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Paper 8
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. and APOTEX CORP.,
Petitioners,

v.

CELGENE CORPORATION,
Patent Owner.

Case IPR2018-00685
Patent 8,741,929 B2

Before TONI R. SCHEINER, GRACE KARAFFA OBERMANN, and TINA E. HULSE, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 U.S.C. § 314(a)

I. INTRODUCTION

Apotex Inc. and Apotex Corp. (collectively, "Petitioner")[1] filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review of claims 1–4, 8, 9, 15, and 20 of U.S. Patent No. 8,741,929 B2 (Ex. 1001, "the '929 patent"). Celgene Corporation ("Patent Owner") filed a Preliminary Response to the Petition (Paper 6, "Prelim. Resp."). We have statutory authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

For the reasons set forth below, we conclude that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any challenged claim of the '929 patent. Accordingly, we do not institute an *inter partes* review of claims 1–4, 8, 9, 15, and 20 of the '929 patent.

A. Related Proceedings

The '929 patent has been asserted in *Celgene Corp. v. Apotex Inc.*, C.A. No. 18-cv-00461 (D.N.J. filed Jan. 11, 2018). Pet. 5; Paper 3, 1.

B. The Asserted Grounds of Unpatentability

Petitioner asserts that the challenged claims are unpatentable on the following grounds:

[1] According to Petitioner, "[a]dditional real parties-in-interest are Apotex Pharmaceutical Holdings Inc., and Apotex Holdings Inc." Pet. 5.

References	Basis	Claims Challenged
Drach[2] and Zeldis[3]	§ 103(a)	1–4, 8, 9, 15, and 20
Drach, Zeldis, and Querfeld[4]	§ 103(a)	4 and 20
Celgene Press Release[5]	§ 102(a)	1–4, 8, 9, 15, and 20

Petitioner supports its challenges with the Declaration of Michael J. Thirman, M.D, dated February 23, 2018 (Ex. 1002, "Thirman Declaration").

C. The '929 Patent (Ex. 1001)

The '929 patent, titled "Methods Using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for Treatment of Mantle Cell Lymphomas," issued June 3, 2014, to inventor Jerome B. Zeldis. Ex. 1001 (54), (75). The title compound is "an immunomodulatory compound . . . also known as lenalidomide, Revlimid® or Revimid®." *Id.* at 1:19–23.

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[2] Johannes Drach at al., *Treatment of Mantle Cell Lymphoma: Targeting the Microenvironment*, 5 EXPERT REV. ANTICANCER THER. 477–485 (2005) (Ex. 1003, "Drach"). We refer to the page numbers of the exhibit, rather than the page numbers of the journal article.

[3] Jerome B. Zeldis, U.S. Patent Application Publication US 2004/0029832 A1, published February 12, 2004 (Ex. 1004, "Zeldis").

[4] Christiane Querfeld et al., *Preliminary Results of a Phase II Study of CC-5013 (Lenalidomide, Revlimid®) in Patients with Cutaneous T-Cell Lymphoma*, 106 BLOOD 3351 (2005) (Ex. 1005, "Querfeld").

[5] Celgene Press Release, titled "Revlimid® (Lenalidomide) Clinical Results in Non-Hodgkins Lymphoma Presented at the 11th Congress of the European Hematology Association" (2006) (Ex. 1006, "Celgene Press Release").

The specification teaches that lymphomas comprise a heterogeneous group of neoplasms arising in the reticuloendothelial and lymphatic systems. Within that group, the term non-Hodgkin's lymphoma (NHL) refers to a subset of neoplasms involving malignant monoclonal proliferation of lymphoid cells in the immune system, including the lymph nodes, bone marrow, spleen, liver, and gastrointestinal tract. *Id.* at 1:64–2:2. The specification further teaches that mantle cell lymphoma (MCL) is a lymphoproliferative disorder characterized by a specific chromosomal translocation which results in overexpression of the protein cyclin D1, which plays a key role in cell cycle regulation and progression of cells from G1 phase to S phase by activation of cyclin-dependent kinases. *Id.* at 2:16–29.

According to the specification, MCL "is a distinct entity among the non-Hodgkin's lymphomas . . . account[ing] for 8% of all non-Hodgkin's lymphomas" (*id.* at 2:4–5), and "is an incurable lymphoma with limited therapeutic options for patients with relapsed or refractory disease" (*id.* at 2:36–38).

The specification describes the results of a Phase II clinical trial designed to evaluate the therapeutic potential and safety of oral lenalidomide monotherapy in patients with relapsed and refractory aggressive non-Hodgkin's lymphoma. *Id.* at 23:12–20.

> Twenty-five patients age 45 to 80 years . . . with relapsed and refractory aggressive NHL and who had received a median of 2.5 prior treatments . . . were administered with lenalidomide in an amount of 25 mg orally once daily for 21 days in the treatment cycle. Sixteen patients with aggressive NHL were

> evaluable for tumor assessment. Of the 16 patients, eight had diffuse large cell lymphoma, three had mantle cell lymphoma, two patients had follicular lymphoma, one had transformed lymphoma, and two had aggressive lymphomas of unknown histology.
>
> There were five (31 percent) patients who experienced objective responses to lenalidomide monotherapy . . . One patient with diffuse large cell lymphoma achieved complete response with progression free survival of more than 180 days. One patient with diffuse large cell lymphoma achieved partial response with progression free survival for 135 days. One patient with diffuse large cell lymphoma achieved partial response with progression free survival for 242 days. One patient with follicular lymphoma achieved partial response with progression free survival for more than 55 days. One patient with mantle cell lymphoma achieved partial response with progression free survival for more than 57 days.

