B cells. And a POSA would have known that a research group administered rituximab to patients in combination with a doxorubicin-containing chemotherapy regimen called “CHOP” and reported a remarkable 100% overall response rate, without unexpected toxicities, in low-grade NHL patients that had completed all scheduled therapy. The group explained that the rationale for combining rituximab with CHOP was “known synergy with doxorubicin.” Ex. 1041, 003.

The ’821 patent does not claim methods of administering rituximab in combination with CHOP chemotherapy, as disclosed by the alleged prior art. Rather, the ’821 patent claims methods of administering rituximab “during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)”—a chemotherapy that does not include doxorubicin.

Grounds 3, 4, and 5 all fail because Petitioner never demonstrates that a POSA would have been motivated to modify the alleged prior art by substituting

the claimed CVP, which does not contain the known synergistic agent doxorubicin, for CHOP, which does. The Board previously rejected the same argument that "an ordinary artisan would have omitted the doxorubicin component of CHOP, and instead used CVP therapy" in low-grade NHL patients, in connection with an earlier IPR petition challenging the sole claim of a related patent. *Boehringer Ingelheim Int'l GmbH v. Biogen Inc.*, IPR2015-00418 (Paper 14) at 19 (July 13, 2015) (attached as Exhibit 2010 for convenience).

Petitioner also fails to establish that a POSA would have had any reasonable expectation of success with substituting CVP for CHOP. Petitioner does not contend that rituximab was known to be synergistic with any component of CVP, such that the combination could have been expected to yield results similar to the combination of rituximab and CHOP, as Petitioner contends.

Grounds 3, 4, and 5 also fail because each relies on Ex. 1006, which Petitioner refers to as "IDEC's 10-K/A." Petitioner fails to establish that Ex. 1006 was a prior art printed publication on which inter partes review may be based. Petitioner essentially argues that any SEC filing bearing a particular date is per se publicly accessible—and therefore a printed publication—as of that date. There is no such per se rule. It was Petitioner's burden to submit evidence that Ex. 1006

was disseminated or otherwise made available to the extent that a POSA exercising reasonable diligence could have located it, and Petitioner fails to carry that burden.

Grounds 3, 4, and 5 further fail with respect to claims 1 and 4 because Petitioner fails to address the "beneficial synergistic effect" limitations, as properly construed.

Petitioner is unable to establish a reasonable likelihood of prevailing on any articulated grounds. The Board should therefore decline to institute IPR.

II. BACKGROUND

A. Technical Background

1. Non-Hodgkin's Lymphomas

"Lymphomas are a heterogeneous group of malignancies of B cells or T cells that usually originate in the lymph nodes but may originate in any organ of the body." Ex. 1008, 023.

Though sometimes referred to in the singular, Non-Hodgkin's Lymphoma (NHL) "is not a single disease but a diverse group of diseases ranging from the very aggressive and rapidly fatal to the more indolent" low-grade varieties. Ex. 2001, 004.

"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, 4:61-64. Low-grade lymphoma may be slow-growing, but it is nonetheless deadly. As Petitioner observes, "[m]ost patients eventually die from the disease or its complications." Pet. 7.

"Approximately 80% of non-Hodgkin's lymphomas are B-cell malignancies and 95% of these express the CD20 antigen on the cell surface." Ex. 1001, 5:40-42.

2. Rituximab

Rituximab is a genetically-engineered antibody that binds to CD20 on the surfaces of B cells, leading to depletion of those B cells by the immune system. Ex. 1001, 1:59-61 and 15:24-26. Rituximab is also known by the name Patent Owner gave it during development: "C2B8." *Id.* at 3:3-5.

The FDA initially approved rituximab as a monotherapy "for use in relapsed and previously treated low-grade non-Hodgkin's lymphoma (NHL)." *Id.* at 1:58-61. Although rituximab was "reported to be effective for treatment of B-cell lymphomas, such as non-Hodgkin's lymphoma, the treated patients [were] often subject to disease relapse." *Id.* at 1:67-2:2.

3. Treating Low-Grade NHL Using Rituximab With CHOP

Seeking "new therapeutic strategies with improved antitumor activity and acceptable toxicity," a research group with an investigator named Dr. Myron Czuczman combined rituximab with a chemotherapeutic regimen containing an agent called "doxorubicin." Specifically, Czuczman et al. experimented with the approach of "treating low-grade lymphoma with standard-dose CHOP and IDEC-C2B8 [rituximab] (a chimeric anti-CD20 antibody)." Ex. 1041, 003.

CHOP is a combination chemotherapy consisting of four drugs: cyclophosphamide ("C"), doxorubicin ("H"),[1] vincristine ("O"),[2] and prednisone ("P"). Ex. 1001, 12:48-49. Czuczman et al. administered rituximab to patients in combination with six cycles of CHOP chemotherapy. Ex. 1041, 003.

In a 1996 paper reporting results from their study, Czuczman et al. explained that "[t]he rationale for combination of IDEC-C2B8 [rituximab] with CHOP

[1] Doxorubicin also is known as "hydroxydaunorubicin," represented by the "H" in CHOP, and also by the brand name "Adriamycin," sometimes represented by an "A." Ex. 1002 ¶ 39.

[2] Vincristine, which is sometimes abbreviated using its first letter "V," also is known by the brand name Oncovin, represented by the "O" in CHOP. Pet., 8 n.1.

includes non-cross-resistant mechanism of action, individual efficacy, nonoverlapping toxicities, and ***known synergy with doxorubicin***." Ex. 1041, 003 (emphasis added).

As the investigators reported in a reference that Petitioners refer to as "Czuczman," the results of their study were extraordinary: "Overall response rate for the 14 pts [patients] completing all scheduled therapy to date is 100%." Ex. 1011, 003; Ex. 1002, ¶57. No "unexpected toxicities" were observed. Ex. 1011, 003. Remarkably, this 100% response rate was maintained through study completion—even after 24 more patients received treatment, bringing the total number of responses to 38 out of 38 patients who received treatment. Ex. 1020, 003 (reporting that the median time to progression for these patients had not been reached after a median observation time of more than 29 months).[3] By contrast, the overall response rate to rituximab monotherapy in the Phase III pivotal trial leading to initial FDA approval of rituximab was only 48%,

[3] Forty patients enrolled in the study. Two ended up receiving no treatment, but the investigators counted them as "nonresponders" anyway and reported in their full write up at the end of the study that "[t]he overall response rate was 95% (38 of 40 patients)." Ex. 1020, 002.

Ex. 2002, 001, and CHOP therapy alone induced an overall response rate of 60% in patients with low-grade NHL in another study around the same time. Ex. 1047, 003; Ex. 1002, ¶40. The 100% response rate reported by Czuczman et al. was beyond "impressive," even according to the standards of Petitioner's own expert. Ex. 1002, ¶60 (describing an overall response rate of 96% as "impressive").

The '821 patent does not claim methods of treating NHL using Czuczman et al.'s combination of rituximab and CHOP therapy. Rather, it claims new methods of treating NHL by administering rituximab during CVP therapy.

B. Prosecution History

The '821 patent issued from application No. 13/524,896 ("the '896 application"), filed on June 15, 2012. Ex. 1069. The '896 application is a divisional of application No. 11/840,956, which was filed on August 18, 2007, Ex. 2003, and issued as U.S. Patent No. 8,329,172 on December 11, 2012. Ex. 2004. That application, in turn, is a continuation of application No. 10/196,732, filed on July 17, 2002, Ex. 2005, which is a continuation of application No. 09/372,202, filed on August 11, 1999 ("the '202 application"). Ex. 1034. The '202 application issued as U.S. Patent No. 6,455,043 on September 24, 2002 and claims priority to provisional application No. 60/096,180, filed on August 11, 1998. For purposes of this POPR, Patent Owner will refer to "the priority date" as August 11, 1999.

The ’202 application, entitled “Combination Therapies for B-Cell Lymphomas Comprising Administration of Anti-CD20 Antibody,” Ex. 1034, 004, discloses methods of treating lymphomas by administering rituximab and various chemotherapeutic regimens. The claims of the ’821 patent are directed to administering rituximab during CVP therapy. Initially, these claims were rejected under 35 U.S.C. §112 based on the very same arguments that Petitioner makes in the petition. *See e.g.,* Ex. 1069, 126. Examiner Schwadron eventually withdrew the rejections “in view of the amended claims and applicants arguments.” *Id.* at 217.

III. CLAIM CONSTRUCTION

Petitioner proposes construing only one term, “beneficial synergistic effect,” and states that it otherwise relies on plain and ordinary meaning. Pet. 30. Petitioner’s proposed construction reads out a limitation of the term, however, thereby impermissibly broadening the broadest reasonable interpretation, as explained below. The Board should reject Petitioner’s construction and adopt Patent Owner’s construction instead. It should also adopt Patent Owner’s construction of “C2B8,” with which Petitioner appears to agree.

A. “beneficial synergistic effect”

Claims 1 and 4 each describe a method of administering rituximab during a CVP regimen “wherein the method provides a beneficial synergistic effect in the

patient." The intrinsic evidence makes clear that a "beneficial synergistic effect" for a combination of two therapies is an effect better than the additive effects of the two therapies administered alone, not just any beneficial effect. Accordingly, the Board should construe "beneficial synergistic effect," in the context of the claims, to mean "an effect better than the additive effects of rituximab and CVP administered alone." Petitioner's proposed construction should be rejected because it reads the word "synergistic" out of the claims.

1. The Plain Language Of The Claims And The Specification Support Patent Owner's Construction

Claims 1 and 4 require not just any beneficial effect. They require a "beneficial ***synergistic*** effect." Ex. 1001 (emphasis added). The specification explains what "synergistic" means.

