

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. and APOTEX CORP.,
Petitioner,

v.

CELGENE CORPORATION,
Patent Owner.

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 Petitioner's Request for Rehearing of
Decision Denying Institution of *Inter Partes* Review
37 C.F.R § 42.71(d)

I. INTRODUCTION

Apotex Inc. and Apotex Corp. (collectively, “Petitioner”) 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”) on three asserted grounds:

	Claims	35 U.S.C. §	Reference(s)/Basis
I	1–4, 8, 9, 15, 20	103(a)	Drach, ¹ Zeldis ²
II	4, 20	103(a)	Drach, Zeldis, Querfeld ³
III	1–4, 8, 9, 15, 20	102(a)	Celgene Press Release ⁴

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

¹ Johannes Drach et 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.

² Jerome B. Zeldis, U.S. Patent Application Publication US 2004/0029832 A1, published February 12, 2004 (Ex. 1004, “Zeldis”).

³ 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”).

⁴ 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”).

Celgene Corporation (“Patent Owner”) filed a Preliminary Response (Paper 6, “Prelim. Resp.”).

In the Decision on Institution (Paper 8, “Decision” or “Inst. Dec.”), we determined that the Petition failed to establish a reasonable likelihood that Petitioner would prevail in establishing the unpatentability of at least one claim challenged in the Petition, and declined to institute an *inter partes* review on any of the three grounds asserted. Specifically, with respect to grounds I and II, we declined to institute pursuant to our discretion under 35 U.S.C. § 325(d). Inst. Dec. 22–26. With respect to ground III, we determined that Petitioner had not met its burden of establishing that the Celgene Press Release was available as a printed publication. *Id.* at 27–31.

Petitioner’s Request for Rehearing (Paper 9, “Req. Reh’g”) seeks rehearing of our decision to deny institution of grounds I and II only.

For the reasons set forth below, we *deny* the relief requested.

II. STANDARD OF REVIEW

A party requesting rehearing bears the burden of showing that a decision should be modified. 37 C.F.R. § 42.71(d). The party must identify all matters it believes the Board misapprehended or overlooked, and the place where each matter was addressed previously in a motion, an opposition, or a reply. *Id.* When rehearing a decision on petition, we review the decision for an abuse of discretion. 37 C.F.R. § 42.71(c). An abuse of discretion occurs when a “decision was based on an erroneous conclusion of law or clearly erroneous factual findings, or . . . a clear error of judgment.”

PPG Indus. Inc. v. Celanese Polymer Specialties Co., 840 F.2d 1565, 1567 (Fed. Cir. 1988) (citations omitted).

III. DISCUSSION

35 U.S.C. § 325(d)

In the Decision, we evaluated Petitioner's arguments and evidence with respect to grounds I and II, together with the prosecution history of the '929 patent, in light of the non-exclusive factors outlined in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph). Inst. Dec. 22–26. The *Becton, Dickinson* factors are as follows:

(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.

Factors (a), (b), and (d) relate to whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 10 (Feb. 13,

2020) (precedential). Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.* If the same or substantially the same art or arguments were previously presented to the Office, we then consider whether petitioner has demonstrated the Office erred. *Id.*

In evaluating the Petition and accompanying evidence in light of the *Becton, Dickinson* factors, we determined that grounds I and II were “based on substantially the same prior art and arguments previously presented to the office,” and that Petitioner had “neither sufficiently pointed out how the Examiner erred, nor provided additional evidence or facts that warrant reconsideration of the Examiner’s decision.” Inst. Dec. 26. Accordingly, we exercised our discretion under 35 U.S.C. §325(d) and denied institution of grounds I and II on that basis.

According to Petitioner, our analysis erred in several crucial respects. We will address each of these purported errors in turn, but first, to provide context, we reproduce illustrative claim 1, and briefly discuss the basis of our decision to deny institution. Claim 1 is as follows:

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^[5] or a pharmaceutically acceptable salt or hydrate thereof for 21 days followed by seven days rest in a 28 day cycle; and (b)

⁵ The compound recited in claim 1 is “also known as lenalidomide, Revlimid® or Revimid®.” Ex. 1001, 1:19–23.

repeating step (a), wherein the mantle cell lymphoma is relapsed, refractory, or relapsed and refractory to conventional therapy.

Ex. 1001, 23:63–24:4.

The Examiner issued a final office action rejecting the claims that eventually issued as challenged claims 1–4, 8, 9, 15, and 20 as obvious over Zeldis, in view of three additional references: Damaj,⁶ Wilson,⁷ and Kaufmann.⁸ Ex. 2007 (excerpt of the file history of the '929 patent), 4, 36, 61; Inst. Dec. 14, 22. In particular, the Examiner found that one of skill in the art would “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.” Ex. 2007, 69; Inst. Dec. 16. Nevertheless, after considering the Declaration of Dr. Lei Zhang (Ex. 1008⁹) and Goy, an underlying reference

⁶ G. Damaj et al., *Thalidomide Therapy Induces Response in Relapsed Mantle Cell Lymphoma*, 17 LEUKEMIA 1914–1915 (2003) (Ex. 2009, “Damaj”).

⁷ 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”).

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”).

⁹ 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.”).

(Ex. 2006¹⁰), the Examiner ultimately concluded that Applicant's evidence of unexpected results outweighed the evidence supporting the 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; Inst. Dec.18.