Id. at 23:24–48.

Finally, the specification discloses "methods of treating, preventing or managing non-Hodgkin's lymphomas, including . . . mantle cell lymphoma" (*id.* at 1:23–26), particularly disease that is "relapsed, refractory, or resistant to conventional chemotherapy" (*id.* at 2:47–48).

D. Illustrative Claim

Petitioner challenges claims 1–4, 8, 9, and 20 of the '929 patent, of which claim 1 is independent. Claim 1, reproduced below, is illustrative. Ex. 1001, 29:1–11.

> 1. A method of treating mantle cell lymphoma in a human, which comprises (a) administering to a human having mantle cell lymphoma from about 5 mg to about 25 mg per

> day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or a pharmaceutically acceptable salt or hydrate thereof for 21 days followed by seven days rest in a 28 day cycle; and (b) repeating step (a), wherein the mantle cell lymphoma is relapsed, refractory, or relapsed and refractory to conventional therapy.

Ex. 1001, 23:63–24:4.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under this standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history.").

According to Petitioner, "[t]he words of the claims at issue here should be given their plain meanings, because such a construction would be consistent with the specification and prosecution history." Pet 14. Patent Owner "does not dispute Petitioners' contention . . . that the claims do not require construction" at this stage of the proceeding. Prelim. Resp. 22. We

determine that no claim term requires express construction for purposes of deciding whether to institute a review in this case. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art "would have been a hematologist and/or oncologist, i.e., a medical doctor with hematology and/or oncology training, with several years of experience in treating blood cancers." Pet. 7; Ex. 1002 ¶ 14. Patent Owner contends that "[t]he challenged claims each recite a method of treating MCL; accordingly, a POSA would be someone within Petitioners' definition whose experience *specifically included experience in treating MCL*." Prelim. Resp. 21.

We adopt Petitioner's definition for purposes of this decision, but note that our disposition of the case would not change under either definition.

C. Overview of the Asserted Prior Art

1. Zeldis (Ex. 1004)

Zeldis discloses "methods of treating and preventing certain types of cancer, including primary and metastatic cancer, as well as cancers that are refractory or resistant to conventional chemotherapy" by administering an immunomodulatory compound. Ex. 1004 ¶ 17.

According to Zeldis, "the term 'cancer' includes, but is not limited to, solid tumors and blood born[e] tumors" (*id.* ¶ 107), for example, "Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, [and] low grade follicular lymphoma" (*id.*).

Further according to Zeldis, the term "immunomodulatory compounds" refers to "small organic molecules that markedly inhibit TNF-α, LPS induced monocyte IL1β and IL12, and partially inhibit IL6 production" (*id.* ¶ 31), and one of the "most preferred immunomodulatory compounds" is lenalidomide (Revimid) (*id.* ¶¶ 81, 82), a derivative or analog of thalidomide (*id.* ¶ 34).

Zeldis teaches that *in vitro* studies demonstrate that lenalidomide "is similar to, but at least 200 times more potent than, thalidomide" with respect to "[i]nhibition of TNF-α production following LPS-stimulation of human PBMC and human whole blood." *Id.* ¶ 219. In addition, "it has been shown that the compound is approximately 50–100 times more potent than thalidomide in stimulating the proliferation of T-cells following primary induction by T-cell receptor (TCR) activation" and lenalidomide "is also approximately 50 to 100 times more potent than thalidomide in augmenting the production of IL-2 and IFN-γ following TCR activation of PBMC (IL-2) or T-cells (IFN-γ)." *Id.* ¶ 220.

Zeldis further describes several Phase I clinical studies designed to determine the maximum tolerated dose of lenalidomide in patients with

relapsed multiple myeloma (*id.* ¶¶ 238–243), malignant melanoma, carcinoma of the pancreas, renal carcinoma, breast carcinoma, non-small cell lung carcinoma, adrenal carcinoma, malignant mesothelioma (*id.* ¶¶ 244–246), refractory solid tumors and/or lymphomas (*id.* ¶ 247). Additionally, 13 patients with metastatic melanoma were treated with escalating doses of lenalidomide (5 mg/day for 7 days, increasing every 7 days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks). *Id.* ¶ 258. Five of the 13 melanoma patients showed either disease stabilization or a partial response, and the duration of response was approximately 6 months. *Id.*

Finally, Zeldis teaches that lenalidomide "may be administered in an amount of from about 5 to 25 mg per day" (*id.* ¶ 113), and may be administered in four week cycles—25 mg/day for 21 days, with 7 days rest before resuming the next cycle (*id.* ¶ 229).

2. Drach (Ex. 1003)

Drach teaches that "[m]antle cell lymphoma is a distinct entity among the non-Hodgkin's lymphomas" (Ex. 1003, 6), with an "aggressive clinical course, and . . . belongs to the lymphomas with the worst prognosis" (*id.*).