In the "Summary Of The Invention," the patent reports that "it has been found that treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with cytokines, radiotherapy, myeloablative therapy, or chemotherapy." Ex. 1001, 2:24-28.

The patent describes, in the context of a cytokine embodiment, what "synergistic" means. Specifically, in column 3, it describes a "synergistic"

therapeutic combination of two therapies as producing a therapeutic effect "better than the additive effects of either therapy administered alone." Ex. 1001, 3:44-47.

Accordingly, a beneficial synergistic effect for a combination of rituximab and CVP therapy is an effect better than the additive effects of rituximab and CVP administered alone.

2. The Prosecution History Supports Patent Owner's Construction

During prosecution of the '821 patent's parent application, the applicant equated more-than-additive results with "synergistic" results. Specifically, in observing data from a study conducted after the priority date, the applicant wrote: "The complete responses (CRs) and extended median TTP[4] achieved with the presently claimed combination were more than additive, *i.e.* they were synergistic results." Ex. 2006, 014-015; Ex. 2007, 032-033 (noting results "were more than additive, i.e. they were synergistic results").

The applicant alluded to this same data during prosecution of the '896 application, stating that "the evidence of record confirms that the method provides a beneficial synergistic effect in the patient as recited in claim 1." Ex. 1069, 137; *id.* at 121 ("These data point to the beneficial synergistic effect in the patient

[4] "TTP" refers to Time To Progression of disease.

treated according to the presently claimed invention and would have been unexpected from the cited art.").

During prosecution of the '202 application, the applicant argued that "[e]vidence of a greater than expected results may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating 'synergism.'" Ex. 2008, 011 (citing *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804 (Fed. Cir. 1989)).

Both the specification and prosecution history therefore support Patent Owner's construction of "beneficial synergistic effect" as "an effect better than the additive effects of rituximab and CVP administered alone."

3. Petitioner's Construction Ignores The Word "Synergistic"

Petitioner's proposed construction—"an improvement in clinical outcome"—may be a construction for "beneficial effect," but the claim term at issue is "beneficial ***synergistic*** effect," not just "beneficial effect." The word "synergistic" in the claim language cannot be ignored. *See Funai Elec. Co. v. Daewoo Elecs. Corp.*, 616 F.3d 1357, 1372 (Fed. Cir. 2010) ("We must give meaning to all the words in [the] claims"); *Ex Parte Behzad*, Appeal 2011-007124 at 4 (Mar. 28, 2014) ("It is a well-settled canon of claim construction that claims should be interpreted such that each word is given meaning.").

Petitioner tries to justify its proposed construction by citing the above-quoted excerpt from the "Summary Of The Invention" and by citing a portion of the "Background Of The Invention" generally stating that "it would be beneficial if more effective treatment regimens [than rituximab monotherapy] could be developed." Pet. 30-31. Neither excerpt actually supports Petitioner's proposed construction. Both excerpts are consistent with Patent Owner's construction. A method of administering rituximab during CVP chemotherapy that yields "an effect better than the additive effects of rituximab and CVP administered alone" is, by definition, a more effective treatment regimen than rituximab monotherapy.

According to Petitioner, "[d]uring prosecution, Applicant argued that data referenced in the 2006 label (Ex. 1060) and the Marcus publication (Ex. 1005) showed that patients who received rituximab during CVP chemotherapy . . . 'demonstrat[ed] a beneficial synergistic effect in the patient[s].'" Pet. 31 (quoting Ex. 1069, 120). Applicant summarized such data in the following table from the next page of the exhibit cited by Petitioner:

Treatment Regimen	Median Time to Progression (TTP) (months)	Complete Response (CR) (% of patients)
Rituximab (R)	9 months*	6%**
Cyclophosphamide, Vincristine, Prednisolone (CVP)	15 months#	10%#
R-CVP	32 months#	41%#

* Marcus et al. top column 1 on page 1418
** Present application, page 20, line 3
# Marcus et al., abstract

Ex. 1069 at 121. Petitioner does not even contend, much less show, that this data is inconsistent with an effect for rituximab ("R") during CVP chemotherapy ("R-CVP") that is better than the additive effects of rituximab and CVP administered alone, as required by Patent Owner's construction.

B. "C2B8"

The specification and prosecution history disclose that "C2B8" is rituximab. Ex. 1001, 3:3-5 ("[A] preferred chimeric antibody is C2B8 (IDEC Pharmaceuticals, Rituximab)."); Ex. 2008, 005 (referring to "C2B8 (Rituximab[]) as employed in the present invention"). Petitioner agrees. *See, e.g.* Pet. 41 ("The '821 patent states that C2B8 is rituximab."); *id.* at 14 n.4 ("'IDEC-C2B8' is another designation for rituximab."). Thus, "C2B8" should be construed as "rituximab."

IV. THE ’821 PATENT IS ENTITLED TO THE BENEFIT OF AT LEAST AN AUGUST 11, 1999 PRIORITY DATE

The ’821 patent claims priority through a series of continuation applications to the ’202 application, which was filed on August 11, 1999, as discussed in Section II.B above. Petitioner does not challenge the chain of priority. Rather, Petitioner argues that “[t]he claims of the ’821 patent are not entitled to a priority date earlier than June 15, 2012 because the challenged claims lack written description support in the ’202 application.” Pet. 19. The Board should reject Petitioner’s position, which simply recycles arguments that were already addressed at length by the Office during prosecution. As Petitioner acknowledges with respect to its written description argument, “Examiner [Schwadron] repeatedly rejected applicant’s attempts to claim priority to the ’202 application on this basis,” Pet. 21, but Patent Owner overcame those rejections. *Id.* at 21.

A. Petitioner Bears The Burden Of Persuading The Board That The ’821 Patent Is Not Entitled To The Benefit Of Its Priority Date

Petitioner misstates the law when it asserts that “it is the Patent Owner’s burden to establish that the ’821 patent is entitled to a priority date set by the August 1999 filing of the ’202 application.” Pet. 20.

A patent owner is not burdened with persuading the Board that an issued patent is entitled to priority. At most, a patent owner bears a burden of production

on the issue of priority. If a petitioner "has introduced sufficient evidence to put at issue whether there is prior art alleged to anticipate the claims being asserted," a patent owner then bears the burden of going forward with evidence "that the prior art does not anticipate" and/or "that it is not prior art because the asserted claim is entitled to the benefit of a filing date prior to the alleged prior art." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008); *id.* at 1329.

It remains Petitioner's burden, however, to persuade the Board that Patent Owner "is ***not*** entitled to the benefit of the earlier filing date." *Id.* at 1328 (emphasis added); *HTC Corp., et al. v. Advanced Audio Devices,* LLC, IPR2014-01158 (Paper 36) at 10-11 (Jan. 22, 2016) (emphasizing that "the ultimate burden of persuasion in an *inter partes* review, however, remains on the Petitioner," who must "convince the Board that the challenged claim is not entitled to the benefit of the earlier filing date"); *Microsoft Corporation v. Keith A. Raniere*, IPR2016-00669 (Paper 11) at 7 (Nov. 10, 2016) (noting that the petitioner "asserted that Delaney discloses each limitation of the challenged claims and that Delaney predates those claims," and explaining that petitioner "has the burden of persuasion based on all of the evidence, on both of these assertions").

B. <u>The '202 Application Discloses That The Inventor Had Possession Of Administering Rituximab During A CVP Regimen To Treat Low-Grade B-Cell NHL, Including With Synergistic Effect.</u>

Under § 112, ¶1, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* at 1351.

"The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). "The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge." *Id.* at 1358. "The 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way." *Id.* at 1358.

"[T]he written description requirement does not demand either examples or an actual reduction to practice;" and it "does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*." *Ariad*, 598 F.3d at 1352; *Apple Inc. v. Papst Licensing GMBH & Co. KG,*

IPR2016-01844 (Paper 10) at 20 (Mar. 10, 2017) ("[W]hen examining the written description for support for the claimed invention, . . . the exact terms appearing in the claim 'need not be used *in haec verba*.'") (quoting *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1345-46 (Fed. Cir. 2016)). "[T]he specification 'need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed.'" *All Dental Prodx v. Advantage Dental Prods.*, 309 F.3d 774, 779 (Fed. Cir. 2002) (quoting *Eiselstein v. Frank*, 52 F.3d 1035, 1038-39 (Fed. Cir. 1995)). "[Even] the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented." *Id.* at 779.

The written description requirement is satisfied "when 'the essence of the original disclosure' conveys the necessary information – 'regardless of *how* it' conveys such information." *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1354 (Fed. Cir. 2015).

1. The ’821 Patent Claims Are Entitled To The Benefit Of The ’202 Application’s Filing Date.

The ’202 Application discloses various genera, subgenera, and species of inventions.

Genus Disclosure

One invention disclosed in the ’202 Application is the genus of administering an anti-CD20 antibody in a combined therapeutic regimen with another therapy, such as chemotherapy, and achieving a synergistic effect. Ex. 1034, 006 (“In particular, it has been found that treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with cytokines, radiotherapy, myeloablative therapy, or chemotherapy.”).

Subgenera Disclosures

The ’202 Application also discloses various subgenus methods “for treating B-cell lymphoma comprising administering to a patient a therapeutically effective amount of a chimeric anti-CD20 antibody before, during or subsequent to a chemotherapeutic regimen.” *Id.* at 009; *id.* at 058 (Original claim 17: “A method for treating B-cell lymphoma comprising administering to a patient a therapeutically effective amount of an anti-CD20 antibody before, during or subsequent to a chemotherapeutic regimen.”).

The ’202 Application confirms that these subgenus methods encompass treating various “B-cell lymphomas.” *Id.* at 010-011 (“The methods of the present invention may be used to treat a variety of B-cell lymphomas, including low grade/ follicular non-Hodgkin’s lymphoma (NHL), small lymphocytic (SL) NHL, intermediate grade/follicular NHL, intermediate grade diffuse NHL, high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small non-cleaved cell NHL, bulky disease NHL and Waldenstrom’s Macroglobunemia.”).

Similarly, the ’202 Application states that “any anti-CD20 antibodies can be used for the methods of the present invention,” though it notes that “a preferred chimeric antibody is C2B8 (IDEC Pharmaceuticals, Rituximab[]).” *Id.* at 007.

According to the ’202 Application, the anti-CD20 antibody can be administered in “combined therapeutic regimens” with chemotherapy according to “the present invention,” *id.* at 008, i.e., “before, during, or subsequent to a chemotherapeutic regimen.” *Id.* at 009 (describing such administration as “[a]lso included in the present invention”); *id.* at 008 (explaining that “the combined therapeutic regimens of the present invention can be performed whereby the therapies are given simultaneously, i.e., the anti-CD20 antibody is administered concurrently or within the same time frame” or “prior to or subsequent to the other therapies”).

The ’202 application discloses a variety of chemotherapeutic regimens, including CVP, for use in combination with the anti-CD20 antibody. In fact, the application discloses such use of CVP no fewer than three times, in connection both with B-cell lymphoma, *id.* at 032 (describing the combination of rituximab plus CVP to treat low-grade lymphoma), and chronic lymphocytic leukemia (CLL). *Id.* at 029 (stating that “[a]ntibody treatment of CLL can be combined with other conventional chemotherapeutic treatments,” including chlorambucil, and noting that “[c]yclophosphamide is an alternative to chlorambucil, the usual dose being 1-2 g/m^2 every 3-4 weeks together with vincristine and steroids (e.g., COP regimen)[[5]].”); *id.* (stating that “[v]arious drug combinations have been used for CLL, including COP (cyclophosphamide, Oncovin, and prednisone”). Accordingly, there can be no doubt that the inventor of the ’821 patent was in possession of using CVP in connection with the subgenera of inventions disclosed in the ’202 Application.

[5] “COP” is another name for “CVP,” where the “O” refers to “Oncovin,” a brand name for vincristine.

Species Disclosures

The ’202 Application expressly discloses numerous species of the various subgenera, including the species in which the B-cell lymphoma is low-grade NHL, the chimeric anti-CD20 antibody is rituximab, the anti-CD20 antibody is administered subsequent to the chemotherapeutic regimen, and the chemotherapeutic regimen is CVP.

For example, page 28 of the application discloses that “[a] Phase III study conducted by ECOG in patients with low-grade NHL is comparing the combination of cyclophosphamide and fludarabine (Arm A) with standard CVP therapy (Arm B),” and that “[r]esponders in both arms will undergo a second randomization to Rituximab® maintenance therapy (375 mg/m^2 weekly times 4 every 6 months for 2 years (Arm C) or to observation (Arm D),” Ex. 1034, 032, i.e., the rituximab is administered subsequent to CVP therapy.

By expressly disclosing the species of treating low-grade NHL by administering rituximab subsequent to a CVP regimen in particular, the ’202 Application confirms that CVP was one of the therapies that the inventor contemplated using in combined therapeutic regimens with an anti-CD20 antibody, including by administering the anti-CD20 antibody before, during or subsequent to the CVP therapy.

As noted above, the application discloses that the "the present invention" encompasses administering the anti-CD20 antibody any time relative to administration of the chemotherapeutic regimen. Ex. 1034, 008-009; *see also id.* at 058 ("17. A method for treating B-cell lymphoma comprising administering to a patient a therapeutically effective amount of anti-CD20 antibody before, during or subsequent to a chemotherapeutic regimen."). Thus, a POSA plainly would have understood from the '202 Application that the inventor possessed any order of administration for the combined therapeutic regimens of his invention. Nothing required the inventor to repeat the general "before, during, or subsequent to" language every time he discussed a specific example in the application, as Petitioner seems to suggest.

Nowhere does the application suggest that the inventor contemplated administering the anti-CD20 antibody ***only*** at certain times relative to any particular chemotherapeutic regimen—i.e., only before, but not during or subsequent to the chemotherapy; or only subsequent to, but not before or during the chemotherapy. To the contrary, the '202 Application emphasizes:

> It should be clear that the combined therapeutic regimens of the present invention can be performed whereby said therapies are given simultaneously, i.e., the anti-CD20 antibody is administered concurrently or within the same time frame (i.e., the therapies are

> going on concurrently, but the agents are not administered precisely at the same time). The anti-CD20 antibodies of the present invention may also be administered prior to or subsequent to the other therapies.

Id. at 008.

By expressly disclosing the particular species of treating low-grade NHL by administering rituximab subsequent to a CVP regimen on page 28, lines 16-21, the ’202 Application shows that the inventor was in possession of at least the subgenus of treating low-grade NHL by administering rituximab before, during or subsequent to a CVP regimen.

In re Herschler

The CCPA considered similar circumstances in *In re Herschler* and concluded that the disclosure of a broad genus and a particular species demonstrated that the inventor possessed a subgenus that encompassed the species. *In re Herschler*, 591 F.2d 693 (C.C.P.A. 1979).

In *In re Herschler*, the Board rejected claims in an application asserting priority to a great-grandparent application. *Id.* at 698-99. The rejection was based on references dated after the great-grandparent because the Board found that the great-grandparent did not support the pending claims. *Id.* at 698-99.

The great-grandparent application disclosed a genus of methods of using dimethyl sulfoxide (DMSO) to enhance the penetration of physiologically active substances through skin tissue. *Id.* at 695, 700. It also disclosed a specific example of using DMSO to enhance penetration of the glucocorticosteroid dexamethasone 21-phosphate through skin tissue, but it did not expressly disclose using DMSO to enhance penetration of any other steroids, or of steroids generally. *Id*. at 700 ("No other language in that specification specifically discusses topical application of a steroid-containing composition.").

The rejected claims in *In re Herschler* were directed to the subgenus method of using DMSO to enhance the penetration of steroids generally.

On appeal, the CCPA acknowledged that the subgenus of enhancing penetration of all steroids was "not found In haec verba in the great-grandparent application," *id*. at 700, but emphasized that "[t]he claimed subject matter need not be described In haec verba to satisfy the description requirement." *Id*. at 701. The court of appeal explained: "It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." *Id.* at 701. Based on the disclosure of the dexamethasone species, the court concluded "that one having ordinary skill in this

art would have found the use of the subgenus of steroids to be apparent in the written description of the great-grandparent application." *Id.*

Just as the disclosure of using DMSO to enhance penetration of a particular steroid (dexamethasone) in *In re Herschler* showed that the inventor there possessed the subgenus of using DMSO to enhance penetration of any steroid, so too does the disclosure of treating low-grade lymphoma by administering rituximab at a particular time relative to CVP therapy (subsequent to CVP therapy) show that the inventor here possessed the subgenus of treating low-grade lymphoma by administering rituximab at any time relative to the CVP therapy—i.e., before, during, or subsequent to the CVP therapy.

Possession of the subgenus of treating low-grade NHL by administering rituximab before, during or subsequent to a CVP regimen necessarily includes possession of treating low-grade NHL by administering rituximab during a CVP regimen, as claimed, because the phrase "before, during or subsequent to" is disjunctive, presenting three distinct alternatives. The '202 Application therefore discloses that the inventor had possession of each alternative, including the method of administering rituximab during a CVP regimen to treat low-grade B-cell NHL, as claimed.

Moreover, it is well established that when multiple alternative parts of an invention are disclosed and distinguished in a patent application, the inventor is permitted to claim one to the exclusion of the others. *Cf. Inphi*, 805 F.3d at 1355 (finding that a patent specification disclosing and distinguishing three signal types—"CS, CAS, RAS, and bank address"—was sufficient to support a negative limitation requiring signals "that are not CAS, RAS, or bank address signals"). Here, the '202 Application disclosed and distinguished administration of rituximab before, during, or subsequent to the chemotherapeutic regimens, and therefore the inventor was entitled to claim one of these alternatives ("during") to the exclusion of the others (e.g., "before" and "subsequent to").

Not only does the '202 Application disclose that the inventor had possession of methods of administering rituximab during a CVP regimen to treat low-grade B-cell NHL, it further discloses that the inventor had possession of such methods that produce beneficial synergistic effects, as required by claims 1 and 4. The application expressly discloses that "it has been found that treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with . . . chemotherapy." Ex. 1034 at 006.

2. Petitioner Fails To Establish That The '821 Patent Claims Are Not Entitled To The Benefit Of The '202 Application's Filing Date.

Petitioners arguments against priority boil down to piecemeal assertions that the claims do not find *in haec verba* support in the '202 Application. Pet. 22-27; *see, e.g., id.* at 22 ("This disclosure [at page 6, lines 12-14] does not identify CVP, does not specify low-grade NHL, and does not indicate a beneficial synergistic effect."). As noted above, however, it is well-established that "[t]he claimed subject matter need not be described In haec verba to satisfy the description requirement." *In re Herschler,* 591 F.2d at 701; *Ariad*, 598 F.3d at 1352 (explaining that "the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*"); *Apple Inc. v. Papst Licensing GMBH & Co. KG,* IPR2016-01844 (Paper 10) at 20 (Mar. 10, 2017) ("[W]hen examining the written description for support for the claimed invention,…the exact terms appearing in the claim 'need not be used *in haec verba*.'") (quoting *Blue Calypso*, 815 F.3d at 1345-46).