According to Drach, "recent observations suggest that . . . the tumor microenvironment is crucial for survival and/or proliferation of the malignant B-cell clone" in several forms of non-Hodgkin's lymphomas, including follicular lymphoma and B-cell chronic lymphocytic leukemia. *Id.* at 8. Although "[s]tudies exploring interactions between MCL cells and

their microenvironment have not yet been performed" (*id.* at 9), Drach suggests that "observations from B-cell entities . . . as well as from multiple myeloma (MM), where targeting the tumor cell and its microenvironment represents a new treatment paradigm, provide the framework for also exploring this treatment concept in MCL" (*id.*).

In that regard, Drach notes that "thalidomide has pleiotropic effects" (*id.* at 10), and "[s]ome direct effects on tumor cells, including the induction of apoptosis, have been observed, but it appears that the modulation of interactions between tumor cells and stromal cells are even more important" (*id.*). Drach teaches that "[t]halidomide and its analogs (e.g., lenalidomide) are therefore important agents for the new treatment paradigm of targeting both the tumor cell and its microenvironment (mainly by interference with tumor-stromal cell interactions)." *Id.* According to Drach:

> Thalidomide as an agent with antilymphoma properties was first described in two case reports describing objective remissions in three patients with relapsed and chemotherapy-refractory MCL[6, 7]. In these case studies, single-agent thalidomide was used at a daily dose of between 100 and 800 mg, and induced [a partial response] with a duration of several months.

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[6] Edward A. Wilson et al., *Response to Thalidomide in Chemotherapy-Resistant Mantle Cell Lymphoma: a Case Report*, 119 BRITISH JOURNAL OF HAEMATOLOGY 128–130 (2002) (Ex. 2008, "Wilson").

[7] G. Damaj et al., *Thalidomide Therapy Induces Response in Relapsed Mantle Cell Lymphoma*, 17 LEUKEMIA 1914–1915 (2003) (Ex. 2009, "Damaj").

Ex. 1003, 10.

Drach describes a third study,[8] where thalidomide in combination with rituximab was evaluated in patients with pretreated MCL, and 83% "experienced an objective response." *Id.* Rituximab is an antibody with previously "documented efficacy in MCL." Ex. 2010, 2.

In addition, Drach teaches that the thalidomide analog, lenalidomide, "has been evaluated in relapsed MM and appears to have a far more favorable toxicity profile than thalidomide" (*id.*), and that "[c]linical trials of lenalidomide are also underway in various malignant diseases outside of myeloma, including myelodysplastic syndromes, malignant melanoma and refractory solid tumors and lymphomas" (*id.*).

3. Querfeld (Ex. 1005)

Querfeld discloses the results of a Phase II clinical study in which lenalidomide was administered orally to patients with cutaneous T-cell lymphoma (CTCL). Patients received 25 mg daily for 21 days with 7 days rest in 28-day cycles. Three of eight patients experienced an objective response after 1 to 3 cycles. Ex. 1005, 2.

[8] Hannes Kaufmann et al., *Antitumor Activity of Rituximab Plus Thalidomide in Patients with Relapsed/Refractory Mantle Cell Lymphoma*, 104 BLOOD 2269–2271 (2004) (Ex. 2010, "Kaufmann"). We refer to the page numbers of the exhibit, rather than the page numbers of the journal article.

4. The Celgene Press Release (Ex. 1006)

The Celgene Press Release, bearing a date of June 19, 2006, describes a "Phase II clinical study evaluating single agent lenalidomide in patients with relapsed and refractory aggressive Non-Hodgkin's lymphoma (NHL)." Ex. 1006, 1. "Patients in the study received 25 mg of REVLIMID orally once daily for days 1-21 in a 28-day cycle and continued therapy for 52 weeks as tolerated or until disease progression." *Id.* at 2.

> Of the 16 evaluable patients, 1 patient achieved an unconfirmed complete response (CRu) and 4 patients achieved partial responses (PR) to Revlimid monotherapy. Four patients exhibited stable disease and 7 patients had disease progression after a median follow-up of 2 months (range 1–7 months). Of the 16 patients, 8 had diffuse large cell lymphoma, 3 patients had mantle cell lymphoma, 2 patients had follicular lymphoma, 1 patient had transformed lymphoma, and 2 patients had aggressive lymphoma of unknown histology.

Id. One of the patients with mantle cell lymphoma achieved a partial response with progression free survival for more than 57 days. *Id.*

D. Obviousness of Claims 1–4, 8, 9, 15, and 20 over Drach and Zeldis; and Claims 4 and 20 over Drach, Zeldis, and Querfeld

Petitioner contends that claims 1–4, 8, 9, 15, and 20 are unpatentable over Drach and Zeldis, and that claims 4 and 20 are unpatentable over Drach, Zeldis, and Querfeld. Pet. 16–30.

Patent Owner contends, *inter alia*, that both obviousness grounds should be denied under 35 U.S.C. § 325(d) because Petitioner "simply replaces art considered during prosecution with art containing the same

disclosures" (Prelim. Resp. 17), and moreover, "present[s] substantially the same arguments that were overcome during prosecution," without providing "a compelling reason to readjudicate them" (*id.* at 12).

For the reasons discussed below, we exercise our discretion under § 325(d) to decline institution on these grounds because the same or substantially the same prior art or arguments were previously presented to the Office during prosecution.

1. 35 U.S.C. § 325(d)

Institution of *inter partes* review is discretionary. *See Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) ("the PTO is permitted, but never compelled, to institute an IPR proceeding"). In particular, § 325(d) states "[i]n determining whether to institute or order a proceeding under this chapter . . . The Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office."

In evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office under § 325(d), the Board has considered a number of non-exclusive factors, including, for example:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in

> which Petitioner relies on the prior art or Patent Owner distinguished the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its consideration of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the asserted prior art or arguments.

Becton, Dickenson & Co. v. B. Braun Melsungen AG, Case IPR2017-01586, slip op. 17–18 (PTAB Dec. 15, 2017) (Paper 8) (Informative).

2. Prosecution History of the '929 Patent

The Examiner issued a final office action rejecting the claims that ultimately issued as challenged claims 1–4, 8, 9, 15, and 20 as obvious over Zeldis (Ex. 1004) in view of three additional references: Damaj, Wilson, and Kaufmann.[9] Ex. 2007, 10–19.

The Examiner found, in relevant part, that "Zeldis teaches methods of treating, preventing, and/or managing cancer comprising administration of an immunomodulatory compound," and that "[t]he instantly claimed 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (*i.e.*, Lenalidomide; Revlimid™; Revimid™) is disclosed as a preferred compound." Ex. 2007, 62 (citing Ex. 1004, Abstract, Fig. 1, ¶¶ 16, 34, 37). In addition, the Examiner found that Zeldis teaches that lenalidomide is at least 200 times more potent than thalidomide in inhibiting TNF-α production in vitro (*id.* at 64 (citing Ex. 1004 ¶ 219)); 50–100 times more potent than

[9] *See supra* notes 6–8.

thalidomide in stimulating proliferation of T-cell following primary induction by T-cell receptor activation (*id.* at 65 (citing Ex. 1004 ¶ 220)); and more potent than thalidomide against multiple myeloma cell proliferation in vitro (*id.* (citing Ex. 1004 ¶ 222)). The Examiner further found that Zeldis teaches oral administration of lenalidomide in an amount of 5, 10, or 25 mg per day for 21 to 28 days followed by 1 week of rest in a four or six week cycle. *Id.* at 63 (citing Ex. 1004 ¶ 173). The Examiner also noted that lenalidomide provided a clinical benefit in some patients. *Id.* at 69–70 (citing Ex. 1004 ¶¶ 244–249, 257–258).

The Examiner found that Zeldis teaches that "the term 'cancer' includes, but is not limited to solid tumors and blood born[e] tumors" (Ex. 2007, 62 (citing Ex. 1004 ¶ 107)), in particular, "'various types of lymphoma', including, but not limited to, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma or relapsed or refractory low grade follicular lymphoma" (*id.* (citing Ex. 1004 ¶ 107)). The Examiner acknowledged that Zeldis does not disclose treatment of mantle cell lymphoma. Ex. 2007, 66.

The Examiner cited Damaj as teaching that thalidomide induced a response in relapsed mantle cell lymphoma (Ex. 2007, 66 (citing Ex. 2009, 1914)); Wilson as teaching that thalidomide produced partial remission in a patient with relapsed mantle cell lymphoma (*id.* at 66–67 (citing Ex. 2008, 130)); and Kauffman as teaching that a combination of lenalidomide and

rituximab has beneficial activity in treatment of relapsed/refractory mantle cell lymphoma (*id.* at 67 (citing Ex. 2010, Abstract)).

The Examiner concluded that it would have been obvious to treat mantle cell lymphoma with lenalidomide because Zeldis "explicitly teaches, suggests, and motivates one skilled in the art to treat cancer using [lenalidomide], including 'various types of lymphoma' such as non-Hodgkin's lymphoma and B-cell lymphomas" (*id.* at 69); "mantle cell lymphoma is a type of non-Hodgkin's lymphoma/B-cell lymphoma" (*id.*); Damaj, Wilson, and Kaufmann teach that "thalidomide was . . . effective in the treatment of mantle cell lymphoma" (*id.*); and Zeldis teaches that lenalidomide "is significantly more potent tha[n] thalidomide" in various in vitro assays (*id.*), and provides a clinical benefit in some patients with other forms of cancer (*id.* at 69–70).

Finally, according to the Examiner, "[t]he skilled artisan would thus have been imbued with at least a reasonable expectation that [lenalidomide] would be effective in treating mantle cell lymphoma given the broad spectrum anticancer [activity] of this compound as demonstrated by Zeldis." *Id.* at 69.

Applicant, supported by the Declaration of Dr. Lei Zhang,[10] contested the final rejection, arguing, in relevant part:

[10] Declaration of Lei Zhang, M.D., submitted under 37 C.F.R. § 1.132, and dated October 15, 2013 (Ex. 1008, "Zhang Declaration" or "Zhang Decl.").

> [T]he efficacy of lenalidomide in relapsed, refractory, or relapsed and refractory mantle cell lymphoma, as demonstrated by the response rates, median duration of response and median overall survival in a Phase II clinical study [described in an accompanying article by Goy[11]], would have been unexpected and surprising at the time the claimed invention was made.

Ex. 1007, 8–9 (citing Ex. 1008 generally).

The Examiner, after considering the Zhang Declaration (Ex. 1008) and the underlying Goy reference (Ex. 2006), was "persuaded by Applicant's argument of unexpected results as it pertains to the treatment of mantle cell lymphoma relapsed, refractory, or relapsed and refractory to conventional therapy comprising administration of lenalidomide in the [claimed] dosing regimen." Ex. 2007, 81.