Petitioner's lead argument focuses on a list of chemotherapeutic regimens on page 6 of the '202 Application and argues that "[t]he omission of CVP from this list means this disclosure does not support CVP." Pet. 23. The Board should reject Petitioner's argument. Page 6 identifies a non-exclusive group of therapies from

which the "chemotherapeutic regimen ***may*** be selected," stating that the group includes "***at the very least***" nearly 20 therapies. Ex. 1034, 009 (emphasis added). Although CVP does not appear by name in that non-exclusive group, there can be no doubt that a POSA would have understood the inventor to be in possession of CVP as a chemotherapeutic regimen for use as part of the invention—even without the express disclosure of CVP later in the application—because of knowledge that the POSA would have brought to the table.

"[T]he patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before." *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Accordingly, "[t]he descriptive text needed to meet [Section 112] requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon*, 418 F.3d at 1357 (finding that "[t]he Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties"). Here, Petitioner's own expert acknowledges that a POSA would "have understood that CVP was a 'standard chemotherapy' in August 1998." Ex. 1002 at ¶65; *id.* at ¶85 ("CVP was a standard therapy for lymphoma"); *id.* at ¶101 (stating that "CVP was a well-known standard chemotherapy treatment"); *id.* at ¶108 (stating that "CVP was a standard chemotherapy

regimen"). Thus, a POSA would have understood that the '202 application's disclosure of methods "for treating B-cell lymphoma comprising administering to a patient a therapeutically effective amount of a chimeric anti-CD20 antibody before, during, or subsequent to a chemotherapeutic regimen" included methods of administering the antibody before, during, or subsequent to CVP therapy, and that the inventor was in possession of those methods. As the Federal Circuit has explained, "it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention." *Falkner*, 448 F.3d at 1366.

Petitioner argues that the inventor did not have possession of embodiments using CVP—even though CVP is expressly mentioned in the '202 Application and was known to be a standard chemotherapy before the priority date—because the passage on page 6 states that the chemotherapy "may be ***selected from the group consisting of,*** at the very least," a list in which CVP does not expressly appear. Pet. 23. Petitioner argues that "[i]t is axiomatic that 'the group consisting of' in patent lexicon exclusively means a closed term." *Id.* But that argument ignores that the passage also permissively states that the chemotherapy "may" be selected from the listed examples and introduces the list as including "at the very least" those examples. Moreover, as the *Vehicular Technologies* case cited by Petitioner

confirms, such language identifies a closed term when it appears in patent claims. *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382-83 (Fed. Cir. 2000) (describing "consisting of" language in claims as closed ended). Petitioner cites no case for the proposition that "consisting of" is so limiting in the written disclosure. Here, not only does the "selected from a group consisting of" language appear in the written disclosure instead of the claims, it is surrounded by language expressly stating that the disclosure is intended to be open ended. Thus, a POSA would have understood that the list on page 6 is not exhaustive.

A POSA also would have understood that the list on page 6 is not exhaustive because additional, unlisted chemotherapeutic regimens (in addition to CVP) appear in combination with an anti-CD20 antibody elsewhere in the '202 Application. For example, the application discloses administering "Rituximab weekly times 8 and oral cyclophosphamide daily" to "patients with low-grade NHL." Ex. 1034, 032. Cyclophosphamide administered daily appears nowhere in the list on page 6 of the '202 application. *Id.* at 009. Petitioner cannot reasonably contend that such a regimen therefore was excluded from the patent. Petitioner cannot ignore that the regimen appears elsewhere in the application. So, too, with CVP. The Board should reject Petitioner's attempt to elevate the disclosure of one portion of the specification that it prefers and to ignore the remainder. *See In re*

Skvorecz, 580 F.3d 1262, 1270 (Fed. Cir. 2009) (reversing the Board's finding that the written description requirement was not met where the Board focused on two "partial figures" as lacking disclosure of claimed structure when "the full structure [was] shown in other drawings of the various embodiments"); *In re Wright*, 866 F.2d 422, 425 (Fed. Cir. 1989) (reversing a written description rejection, explaining that "the specification as a whole must be considered" in deciding whether the written description requirement is satisfied).

Petitioner argues that the '202 Application merely renders obvious the subject matter of treating low-grade lymphoma with the combination of rituximab and CVP. But such subject matter is not obvious, it is expressly disclosed. As discussed above, the express disclosure appears as a description of an arm of a clinical study of rituximab and CVP. Of necessity, that arm had to administer the rituximab either before, during, or subsequent to the CVP. Here, it was the latter of those three options. But that does not make the '202 Application any less a disclosure of treating low-grade NHL by administering rituximab before, during or subsequent to CVP.

C. The ’202 Application Discloses That The Inventor Had Possession Of Dosing Rituximab Once Every 3 Weeks For 8 Doses During CVP.

The ’202 Application demonstrates that the inventor had possession of administering rituximab during CVP therapy, as discussed in Section IV.B above.

The ’202 Application discloses that CVP is usually administered every 3-4 weeks—i.e., on a 21-day or a 28-day cycle. Ex. 1034, 029 (“Cyclophosphamide is an alternative to chlorambucil, the usual dose being 1-2 g/m^2 every 3-4 weeks together with vincristine and steroid (e.g., COP regimen).”). This is consistent with what was known in the art as of the priority date. Ex. 1008, 029; Ex. 1036, 003.

The ’202 Application also discloses combination therapies for B-cell lymphomas comprising administering rituximab on day one of 21-day chemotherapy cycles—i.e., once every 3 weeks. For example, the application discloses “Rituximab® [] administered on Day 1 and CHOP [] given on Days 1 - 3 every 21 days for 6 cycles.” Ex. 1034, 040. Because there were six cycles of CHOP chemotherapy in this example, administering rituximab on day one of each 21-day cycle meant administering rituximab every 3 weeks for only six doses. But as Petitioner’s expert asserts, “[i]n clinical practice at that time, either CHOP or CVP was routinely used for 6 to 8 cycles.” Ex. 1002 ¶ 118; *id.* at ¶ 119 (describing “routine use of 6 to 8 cycles of chemotherapy regimens for lymphoma patients”).

Thus, a POSA would have understood that the inventor of the ’821 patent was also in possession of administering rituximab every 3 weeks for 8 doses. Indeed, administering a total of 8 doses of rituximab to treat lymphomas is expressly disclosed in the ’202 Application. Ex. 1034, 026 (describing “a Phase II study of eight weekly doses of 375 mg/m^2 Rituximab®”); *id.* at 032 (“Twenty patients will receive Rituximab® alone for 8 weekly doses.”).

Accordingly, a POSA would have understood that the inventor of the ’821 patent was in possession of administering rituximab every 3 weeks for 8 doses during CVP therapy.

Petitioner contends that “[t]he ’202 specification disclosures demonstrate that the inventor did not possess the dosing regimen recited in claims 4-6,” Pet. 28, 30,[6] but Petitioner fails to carry its burden of proving the same. *Tech. Licensing*, 545 F.3d at 1328. Again, Petitioner’s arguments wrongly assume that the written description requirement cannot be satisfied without *in haec verba*

[6] Given the numerous examples in the ’202 Application of administering 375 mg/m^2 of rituximab to treat lymphomas, *see, e.g.,* Ex. 1034, 022, 025-028, 032-034, 038-039, 044, Petitioner never contends that the inventor was not in possession of methods using rituximab infusions of that amount.

support in the specification. But the written description requirement "does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*." *Ariad*, 598 F.3d at 1352; *Falkner*, 448 F.3d at 1366 ("[I]t is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention.").

V. PETITIONER FAILS TO ESTABLISH THAT EX. 1006 ("IDEC's 10-K/A") WAS A PRIOR ART PRINTED PUBLICATION.

A patent claim can be challenged in inter partes review "only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). "'[P]ublic accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. § 102(b)." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it." *Id.*

Petitioner asserts that Ex. 1006 is a document filed with the SEC, Pet. 33, but fails to show that Ex. 1006 was "disseminated or otherwise made available to

the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence" could have located it. *SRI Int'l*, 511 F.3d at 1194.

The only evidence Petitioner offers as support for its "printed publication" claim is a document it refers to as a September 1996 "EDGAR Filing Manual" (Ex. 1055) and a document it calls "EDGAR Filing Details" (Ex. 1056). Even assuming that these documents establish that Ex. 1006 was filed with the SEC on March 3, 1998, as Petitioner contends, Pet. 33 n.11, the documents do not also establish the necessary public accessibility.

Petitioner asserts that "[t]he EDGAR Filer Manual from September 1996 explains that the public portions of live filings, such as the IDEC 10-K/A, are 'immediately disseminated to the public.' (Ex. 1055 at 020 (distinguishing live filings from test filings))." Pet. 33 n.11. Assuming that Ex. 1055 is a copy of the "EDGAR Filer Manual" from September 1996, and that such manual was operative 18 months later when Ex. 1006 allegedly was filed, the manual would not establish that Ex. 1006 was in fact actually disseminated to the public at that time (or any time). At most, it would simply be evidence that EDGAR users were

generally advised that public portions of live filings could be "immediately disseminated to the public." Ex. 1055, 020.[7]

Petitioner fails even to establish that Ex. 1006 was a "live filing" in the first place. Even assuming that Ex. 1006 was an electronic submission, Petitioner's "EDGAR Filer Manual" states that "[t]he SEC accepts electronic submissions by

[7] In a footnote, Petitioner also argues that Ex. 1006 was made public "pursuant to 15 U.S.C. §80a-44, which requires that '[t]he information contained in any registration, statement, application, report, or other document filed with the Commission shall be made available to the public . . . .'" Pet. 15 n.6 (ellipses in original). But the very next part of the statute, which Petitioner replaced with ellipses in its quote, is a list of exceptions. 15 U.S.C. §80a-44 (stating that such information "shall be made available to the public, ***unless and except***" certain circumstances apply) (emphasis added). Petitioner fails to establish that none of those exceptions applied to information in Ex. 1006. Moreover, Petitioner would fail to show that Ex. 1006 is a printed publication as of March 3, 1998 even if it had demonstrated that none of the exceptions applied, because the statute simply says that such information "shall be made available to the public." It does not say when.

direct telephone transmission, on magnetic tape, or on computer diskette." Ex. 1055, 005.

Even assuming that Ex. 1006 was a "live filing," Petitioner also fails to establish that the portions of Ex. 1006 on which it relies were "public portions." Petitioner does not contend that anything other than "***public portions*** of live filings . . . are 'immediately disseminated to the public'" per the EDGAR Filer Manual. Pet. 33 n.11 (emphasis added).

Additionally, Petitioner fails to establish that Ex. 1006 was catalogued or indexed in a way that might establish public accessibility. *In re Lister*, 583 F.3d 1307, 1312 (Fed. Cir. 2009) (describing cases where documents available for public inspection but not "'cataloged or indexed in a meaningful way'" were not "publicly accessible") (quoting *In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989)).

Petitioner offers no testimony in support of the alleged public accessibility of Ex. 1006. *See Liberty Mut. Ins. Co. v. Progressive Cas. Ins. Co.*, CBM2013-00009 (Paper 68) at 18 (Feb. 11, 2014) (declining to find a 10-K filing a printed publication because the petitioner "explains little, if anything, about how '10-K' forms are indexed or catalogued at the Security and Exchange Commission, or how

else the public may search the 10-K forms based on the technical content contained therein").

In essence, Petitioner's argument is that SEC filings are *per se* prior art printed publications. That is not the law. *See Liberty Mut.*, CBM2013-00009 at 18 ("[A]lthough Geostar 10-K is an official record, that does not mean it is a printed publication."); *id.* (emphasizing that the status of a document as a printed publication is "determined on a case-by-case basis").

Petitioner cites the Board's decision in *Coalition for Affordable Drugs (ADROCA) LLC v. Acorda Therapeutica, Inc.*, but that decision does not state that all SEC filings are prior art printed publications.[8] To the contrary, the Board stated

[8] In a footnote, Petitioner also cites two district court cases, but neither case holds that SEC filings are *per se* printed publications either. One of the cases, *American Stock Exch., LLC v. Mopex, Inc.*, 250 F. Supp. 2d 323, 328-29 (S.D.N.Y. 2003) contains a deeply factual analysis of whether a particular SEC submission was a printed publication, and the other case, *Wynn v. Chanos*, 75 F. Supp. 3d 1228, 1235 (N.D. Cal. 2014), is a Foreign Corrupt Practices Act case, not a patent case, and it contains no "printed publication" analysis at all, contrary to Petitioner's representation.

in *Acorda* that "'[t]he determination of whether a reference is a 'printed publication' under 35 U.S.C. §102(b) involves a case-by-case inquiry into the facts and circumstances.'" IPR2015-01850 (Paper 14) at 11 (Mar. 11, 2016) (quoting *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004)).

In *Acorda*, the issue was whether a document referred to as "S-1" was a printed publication. *Id.* at 11. The petition relied "upon the testimony of Dr. Bennett, who testifie[d] that the S-1 HTML properties demonstrate[d] that the SEC received the Acorda Therapeutics filing, including the S-1 form, on September 26, 2003 and made the S-1 available to the public on September 29, 2003." *Id.* at 12. The petition also relied on the testimony of Dr. Pleasure, who "testifie[d] that one of ordinary skill in the art, aware of Acorda's activities, would have been motivated to be kept apprised of Acorda's research and studies and would have monitored and sought information about such studies by looking for and accessing statements and publications by researchers and companies conducting such studies, including Acorda's clinical trial research and disclosures, such as Acorda's S-1." *Id.* at 12-13.

After considering the evidence, The Board stated: "Based on the evidence of record, we credit Dr. Pleasure's testimony and hold that there is sufficient evidence of record before us, to demonstrate that a person of ordinary skill in the art would

have been aware of Acorda's clinical trials and would have monitored and sought information about such studies by looking for and accessing statements and publications by Acorda and its researchers." *Id.* at 14. The Board concluded: "On this record, and for purposes of this decision, we hold that S-1 is a printed publication." *Id.* Thus, far from concluding that SEC filings are printed publications *per se*, the Board in *Acorda* analyzed the evidence and concluded that the particular SEC filing at issue qualified as a printed publication on the record before it, which included the testimony of two witnesses.

Unlike the petitioner in *Acorda*, Petitioner here does not rely on any testimony to support its printed-publication claim. Even assuming that Ex. 1006 were publicly available as an SEC filing before the priority date, Petitioner neglects to demonstrate that a POSA would have looked to such an SEC filing for guidance on how to treat NHL patients.

For all of these reasons, Petitioner fails to establish that Ex. 1006 is a prior art printed publication.

VI. PETITIONER FAILS TO ESTABLISH THAT ANY CHALLENGED CLAIM IS LIKELY UNPATENTABLE.

A. Ground 1: Marcus Does Not Anticipate Claims 1-6

Petitioner argues that "Marcus anticipates all claims of the '821 patent." Pet. 40. Petitioner's argument should be rejected because Marcus, which describes

a study sponsored by Patent Owner's collaborator F. Hoffmann-La Roche Ltd, is not prior art to the '821 patent. Even if it were prior art, Marcus falls short of anticipating at least claims 1, 3, 4, and 6 because Petitioner has not met its burden of establishing that Marcus disclosed certain features of these claims. Marcus was fully considered by the Office during prosecution. Ex. 1001, 007.

1. Marcus Is Not Prior Art To Claims 1-6

The '821 patent claims priority to the '202 Application, which was filed on August 11, 1999. Ex. 1001, 018. As explained in Section IV above, it is Petitioner's burden to establish that the '821 patent is ***not*** entitled to that priority date, and Petitioner fails to carry that burden.

Petitioner does not contend that Marcus was publicly available before the August 11, 1999 priority date. Rather, Petitioner contends that "Marcus is an article published in the journal *Blood* in February 2005," Pet. 32, more than five years ***after*** the priority date.

Accordingly, Petitioner cannot carry its burden of establishing that Marcus is prior art, much less anticipatory prior art, 35 U.S.C. § 316(e), and Ground 1 fails. *See Teva Pharms. Inc. v. Indivior UK Ltd.*, IPR2016-00280 (Paper 23) at 8 (June 10, 2016) (holding that a ground cannot be considered for institution if Petitioner

fails to "provide[] a sufficient threshold showing that the [cited references] constitute prior art").

2. Petitioner Never Attempts To Establish That The Treatment Of Marcus Achieved A "Beneficial Synergistic Effect" Under The Proper Construction Of Claims 1 And 4

"Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference." *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009) (reversing finding of anticipation under broadest reasonable interpretation standard).

Even if Marcus were prior art, Petitioner would fail to show that it anticipates at least claims 1 and 4, which require a "beneficial synergistic effect," because Petitioner never attempts to establish that the treatment disclosed in Marcus achieved a "beneficial synergistic effect" under the proper claim construction.

As discussed in Section III.A above, the term a "beneficial synergistic effect" means an effect that is better than the additive effects of rituximab and CVP administered alone. Petitioner does not contend that the treatment disclosed in Marcus achieved such an efficacy result. Instead, Petitioner ignores the requirement for synergy and argues under its erroneous "beneficial effect" construction that the claimed effect was achieved by the treatment of Marcus

because it "significantly lengthened time to treatment failure and more than doubled time to progression, with significantly improved response rates, duration of response, disease-free survival, and time to next antilymphoma treatment." Pet. 38-39, 41. Although these may be beneficial effects, Petitioner does not show that they are beneficial ***synergistic*** effects relative to the effects of rituximab and CVP alone. Given this failure of proof, Petitioner has not established that each and every limitation of at least claims 1 and 4 is met by Marcus.

3. Petitioner Never Attempts To Establish That The Rituximab Used In Marcus Was "Produced From Nucleic Acid," As Required By Claims 3 And 6

Even if Marcus were prior art, Petitioner would also fail to establish that Marcus anticipates claims 3 and 6. Claims 3 and 6 require that "the chimeric anti-CD20 antibody is produced from nucleic acid encoding a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2." Ex. 1001.

Petitioner argues that "Marcus inherently discloses rituximab's amino acid sequence, as depicted in SEQ ID NO: 1 and SEQ ID NO: 2 of the '821 patent" by disclosing use of rituximab. Pet. 39. But the claims do not merely recite those amino acid sequences. The claims require that "the chimeric anti-CD20 antibody is produced from nucleic acid encoding" such amino acid sequences. Ex. 1001,

029-030. Petitioner ignores that requirement, saying nothing whatsoever about how the anti-CD20 antibody of Marcus was produced. Nor does Petitioner even contend—let alone offer evidence—that the only way to produce an anti-CD20 antibody was from nucleic acid. This failure of proof is fatal to Petitioner's anticipation argument. Marcus does not expressly or inherently disclose that the rituximab it used was "produced from nucleic acid," let alone any particular nucleic acid. Accordingly, Petitioner fails to establish that Marcus meets every limitation of at least claims 3 and 6.