> Specifically, as set forth in the [Zhang] Declaration filed 12/18/2013, prior to June 2013 there was only one drug approved by the FDA for the treatment of patients with relapsed

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[11] Andre Goy et al., *Single-Agent Lenalidomide in Patients with Mantle-Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: Phase II MCL-001 (EMERGE) Study*, 31 JOURNAL OF CLINICAL ONCOLOGY 3688–3695 (2013) (Ex. 2006, "Goy").

Goy is a post-filing date reference describing a clinical trial in which lenalidomide was administered to 134 patients with relapsed or refractory mantle cell lymphoma "on days 1 through 21 every 28 days until disease progression or intolerance." Ex. 2006, 3688. The overall response rate with lenalidomide was 28% (7.5% CR/Cru), exceeding the prespecified 15% target, with prolonged responses showing a median duration of response of 16.6 months, including 18 patients who responded for ≥ 6 months and 10 who responded for ≥ 12 months (maximum, 29.2+ months). *Id.* at 3694.

> or refractory MCL (bortezomib). Surprisingly, Applicant demonstrated that lenalidomide administered in the claimed dosing regimen was effective in treating heavily pretreated MCL patients, including patients previously treated with bortezomib.
>
> Given the extremely poor prognosis of mantle cell lymphoma patients relapsed, refractory, or relapsed and refractory to conventional therapy and the lack of available effective therapies for such patients, it is surprising and unexpected that lenalidomide elicits an overall response rate of 28% in heavily pretreated MCL patients.

Ex. 2007, 81–82.

In summary, as indicated by the prosecution history of the '929 patent, the Examiner ultimately concluded that Applicant's evidence of unexpected results—i.e., the 28% overall response rate elicited by lenalidomide in pretreated relapsed and/or refractory mantle cell lymphoma patients—outweighed the evidence supporting his initial determination that it would have been *prima facie* obvious for one of ordinary skill in the art to use lenalidomide to treat mantle cell lymphoma. Ex. 2007, 81–82.

3. Petitioner's Obviousness Challenges

Petitioner contends that claims 1–4, 8, 9, 15, and 20 would have been obvious over the combined teachings of Drach and Zeldis, and that claims 4

and 20 would have been obvious over the combined teachings of Drach, Zeldis, and Querfeld.[12]

Petitioner contends that Drach discloses "thalidomide's use in treatment of relapsed and refractory MCL for human patients," and makes "an explicit suggestion for using lenalidomide in MCL treatment." Pet. 16 (citing Ex. 1003, 10). Petitioner further contends that Zeldis teaches that lenalidomide is "one of the 'most preferred' immunomodulatory compounds for treating cancers that are refractory or resistant to conventional chemotherapy" (Pet. 17 (citing Ex. 1004 ¶¶ 17, 34, 81, 82)), and that both Drach and Zeldis disclose "lenalidomide's use in treating relapsed and/or refractory cancers related to MCL" (*id.* at 16 (citing Ex. 1003, 10; Ex. 1004 ¶¶ 238–243)). Finally, Petitioner contends that Zeldis discloses that lenalidomide can be administered according to the same dosing and cycling protocol required by the claims. *Id.* at 17 (citing Ex. 1004 ¶¶ 113, 171, 173, 229, 239–243).

Petitioner contends that one of ordinary skill in the art "would have been motivated to substitute thalidomide with lenalidomide . . . for MCL treatment" (Pet. 19), because "Drach teaches that thalidomide was being used to treat relapsed and/or refractory MCL as of June 2005" (Pet. 18

[12] Petitioner does not specifically address 35 U.S.C. § 325(d), but does indicate that Drach and Querfeld were not considered by the Examiner during prosecution of the '929 patent. Pet. 15.

(citing Ex. 1002 ¶ 68; Ex. 1003, 10)); "thalidomide and its analogs inhibit cytokines and are immunomodulatory, both of which were thought to be relevant pathways to address for MCL treatment" (Pet. 18 (citing Ex. 1002 ¶ 68; Ex. 1003, 10)); "lenalidomide had a better toxicity profile than thalidomide" (Pet. 18 (citing Ex. 1002 ¶¶ 71, 76; Ex. 1004, ¶¶ 220, 222, 238–243, Fig. 1)); Zeldis teaches that "lenalidomide was known to be more potent than thalidomide" (Pet. 20 (citing Ex. 1002 ¶ 68; Ex. 1003, 10)); and "***Drach explicitly taught that lenalidomide was an important agent for the new treatment paradigm of MCL at the time***" (Pet. 18 (citing Ex. 1002 ¶ 68; Ex. 1003, 10)).

Petitioner also contends that one of ordinary skill in the art "would have expected success in treating MCL with lenalidomide based on its structural similarity to thalidomide." Pet. 19 (citing Ex. 1002 ¶ 65). In addition, Petitioner contends that "Zeldis teaches that . . . lenalidomide was more potent than thalidomide in the inhibition of MM [multiple myeloma] cell proliferation" (*id.* at 20 (citing Ex. 1002 ¶ 75; Ex. 1004 ¶¶ 222, 238–243, Fig. 1)), and "it was known that both MM and MCL were B-cell cancers that utilized a common biochemical pathway" (*id.* (citing Ex. 1002 ¶ 75 (Dr. Thirman testifying that "one of the pathways involved in MM (support of the microenvironment) was thought to potentially be involved in MCL"); Ex. 1010, 3; Ex. 1011, 4; Ex. 1003, 11)).