B. Ground 2: The Combination Of Marcus And The '137 Patent Does Not Render Claims 3 And 6 Obvious.

Petitioner argues that "[c]laims 3 and 6 of the '821 patent would have been obvious over Marcus (Ex. 1005) in view of the '137 patent (Ex. 1007)." Pet. 44. Like Marcus, the '137 patent was fully considered by the Office during prosecution. Ex. 1001, 001. The Board should reject Ground 2 because Petitioner fails to carry its burden of proving that Marcus is prior art, as explained in Section IV above. *See Teva Pharms.*, IPR2016-00280 (Paper 23) at 8.

Moreover, even if Marcus were prior art, Petitioner again ignores completely the requirement that the chimeric anti-CD20 antibody of claims 3 and 6 "is produced from nucleic acid." Ex. 1001, 029-030. Petitioner's failure to address this

claim element in any respect leaves an enormous hole in its obviousness argument. A claim is not obvious unless "the differences between the subject matter sought to be patented and the prior art are such that ***the subject matter as a whole*** would have been obvious at the time the invention was made to a person having ordinary sill in the art to which said subject matter pertains." 35 U.S.C. §103 (pre-AIA) (emphasis added).

For at least these reasons, Petitioner fails to establish that Marcus and the '137 patent render obvious claims 3 and 6.

C. Ground 3: The Combination Of Czuczman, "IDEC's 10-K/A," Foon, And Dana Does Not render Claims 1-3 Obvious.

Petitioner argues that "[c]laims 1-3 of the '821 patent would have been obvious over Czuczman (Ex. 1011), in view of IDEC's 10-K/A (Ex. 1006), Foon (Ex. 1008), and Dana (Ex. 1009)." Pet. 45. The Board should reject Petitioner's argument because Petitioner fails to establish that "IDEC's 10-K/A" (Ex. 1006) was a prior art printed publication. In any event, Petitioner also fails to demonstrate that a POSA would have modified Czuczman by substituting CVP, which does not contain doxorubicin, for CHOP, which does. Even if a POSA would have made such a modification, Petitioner fails to establish that a POSA would have had a reasonable expectation of success in arriving at the claimed

inventions, including a method of achieving a "beneficial synergistic effect" by administering rituximab during CVP therapy. Czuczman, Foon, and Dana all were considered by the Office during prosecution. Ex. 1001, 010-011, 016

1. Petitioner Fails To Establish That "IDEC's 10-K/A" Was A Prior Art Printed Publication.

Because Petitioner fails to establish that "IDEC's 10-K/A" (Ex. 1006) was a prior art printed publication, as explained in Section V above, Petitioner likewise fails to establish a reasonable likelihood of showing that claims 1-3 are rendered obvious by the combination of Ground 3, which relies on "IDEC's 10-K/A." *See Cisco Sys., Inc. v. Constellation Techs. LLC*, IPR2014-01085 (Paper 11) at 9 (Jan. 9, 2015) ("Petitioner has not made a sufficient showing that Rosenberg qualifies as a printed publication under 35 U.S.C. § 102(b) and, thus, falls within the proper scope of an *inter partes* review."); *Hughes Network Sys., LLC v. Cal. Inst. Tech.*, IPR2015-00067, 2015 WL 1940217, at *6 (Apr. 27, 2015) (denying institution "[b]ecause each of Petitioner's asserted grounds of unpatentability is based, in part, on [a reference found not to be a printed publication] and, thus, [fails to satisfy] the statutory requirement of 35 U.S.C. § 311(b)").

2. Petitioner Fails To Demonstrate That A POSA Would Have Modified Czuczman By Substituting CVP, Which Does Not Contain Doxorubicin, For CHOP, Which Does.

a) *A POSA Would Not Have Substituted CVP For CHOP, Given The Synergy Between Rituximab And The Doxorubicin In CHOP*

As discussed above, Czuczman is an abstract that discloses use of C2B8 (rituximab) and CHOP to treat low-grade lymphoma. Ex. 1011, 003. Before the August 11, 1999 priority date, the authors of Czuczman explained that one of "[t]he rationale[s] for combination of IDEC-C2B8 [rituximab] with CHOP" was "known synergy with doxorubicin." Ex. 1041, 60.[9] This synergy also was reported by others. For example, a 1997 paper explained that "[t]he standard CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) was chosen for combination therapy with rituximab because . . . there is evidence of *in vitro* synergy between the antibody and doxorubicin." Ex. 2009, 001.

Because rituximab was known to be synergistic with doxorubicin, a POSA would have been discouraged from replacing CHOP, which includes doxorubicin, with CVP, which does not. Petitioner fails to demonstrate otherwise.

Petitioner argues that Czuczman refers generally to "synergy with chemotherapeutic agents." Pet. 45. But Czuczman itself does not purport to

[9] The author lists for Exs. 1011 and 1041 are identical, with one exception.

demonstrate synergy with chemotherapeutic agents generally. And Petitioner cites no research that showed rituximab is synergistic with chemotherapy generally. Nor does Petitioner cite any research that showed rituximab is synergistic with any components of CHOP other than doxorubicin—namely CVP. Thus, Petitioner articulates no basis for a POSA to have believed that rituximab is synergistic with chemotherapy generally, or with any of the components of CVP.

In any event, a POSA as of the priority date in 1999 would have understood, based on literature available at the time, that the rationale for combination of rituximab and CHOP was synergy with doxorubicin specifically. Such literature included an article by the Czuczman authors expressly saying the same, Ex. 1041, 003, and the results of *in vitro* research showing such synergy. Ex. 1079, 002; *see also* Ex. 2009, 001. Petitioner cannot ignore this literature. "The person of ordinary skill is a hypothetical person who is presumed to be aware of ***all*** the pertinent prior art." *Custom Accessories v. Jeffrey-Allan Indus.*, 807 F.2d 955, 962 (Fed. Cir. 1986) (emphasis added). The Board should not indulge Petitioner's tunnel vision.

Nor should the Board give weight to the conclusory assertion by Dr. Lossos that "a POSA would not have interpreted . . . [the art] to mean that doxorubicin alone was necessary for the synergy between CHOP and rituximab." Ex. 1002,

¶70. Moreover, Dr. Lossos never explains why anyone supposedly would have believed that "other cytotoxic drugs would also be likely to display parallel synergy with rituximab." *Id.* "Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." 37 C.F.R. §42.65(a); *ActiveVideo Networks, Inc. v. Verizon Communs., Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (discounting expert testimony where the expert "never provided any factual basis for his assertions"); *Delphix Corp. v. Actifio, Inc.*, IPR2015-01678 (Paper 8) at 20 (Feb. 10, 2016) (denying institution where Petitioner relied on "conclusory expert testimony that, itself, does not cite to evidentiary support").

Petitioner asserts, in connection with its "objective indicia" arguments, that "[t]he art resoundingly supports synergy between rituximab and chemotherapy generally, not a unique synergy with doxorubicin" because "several prior art publications describe rituximab's general 'synergy with chemotherapeutic agents' that was not specific to doxorubicin." Pet. 63. But Petitioner cites only one reference other than Czuczman, addressed above, and that other reference is another abstract by the Czuczman authors[10] reporting again on their combination of

[10] With a few substitutions.

rituximab and CHOP. That abstract simply repeats the same general language found in Czuczman, Ex. 1049 at 003, and fails to support Petitioner's position for the same reason that Czuczman itself fails to do so.

Petitioner further asserts that "publications identifying a possible synergy between doxorubicin and rituximab cite back to a study by Demidem, published in 1995 and 1997." Pet. 64. As Petitioner acknowledges, Demidem tested rituximab and a number of cytotoxic agents, including doxorubicin—but not any of the other components of CHOP (those other components being CVP). *Id.* Petitioner also acknowledges that not all of the cytotoxic agents demonstrated synergy. *Id*. (identifying the chemotherapy etoposide as not more active against cells pretreated with rituximab).[11] Thus, Demidem itself is further evidence that a POSA would not have understood Czuczman to be suggesting synergy between rituximab and chemotherapy generally, or between rituximab and the other components of CHOP—namely, CVP. Ex. 1079; *see also* Ex. 1021, 004 (referring to "*in vitro* synergy with ***certain*** cytotoxic drugs (including doxorubicin)") (emphasis added).

[11] Ex. 1008, 031 (identifying in Table 111-8 the "combination chemotherapy" ESHAP, comprising etoposide).

According to Petitioner, "Czuczman also provides a rationale for combining rituximab with CHOP that a POSA would have understood to apply equally to CVP." Pet. 53. But that rationale included synergy, and Petitioner offers no evidence of any known synergy between rituximab and CVP. Moreover, at least by the priority date, a POSA understood that the rationale was based on synergy with doxorubicin specifically, as discussed above. Ex. 1041, 003 (clarifying the rationale with reference to "known synergy with doxorubicin" instead of "known synergy with chemotherapeutic agents").

Even if there were evidence that a POSA would have considered other parts of the Czuczman rationale to be applicable, the question would be whether those other parts of the rationale would have prompted the POSA to subtract the synergistic agent doxorubicin from R-CHOP to arrive at R-CVP.[12] There is no evidence suggesting that they would have. If anything, Czuczman itself suggests that they would ***not*** have—particularly given the remarkable 100% response rate it reports for rituximab in combination with CHOP. Ex. 1011, 003 ("Overall

[12] Whether other parts of the rationale would have prompted a POSA to have combined rituximab and CVP starting from a clean slate is irrelevant. Petitioner bases its challenge on the R-CHOP therapy of Czuczman.

response rate for the 14 pts completing all scheduled therapy to date is 100% (11 CR and 3 PR)."); *see also* Ex. 1020, 002 (reporting that 38 out of 38 treated patients ultimately responded). A POSA would have been motivated to retain CHOP so as to maximize the chances of replicating this extraordinary result in these hard-to-treat cancer patients.

b) ***Petitioner Fails To Demonstrate That Alleged Toxicity Concerns Would Have Led A POSA To Substitute CVP For CHOP***

Petitioner suggests that a POSA might have substituted CVP for CHOP because "[a] POSA would have understood from Foon and Dana that CVP was a standard chemotherapy regimen that was less toxic but equally effective as CHOP for low-grade NHL." Pet. 51. The record does not support this assertion. Foon nowhere addresses the relative toxicities of CVP and CHOP. Ex. 1008. Nor does Dana. Ex. 1009. In fact, Dana does not even address toxicity. *Id.* Dana simply reviews survival data. *Id.* at 002.

Petitioner also cites Marcus 2005 (Ex. 1005), Maloney 1998 (Ex. 1022), Steward 1988 (Ex. 1031), and McNeil 1998 (Ex. 1059), but Petitioner's reliance on those documents is misplaced too:

- Marcus 2005 is not even prior art, because Petitioner failed to establish that the ’821 patent is not entitled to an August 11, 1999 priority date, as explained in Section IV above.
- Maloney 1998 nowhere even addresses CVP, let alone its toxicity. Ex. 1022. Rather, Maloney 1998 simply concludes that the toxicity of rituximab plus CHOP “appeared to be comparable to that observed with the antibody alone and that expected from treatment of CHOP,” *id.*, confirming that the combination yielded no additional toxicities.
- Instead of comparing the toxicities of CVP and CHOP, Steward 1988 refers to studies of numerous alternatives to “the use of combination chemotherapy (predominantly CVP) and single alkylating agents (chlorambucil or cyclophosphamide),” and generally concludes that “[u]nfortunately, these studies . . . ***often*** have resulted in more toxicity,” without comparing any particular agents head to head. Ex. 1031, 007 (emphasis added).
- Like Maloney 1998, McNeil 1998 nowhere addresses CVP, let alone compares its toxicity to that of CHOP. Ex. 1059.[13]

[13] McNeil mentions CHOP studies “under way in the elderly” and notes that

Thus, none of the cited documents supports Petitioner's assertion that a POSA would have understood that CVP was less toxic but equally effective as CHOP for low-grade NHL.

Instead of identifying CVP as a less-toxic, equally-effective substitute for CHOP, Petitioner's references actually identified other chemotherapies as alternatives to CHOP. For example, Foon identifies C-MOPP and CNOP as substitutes for CHOP for patients "who are not able to take doxorubicin." Ex. 1008, 030. Moreover, Bishop divides low-grade lymphomas into "diffuse" and "nodular" types and reports a study showing "that single agent cyclophosphamide is as effective as intense combination chemotherapy in nodular lymphomas" (suggesting single-agent cyclophosphamide, not CVP, as an alternative to CHOP) and that doxorubicin-containing regimens are better for diffuse lymphomas. Ex. 1036, 006. Bishop also reports that high-dose CAVP (a.k.a. CHOP) and CVP were found "equitoxic." *Id.* at 002. Thus, a POSA relying on Bishop would not

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it was thought "that CHOP, like some other chemotherapy regimens, is more toxic in this age group" than in other age groups (not that CHOP is more toxic than CVP). Ex. 1059, 003.

have concluded that CVP is a less-toxic substitute for CHOP, contrary to Petitioner's assertions.

McNeil likewise identified several "drug combinations"—none of which is CVP—"that may be as effective but less toxic than CHOP." Ex. 1059, 267. These drug combinations included "CIEP, in which the less toxic idarubicin and VP16(P) are substituted for CHOP's doxorubicin and vincristine," and "'mini-CHOP,' called COPA," which "uses the same drugs as CHOP given in reduced doses along with supportive agents, such as an antibiotic and an antifungal." Ex. 1059, 004. McNeil reported that "[p]reliminary data . . . suggest that outcomes [for mini-CHOP] are similar to CHOP in the elderly with less chance of side effects." *Id.*

In an earlier IPR on claims of a related patent directed to the use of rituximab as maintenance therapy following administration of CVP, the Board concluded that "even assuming that CVP therapy was known to be less toxic than CHOP," the challenger had not shown that a POSA would have substituted CVP for CHOP, particularly in view of McNeil. Specifically, the Board wrote:

> Given McNeil's express teaching that mini-CHOP can be used to reduce toxicity, alongside evidence in the art of synergy between rituximab and doxorubicin, Petitioner does not persuade us that an ordinary artisan would have omitted the doxorubicin component of CHOP, and instead use CVP therapy followed by rituximab as

> required by claim 1 of the ’172 patent, ***even assuming that CVP therapy was known to be less toxic than CHOP***.

Boehringer Ingelheim Int’l GmbH v. Biogen Inc., IPR2015-00418 (Paper 14) at 19 (July 13, 2015) (attached as Exhibit 2010 for convenience) (emphasis added). The same holds true here with respect to the same arguments that Celltrion is making against the ’821 patent.

c) *A POSA Would Not Have Substituted CVP For CHOP, Given Other Remarkable Results Achieved By The Combination Of Rituximab Plus CHOP.*

By the priority date, skilled artisans knew that “approximately 80% of low-grade NHL” was associated with chromosomal translocation of a gene called “*bcl-2*.” Ex. 1020, 009. They further knew that this translocation “results in increased transcription and accumulation of high levels of bcl-2 protein,” Ex. 1041, 002, “which inhibits apoptosis and is believed to play an important role in lymphomagenesis,” the growth and development of lymphoma. Ex. 1020, 009.

Patients presenting with translocations of *bcl-2*, as measured by a polymerase chain reaction (PCR) assay, were described as “bcl-2 positive.” Ex. 1020, 005. Czuczman noted at the time that “[s]tandard induction or salvage chemotherapy regimens (including CHOP x 6) alone have previously been shown to be unable to clear bcl-2 positivity from marrow.” Ex. 1011, 003; Ex. 1020, 009

("Standard-dose CHOP alone is incapable of converting *bcl-2*-positive bone marrow to PCR negativity.").

Unlike CHOP alone, the combination of rituximab and CHOP was able to convert patients to bcl-2 negativity. In fact Czuczman reports that "[a]ll 4 [bcl-2 positive patients who completed treatment] converted to bcl-2 negativity." Ex. 1011, 003. These remarkable results were maintained through study completion. A total of eight patients in the Czuczman study were "found to be *bcl-2* positive in blood and/or marrow pretreatment," and "[s]even of [those] eight patients converted to PCR negativity after completion of therapy." Ex. 1020, 009. "The seven patients becoming *bcl-2* negative also had documented complete remissions by standard restaging evaluations and were considered to have achieved molecular complete remissions." *Id.* Six patients remained in CR, and five of seven patients remained PCR negative by serial analysis for at least 24 months or longer." *Id.*

These extraordinary results for CHOP in combination with rituximab would have discouraged a POSA from substituting CVP for CHOP to arrive at the claimed combination.

Although Petitioner acknowledges Czuczman's reports that "[a]ll patients who began the study bcl-2 positive converted to bcl-2 negativity at the conclusion

of treatment" and that "standard chemotherapy regimens alone" had been unable to achieve such a result, Pet. 46, Petitioner never acknowledges that those reports would therefore have encouraged a POSA to use the same chemotherapy—CHOP—in pursuit of the same extraordinary results. Petitioner fails to show that a POSA would have substituted CVP for CHOP despite such results.

3. Petitioner Fails To Establish A Reasonable Expectation Of Success In Arriving At The Claimed Inventions.

It is well established that "pharmaceutical development is an unpredictable art." *Mylan Pharmaceuticals Inc. v. Yeda Research & Dev. Co. Ltd.*, IPR2015-00643 (Paper 90) at 19 (Dec. 2, 2016); *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016) (observing that "medicinal treatment" is one of the "unpredictable arts"). Petitioner fails to establish a reasonable expectation of success in this unpredictable art.

a) *Petitioner Does Not Show Even That A POSA Would Have Expected Administering Rituximab During CVP Therapy Would Be Effective.*

Petitioner argues that a POSA "would have had a reasonable expectation that the claimed treatment regimen would be safe and efficacious" based on Czuczman. Pet. 53. This argument fails, even assuming that Petitioner only needed to show that a POSA would have expected administering rituximab during CVP therapy to be "safe and efficacious."

Petitioner argues that "a POSA would have expected the combination of CVP and rituximab to be similarly successful to CHOP in extending remissions," as reported in Czuczman. *Id.* But that assumes—counterfactually—that the POSA would not have expected the doxorubicin in CHOP to contribute to the efficacy of the rituximab-CHOP (R-CHOP) combination. As explained above, a POSA would have understood that rituximab and doxorubicin contribute synergistically to the efficacy of the R-CHOP combination. *See supra* Section VI.C.2 above. Petitioner argues that a POSA would also have believed that rituximab would be synergistic with chemotherapy generally—not just with doxorubicin or the other agents that had actually been tested. Pet. 53-54. The Board should reject that argument too, as also explained above. *See supra* Section VI.C.2 above.

In addition to being counterfactual, Petitioner's argument overlooks the fact that Czuczman reported a remarkable 100% overall response rate in the patients who had completed all scheduled therapy, with no unexpected toxicities. Ex. 1011, 003; Ex. 1020, 002. Petitioner fails to articulate any basis for a POSA to believe that a combination of R-CVP would produce an equally remarkable result.