Petitioner acknowledges that "[d]uring prosecution, Patent Owner argued that the clinical results achieved by lenalidomide in relapsed,

refractory, or relapsed and refractory MCL patients were unexpected" (Pet. 28 (citing Ex. 1007, 7)), but asserts "based on what was known prior to the critical date, those results would have been entirely expected" (Pet. 28). In support of this assertion, Petitioner relies on the following testimony of Dr. Michael Thirman:

> The prior art teaches, at least, the following: (1) thalidomide was being used to treat relapsed and/or refractory MCL (Drach), (2) thalidomide had undesirable side effects (Drach), (3) lenalidomide was a less toxic, more potent, structurally similar analogue of thalidomide being suggested for MCL treatment (Drach and Zeldis), and (4) lenalidomide could be used for MCL treatment in the dosages, dosage forms and cycling regimen claimed by the challenged claims of the '929 patent (Zeldis, Querfield, Celgene Press Release).

Ex. 1002 ¶ 109. "Thus," Dr. Thirman asserts, "the alleged unexpected properties would have been expected." Ex. 1002 ¶ 110.

Moreover, Petitioner argues that "a long-felt and unmet need must be ***satisfied*** by the invention" (Pet. 29), but "Dr. Thirman opines, the '929 patent's claims did not satisfy any unmet need because there is ***still*** a need for new MCL therapy" (*id.* at 30 (citing Ex. 1002 ¶ 113; Ex. 1015, 13[13])).

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[13] Martin Dreyling et al., *Treatment for Patients with Relapsed/Refractory Mantle Cell Lymphoma: European-Based Recommendations*, Leukemia & Lymphoma (2017) (Ex. 1015, "Dreyling").

Dreyling is a post-filing date reference that reviews various treatments for mantle cell lymphoma, and concludes "despite considerable advances, a high unmet need for effective treatments [of MCL] remains, particularly in the elderly and frail patient populations." Ex. 1015, 13. Importantly, however,

4. Analysis

We address the factors outlined in *Becton, Dickinson & Co.* in view of the prosecution history and Petitioner's arguments. *See supra*, Section D1, for a compilation of these non-exclusive factors.

Factors (a)–(d)

As discussed above, the Petition challenges claims 1–4, 8, 9, 15, and 20 as obvious over Zeldis and Drach, and claims 4 and 20 as obvious over Zeldis, Drach, and Querfeld.

Zeldis is the same reference relied on by the Examiner—in combination with Damaj, Wilson, and Kaufmann—to reject the claims during prosecution. Ex. 2007, 4, 36, 61. Moreover, the Examiner relied on Zeldis as disclosing that lenalidomide, an analog of thalidomide, is a preferred immunomodulatory compound in treating various forms of lymphoma, and that it can be administered according to the claimed dosage schedule—the same disclosures Petitioner relies on in its obviousness challenges. Pet. 16–17.

Drach, an article reviewing treatment protocols for mantle cell lymphoma, was not relied on during prosecution in rejecting the claims, but

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Dreyling also concludes that "lenalidomide significantly improved PFS [progression-free survival] compared with IC [investigator's choice]" of monotherapy with rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine, and "[a]nalysis of subgroups and regression analyzes associated superior PFS with lenalidomide over IC therapy irrespective of prior treatment history." *Id.* at 6–7.

was listed in an IDS and indicated as having been considered by the Examiner (Ex. 2007, 28 (additionally listing Damaj and Wilson)), and it was also mentioned in the Background section of the '929 patent (Ex. 1001, 2:4–6). In the Petition, Petitioner relies on Drach in large part for its summaries of Damaj, Wilson, and Kaufmann (the same references cited by the Examiner in rejecting the claims (*see supra* notes 6–8)), and for the same reason as the Examiner: as evidence that it was known to administer thalidomide to patients with relapsed and/or refractory mantle cell lymphoma. Pet. 16 (citing Ex. 1003, 10), 18 (citing Ex. 1003, 10). Thus, Drach is cumulative to Damaj, Wilson, and Kaufmann in at least that respect.

Nevertheless, Petitioner also relies on Drach for a purportedly "explicit suggestion for using lenalidomide in MCL treatment." Pet. 16 (citing Ex. 1003, 10). Although it may be going too far to say that Drach makes an "explicit" suggestion to use lenalidomide to treat MCL, it is a logical inference, given Drach's particular focus on treatment of mantle cell lymphoma. Thus, Drach is somewhat stronger evidence than Damaj, Wilson, and Kaufmann in support of Petitioner's contention that one of skill in the art would have had a reason to administer lenalidomide to patients with relapsed and/or refractory MCL.

Finally, Querfeld was not relied on during prosecution, but is cumulative to Zeldis, as it is relied on for teaching the same 28 day cycles disclosed in Zeldis: 25 mg/day for 21 days, with seven days rest between

cycles—albeit for treating cutaneous T-cell lymphoma. Pet. 27–28 (citing Ex. 1002 ¶ 105; Ex. 1005, 2).

Factors (e) and (f)

As discussed above in Section D2, the Examiner was ultimately persuaded that Applicant's evidence of unexpected results—i.e., the overall response rate elicited by lenalidomide in pretreated mantle cell lymphoma patients—outweighed the evidence supporting his initial determination that it would have been *prima facie* obvious for one of ordinary skill in the art to use lenalidomide to treat mantle cell lymphoma given the combined teachings of Zeldis, Damaj, Wilson, and Kaufmann. Ex. 2007, 81–82.