Thus, Petitioner fails to establish any reasonable expectation of success for the combinations of claims 1-3.

b) ***Petitioner Does Not Show That A POSA Would Have Expected That Administering Rituximab During CVP Therapy Would Yield A "Beneficial Synergistic Effect," As Required By Claim 1***

Petitioner also fails to establish that a POSA would have had a reasonable expectation that administering rituximab during CVP therapy would achieve the claimed "beneficial synergistic effect"—i.e., an effect better than the additive effects of rituximab and CVP administered alone—as required by claim 1. *See supra* III.A above.

Instead, Petitioner simply argues that "Czuczman describes the improvement in clinical outcome for the patients who received rituximab during standard chemotherapy." Pet. 50. As alleged support, Petitioner quotes Czuczman's 100% overall response rate and its statement that "[t]he finding of molecular remissions by PCR suggests that the anti-tumor activity of CHOP and [rituximab] is superior to CHOP therapy alone." Pet. 50. Petitioner does not even contend that such activity is superior to the additive effects of CHOP and rituximab alone, as required by the proper construction of "beneficial synergistic effect." Pet. 50.

In any event, Petitioner fails to establish that synergy observed for rituximab and CHOP would have inspired, in a POSA, a reasonable expectation of synergy for the claimed combination of rituximab plus CVP. Petitioner again asserts that "Czuczman further explains that rituximab exhibits 'synergy with

chemotherapeutic agents,'" Pet. 50, but at least by the priority date, a POSA would have understood the rationale for the Czuczman combination of rituximab and CHOP to be synergy with doxorubicin specifically, not any and every chemotherapy imaginable, as discussed above. *See supra* Section VI.C.2 above.

D. Ground 4: The Combination Of Czuczman, "IDEC's 10-K/A," Foon, Dana, Link, And Piro Does Not Render Claims 4-6 Obvious.

As Ground 4, Petitioner argues that "[c]laims 4-6 of the '821 patent would have been obvious over Czuczman (Ex. 1011) in view of IDEC's 10-K/A (Ex. 1006), Foon (Ex. 1008), Dana (Ex. 1009), Link (Ex. 1010), and Piro (Ex. 1004)." Pet. 54. Thus, Ground 4 includes all of the references of Ground 3 plus two more: Link and Piro, which were considered by the Office during prosecution. Ex. 1001, 006-007.

Ground 4 challenges claims 4-6, whereas Ground 3 challenges claims 1-3. Claims 4-6 contain all of the limitations of claims 1-3, respectively, plus the limitation that the rituximab (or C2B8 or chimeric anti-CD20 antibody) is administered "once every 3 weeks for 8 doses."

Petitioner argues that the references of Ground 3 render obvious the parts of claims 4-6 that are identical to claims 1-3 for the same reasons those references allegedly render obvious claims 1-3. Because the references of Ground 3 do not

render obvious claim 1-3, as discussed in Section VI.C above, those same references do not render obvious the identical portions of claims 4-6, and Ground 4 fails for the all the same reasons that Ground 3 fails.[14]

Moreover, Petitioner fails to demonstrate that a POSA would have arrived at the additional "once every 3 weeks for 8 doses" limitations of claims 4-6 by combining the references of Ground 4.

[14] Petitioner further cites Link in connection with the "beneficial synergistic effect" limitation of claim 4. Pet. 57-58. But as Petitioner concedes, Link reports on a study of rituximab and CHOP in "intermediate- or high-grade NHL patients," not in the low-grade NHL patients of the claims. Pet. 54. In any event, Petitioner does not even contend that rituximab plus CHOP is shown by Link to be better than the additive effects of rituximab and CHOP administered alone, much less that such synergy would have inspired, in a POSA, a reasonable expectation of synergy for the claimed combination of rituximab plus CVP. *Id.*

Petitioner also cites Link and Piro—cumulative to its citation of Czuczman carried over from claim 3—as references in which the SEQ ID NOs of claim 6 are "inherently disclosed" by virtue of their disclosure of rituximab. Pet. 58.

Petitioner asserts that a POSA would have arrived at the dosing schedule by routine optimization. But Petitioner comes nowhere near to making the required showing. There are at least five requirements that must be satisfied in order for "routine optimization" to apply to a variable, and Petitioner fails to establish that these requirements are satisfied with respect to either of the variables implicated by the claimed dosing schedule: the number of doses or the time interval.

First, the result of the "optimization" process must in fact be an "optimum value" for the variable. *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977); *In re Aller*, 220 F.2d 454, 458 (C.C.P.A. 1955) ("No invention is involved in discovering *optimum* ranges of a process by routine experimentation.") (emphasis added). Petitioner never even asserts, much less submits evidence demonstrating, that administering one dose every 3 weeks, administering a total of 8 doses, or administering one dose every 3 weeks for 8 doses, is in fact "an optimum."

Second, each variable being optimized must have been "*known*" to be "*result-effective*." *In re Antonie*, 559 F.2d at 620 (rejecting a routine optimization argument because "the parameter optimized was not recognized to be a result-effective variable") (emphasis added). Petitioner does not contend that both the time interval and the number of doses were considered "result effective," much less that a POSA knew the way in which each of those variables allegedly affects

results or how the variables interact with each other. *See id.*; *In re Yates,* 663 F.2d 1054, 1056 (C.C.P.A. 1981) (rejecting a routine optimization argument because the allegedly optimized parameter "was not recognized to be a result-effective variable"); *cf. In re Urbanksi*, 809 F.3d 1237, 1242 (Fed. Cir. 2016) ("[R]eaction time and degree of hydrolysis are result-effective variables that can be varied in order to adjust the properties of the hydrolyzed fiber *in a predictable manner*.") (emphasis added).

Third, the evidence must show that the experimentation needed to optimize the variable also was known in the art. *In re Fay*, 347 F.2d 597, 602 (C.C.P.A. 1965) ("To support the board's decision that 'routine experimentation within the teachings of the art' will defeat patentability requires a primary determination of whether or not appellants' experimentation comes *within the teachings of the art*.") (emphasis in original). Petitioner fails to provide any evidence describing the experimentation process that allegedly would have been needed to arrive at the claimed dosing schedule, much less evidence that such experimentation would have been known by a POSA.

Fourth, the prior art must "have suggested to one of ordinary skill in the art that this [experimentation] process should be carried out and would have a

reasonable likelihood of success, viewed in light of the prior art." *Merck*, 874 F.2d at 809 (internal quotes omitted). Petitioner identifies no such suggestions in the art.

Fifth, the experimentation required to arrive at the claimed optimum must, as the label "routine optimization" implies, be no more than routine. *Id.* ("The evidence at trial showed that, though requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine."). Petitioner fails to submit evidence establishing that any such experimentation to arrive at the claimed dosing schedule of "once every 3 weeks for 8 doses" would have been merely routine.

There is therefore no evidence that a POSA would have arrived at the claimed dosing of once every 3 weeks for 8 doses through routine optimization, and Petitioner's argument fails. Petitioner is relying on hindsight, not routine optimization. This is impermissible. *See, e.g., St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1381 (Fed. Cir. 2013) ("[W]e must guard against hindsight bias and *ex post* reasoning.") (internal quotes and cites omitted).

E. Ground 5: The Combination Of Czuczman, "IDEC's 10-K/A," Foon, Dana, Link, And Piro, And The '137 Patent Does Not Render Claims 3 And 6 Obvious.

For Ground 5, Petitioner argues that "[c]laims 3 and 6 of the '821 patent would have been obvious over Czuczman (Ex. 1011) in view of IDEC's 10-K/A

(Ex. 1006), Foon (Ex. 1008), Dana (Ex. 1009), Link (Ex. 1010), Piro (Ex. 1004), and the ’137 patent (Ex. 1007).” Pet. 62. Thus, Ground 5 includes all of the references of Ground 4 plus the ’137 patent.

Petitioner asserts that “[t]he ’137 patent discloses the sequence of rituximab.” Pet. 62. Petitioner states that it is citing the patent as a backup “to the extent the Board finds that Czuczman, Link, and Piro do not inherently disclose and therefore anticipate the SEQ ID NO: 1 and SEQ ID NO: 2 claim elements found in claims 3 and 6.” Pet. 62.

Petitioner relies on the references of Grounds 3 and 4 for all the other elements of claims 3 and 6. *Id.* Because those references fail to render obvious the other elements of claims 3 and 6, as explained in sections VI.C and VI.D above, Ground 5 fails for at least the all the same reasons that Ground 3 and Ground 4 fail.

VII. UNCONSTITUTIONALITY OF INTER PARTES REVIEWS

In *Oil States Energy Services, LLC. v. Greene’s Energy Group*, the Supreme Court will consider the constitutionality of inter partes review proceedings. No. 16-712, 2017 U.S. LEXIS 3727 (June 12, 2017) (granting certiorari). Patent Owner preserves the position that this inter partes review proceeding and the challenge to Patent Owner’s duly issued and existing ’821 patent violates the Constitution by allowing for private property rights to be extinguished through an adversarial

process in the Patent and Trademark Office, a non-Article III forum, without a jury. *See McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 608-09 (1898).

VIII. CONCLUSION

For the foregoing reasons, the Board should decline to institute.

Dated: July 10, 2017

Respectfully submitted,

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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 13,852 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: July 10, 2017

Respectfully submitted,

/s/ Susan Langworthy
Susan Langworthy

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. 42.6, the undersigned certifies that on July 10, 2017 a copy of **BIOGEN'S PATENT OWNER PRELIMINARY RESPONSE** and **EXHIBITS 2001-2011** were served by electronic mail upon the following:

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