Petitioner acknowledges that "[d]uring prosecution, Patent Owner argued that the clinical results achieved by lenalidomide in relapsed, refractory or relapsed and refractory MCL patients were unexpected" (Pet. 28), but contends "based on what was known prior to the critical date, those results would have been entirely expected" (*id.*). According to Petitioner:

> [T]he prior art taught at least: (1) thalidomide was being used to treat relapsed and/or refractory MCL (Drach), (2) thalidomide had undesirable side effects (Drach), (3) lenalidomide was a less toxic, more potent, structurally similar analog of thalidomide being suggested for MCL treatment (Drach and Zeldis), and (4) lenalidomide could be used for cancer treatment in the dosages, dosage forms and cycling regimen disclosed by the '929 patent claims (Zeldis, Querfeld, Celgene Press Release).

Pet. 29 (citing Ex. 1002 ¶ 109). "Therefore," Petitioner contends, "if unexpected properties are argued by [Patent Owner] here, they fail to

support patentability." *Id.* Paragraph 109 of Dr. Thirman's Declaration is nearly identical to the above passage from the Petition. Following the summary of those prior art teachings, Dr. Thirman asserts "[t]hus, the alleged unexpected properties would have been expected" (Ex. 1002 ¶ 110), but provides no further evidentiary support for the proposition that the results obtained by treating relapsed and/or refractory MCL with lenalidomide would have been expected.

Again, during prosecution, the Examiner maintained that the combined prior art (Zeldis, Damaj, Wilson, and Kaufmann) would have given one of ordinary skill in the art a reason to use lenalidomide to treat patients with relapsed and/or refractory mantle cell lymphoma, but concluded that the evidence of obviousness was outweighed by Applicant's evidence of unexpected results—namely, a 28% overall response rate in patients with relapsed and/or refractory mantle cell lymphoma. Although Drach—given its particular focus on treating mantle cell lymphoma—is stronger evidence than Damaj, Wilson, and Kaufmann that one of ordinary skill in the art would have had a reason to treat MCL patients with lenalidomide, Drach is no more informative as to expected results than the references the Examiner relied on in making out a *prima facie* case of obviousness, i.e., Damaj, Wilson, and Kaufmann.

Essentially, Petitioner and Dr. Thirman disagree with the Examiner's conclusion that, on balance, the subject matter of the challenged claims would not have been obvious, in light of the level of response in patients

with relapsed and/or refractory MCL (as described in Dr. Zhang's Declaration and the underlying Goy reference), despite one of ordinary skill in the art having had a reason to administer lenalidomide to treat MCL.

5. Conclusion

Having considered Petitioner's obviousness challenges in light of the factors outlined in *Becton, Dickinson & Co.*, we determine that the challenges are based on substantially the same prior art and arguments previously presented to the office. Petitioner disagrees with the Examiner's decision to allow the challenged claims, but has neither sufficiently pointed out how the Examiner erred, nor provided additional evidence or facts that warrant reconsideration of the Examiner's decision.

Where a petitioner fails "to provide a compelling reason why [the Board] should readjudicate substantially the same prior art and arguments as those presented during prosecution and considered by the Examiner," the Board will deny institution pursuant to § 325(d). *Unified Patents Inc. v. Berman*, Case IPR2016–01571, slip op. at 12 (PTAB Dec. 14, 2016) (Paper 10).

Accordingly, pursuant to our discretion under 35 U.S.C. § 325(d), we decline to institute an *inter partes* review of claims 1–4, 8, 9, 15, and 20 on the ground of obviousness over Drach and Zeldis; or claims 4 and 20 on the ground of obviousness over Drach, Zeldis, and Querfeld.

E. Asserted Anticipation of Claims 1–4, 8, 9, 15, and 20 by the Celgene Press Release

Petitioner contends that the Celgene Press Release anticipates claims 1–4, 8, 9, 15, and 20. Pet. 30–35. Patent Owner contends, *inter alia*, that Petitioner has failed to establish that the Celgene Press Release is a printed publication within the meaning of 35 U.S.C. § 311(b). Prelim. Resp. 49–51.

1. Analysis

35 U.S.C. § 311(b) states that "a petitioner in an *inter partes* review may request to cancel . . . claims of a patent only on a ground that could be raised under section 102 or 103 and *only on the basis of prior art consisting of patents or printed publications*" (emphasis added). Thus, before considering Petitioner's anticipation challenge, we must address whether Petitioner has provided a sufficient threshold showing that the Celgene Press Release constitutes prior art under section 102—a legal question based on underlying factual determinations. *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987).

Petitioner has the ultimate burden of persuasion to prove unpatentability by a preponderance of the evidence. *Dynamic Drinkware, LLC v. Natl. Graphics, Inc.,* 800 F.3d 1375, 1378–79 (Fed. Cir. 2015). Petitioner also bears the initial burden of production to establish the existence of prior art that renders the claims unpatentable. *Id.* To satisfy the initial burden of production, we have often required a petitioner to make a threshold showing that the reference relied upon was publicly accessible as a

printed publication prior to the effective filing date of a challenged patent. *See, e.g.*, *Frontier Therapeutics, LLC v. Medac Gesellschaft Fur Klinische Spezialpraparate MBH*, Case IPR2016-00649, slip op. at 22 (PTAB September 1, 2016) (Paper 10) (finding that an alleged "printed package insert" was not a printed publication); *Symantec Corp. v. Trs. of Columbia Univ.*, Case IPR2015-00371, slip op. at 5–9 (PTAB June 17, 2015) (Paper 13); *Temporal Power, Ltd. v. Beacon Power, LLC*, Case IPR2015-00146, slip op. at 8–11 (PTAB Apr. 27, 2015) (Paper 10); *Dell, Inc. v. Selene Comm'n Techs., LLC*, Case IPR2014-01411, slip op. at 21–22 (PTAB Feb. 26, 2015) (Paper 23).

"A reference will be considered publicly accessible if it was '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.'" *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348 (Fed. Cir. 2016) (quoting *Kyocera*, 545 F.3d at 1350).

A party seeking to introduce a reference "should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art to which the document relates and thus most likely to avail themselves of its contents." *In re Wyer*, 655 F.2d 221, 227 (CCPA 1981) (quoting *Philips Elec. & Pharm. Indus. Corp. v. Thermal & Elecs. Indus., Inc.*, 450 F.2d 1164, 1171 (3d Cir. 1971)). As explained by the Federal Circuit, a "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 surrounding the reference's disclosure to members of the public." *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004).

Here, Petitioner asserts, without elaboration, that the Celgene Press Release "published on June 19, 2006, before the Priority Date, and is prior art under 35 U.S.C. § 102(a)." Pet. 15. Dr. Thirman likewise asserts, without elaboration, that the Celgene Press Release "was dated June 19, 2006 and is prior art against the '929 patent." Ex. 1002 ¶ 57 (citing Ex. 1006, 1).

In response, Patent Owner contends:

> Petitioners have failed to provide ***any evidence*** that the [Celgene] Press Release was publicly available before August 3, 2006. Apparently relying on the nominal date on the Press Release, Petitioners state, without any support, that it was "published on June 19, 2006." (Pet. 15.) Dr. Thirman offers even less; he . . . [merely] asserts that it "was dated June 19, 2006 and is prior art against the '929 patent." (Ex. 1002 at ¶ 57.) But there is no evidence in this record of when, where, or to whom the Press Release was allegedly available, or how it was allegedly accessible. Petitioners have thus fallen far short of establishing that the Press Release qualifies as a printed publication under § 311(b). *See Microsoft Corp. v. Corel Software*, IPR2016-01300, Paper 13 at 10–11 (P.T.A.B. Jan. 4, 2017) (finding that a "copyright [date], alone . . . sheds virtually no light on whether the document was publically accessible as of that date, therefore additional evidence is typically necessary to support a showing of public accessibility").

Prelim. Resp. 50–51.

We agree with Patent Owner that Petitioner fails to provide a threshold showing that the Celgene Press Release constitutes a "printed publication" under 35 U.S.C. §§ 102. As noted by Patent Owner, there is no evidence in this record of when, where, or to whom the Celgene Press Release was available, or how it was allegedly accessible. Although Exhibit 1006 bears a date of June 9, 2006 (which does not appear to be a copyright date), this, standing alone, does not establish public availability as of that date. *See Ford Motor Co. v. Versata Dev. Grp.*, IPR2016-01019, slip op. at 5–6 (PTAB Oct. 4, 2016) (Paper 9) (noting that a "copyright date is not helpful [where] there is no evidence as to whether [the documents in question] were published or made sufficiently accessible to the public interested in the art prior to the critical date."). Petitioner's conclusory assertion without evidence of distribution or dissemination is insufficient to establish that a document is a "printed publication." *See Coal. for Affordable Drugs IV v. Pharmacyclics, Inc.*, Case IPR2015-01076, slip op. at 7 (PTAB Oct. 19, 2015) (Paper 33).[14]

[14] We note Petitioner's reliance on *In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013); *Libertad v. Welch*, 53 F.3d 428, 443 n.12 (1st Cir. 1995); and *Buckley v. Airshield Corp.*, 116 F. Supp. 2d 658, 663 (D. Md 2000) in support of its assertion that the Celgene Press Release is a printed publication and/or that Petitioner has made a threshold showing sufficient for purposes of institution. Paper 7 (Submission of Case Law). None of these cases is apposite, however, as none deals with establishing public availability of a document.

As we have determined that Petitioner has not established that Celgene Press Release is available as a prior art printed publication, Petitioner has not shown a reasonable likelihood of prevailing in its assertion that the subject matter of claims 1–4, 8, 9, 15, and 20 of the '929 patent is anticipated by the Celgene Press Release.

Accordingly, we do not institute an *inter partes* review of claims 1–4, 8, 9, 15, and 20 of the '929 patent on the ground of anticipation by the Celgene Press Release.

III. CONCLUSION

For the foregoing reasons, we exercise our discretion under 35 U.S.C. § 325(d), and decline to institute an *inter partes* review of claims 1–4, 8, 9, 15, and 20 on the ground of obviousness over Drach and Zeldis; or claims 4 and 20 on the ground of obviousness over Drach, Zeldis, and Querfeld.

In addition, we decline to institute an *inter partes* review of claims 1–4, 8, 9, 15, and 20 of the '929 patent on the ground of anticipation by the Celgene Press Release, as we determine that Petitioner has failed to make a threshold showing that that document qualifies as a printed publication,

IV. ORDER

Accordingly, it is

ORDERED that that the Petition is denied and no *inter partes* review is instituted.

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