In the Decision, we observed that the Zeldis reference relied on by Petitioner in grounds I and II is the same reference relied on by the Examiner during prosecution. Moreover, we noted that Petitioner's challenges with respect to Zeldis were based on essentially the same disclosures relied on during prosecution. Inst. Dec. 22. That is, both the Examiner and Petitioner relied on Zeldis as disclosing that lenalidomide, an analog of thalidomide, is a preferred immunomodulatory compound in treating various forms of lymphoma, including non-Hodgkin's lymphomas and B-cell lymphomas; that lenalidomide is more potent than thalidomide in several respects; and that it can be safely administered according to the claimed dosage schedule. Inst. Dec. 14–15, 22 (citing Ex. 2007, 62–70; Pet. 16–17).

We further observed that Drach, an article reviewing treatment protocols for mantle cell lymphoma (MCL), although not relied on during prosecution, was listed on an IDS and indicated as considered by the

¹⁰ 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”).

Examiner, and was also cited in the Background section of the '939 patent. Inst. Dec. 22–23 (citing Ex. 2007, 28; Ex. 1001, 2:4–6). Moreover, we noted that Damaj, Wilson, and Kaufmann each were summarized in Drach, and that the Examiner cited each of those references as evidence that it was known to administer thalidomide to patients with relapsed and/or refractory mantle cell lymphoma. Inst. Dec. 16, 22 (citing Ex. 2007, 4, 36, 61). We further noted that the Examiner also clarified that “mantle cell lymphoma is a type of non-Hodgkin’s lymphoma/B-cell lymphoma.” Inst. Dec. 16; Ex. 2007, 69.

We noted that Querfeld discloses the results of a Phase II clinical study in which lenalidomide was administered orally to patients with cutaneous T-cell lymphoma, and three of eight patients experienced an objective response after 1 to 3 cycles. Inst. Dec. 11; Ex. 1005, 2. Querfeld was not relied on during prosecution, but we determined that the reference is cumulative to Zeldis, in that it is relied on in this proceeding 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. Inst. Dec. 23; Ex. 1005, 2.

Turning to Petitioner’s arguments, Petitioner contends that Drach, “which discloses the clinical use of **lenalidomide** and was not substantively considered by the Examiner” (Req. Reh’g 1), “discloses substantially more than what was substantively considered by the Examiner” (*id.*). In particular, Petitioner contends that Drach discloses that lenalidomide “was

successful in treating multiple myeloma (a B-cell cancer like MCL)” and “was the subject of various clinical trials including those related to lymphoma (MCL is a lymphoma).” *Id.* at 4. Petitioner contends we erroneously found that Drach “was cumulative of references the Examiner considered that focused only on the use of ***thalidomide*** to treat MCL” (*id.* at 1), even though “the publications before the Examiner make no reference to lenalidomide whatsoever, much less the clinical application of that drug” (*id.* at 4).

These arguments are unpersuasive. We did not find that Drach’s disclosures regarding lenalidomide were cumulative to the references considered by the Examiner. Rather, we observed that Petitioner relied on Drach “in large part for its summaries of Damaj, Wilson, and Kaufmann . . . and for the same reason as the Examiner: as evidence that it was known to administer *thalidomide* to patients with patients with relapsed and/or refractory mantle cell lymphoma.” *Id.* at 23 (emphasis added). “Thus,” we continued, “Drach is cumulative to Damaj, Wilson, and Kaufmann *in at least that respect.*” *Id.* (emphasis added).

In addition, Petitioner’s contention that “the publications before the Examiner make no reference to lenalidomide whatsoever, much less the clinical application of that drug” (Req. Reh’g 4), is misleading. It is true that Damaj, Wilson, and Kaufmann do not mention lenalidomide. Nevertheless, in the Decision we noted that Zeldis explicitly describes several Phase I clinical studies designed to determine the maximum tolerated dose of

lenalidomide in patients with relapsed multiple myeloma, malignant melanoma, metastatic melanoma, carcinoma of the pancreas, renal carcinoma, breast carcinoma, non-small cell lung carcinoma, adrenal carcinoma, malignant mesothelioma, refractory solid tumors and/or lymphomas. Inst. Dec. 8–9 (citing Ex. 1004 ¶¶ 238–247, 258). We further noted that Zeldis teaches that lenalidomide “may be administered in an amount of from about 5 to 25 mg per day,” and may be administered in four-week cycles—25 mg/day for 21 days, with 7 days rest before resuming the next cycle. Inst. Dec. 9 (citing Ex. 1004 ¶¶ 113, 229).

Similarly, Petitioner contends that we “misapprehended that the Querfeld reference, which was not considered during prosecution, was cumulative of the Zeldis reference.” *Id.* at 2. Petitioner acknowledges that both Zeldis and Querfeld disclose the same dosage schedule—the same schedule required by the claims (Req. Reh’g 7)—but contends that we misapprehended that Querfeld “**additionally** discloses the use of such dosing regimens in patients being treated for cutaneous T-Cell lymphoma **during a Phase II clinical trial**” (*id.* at 7–8). According to Petitioner, “[t]his distinction is crucial, because the clinical application of lenalidomide in a phase II clinical study provides further evidence of reasonable expectation of success . . . that lenalidomide could be used in the claimed dosages and regimens for treatment of MCL.” *Id.* at 8. Petitioner contends “[t]his distinction also undercuts allegations of unexpected results” and “Querfeld

was relied upon by Petitioners and by Dr. Thirman for at least that purpose.”
Id.

These arguments are not persuasive. We agree with Petitioner that Querfeld “provides further evidence of reasonable expectation of success,” but as we explained in Decision, Querfeld teaches the same dosage schedule taught by Zeldis, and the Examiner already found a reasonable expectation of success based on the art cited during prosecution. 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.” Inst. Dec. 16, 23; Ex. 2007, 69. As for Petitioner’s contention that Querfeld was also relied on as undercutting allegations of unexpected results, Petitioner does not identify, and we do not find, where Querfeld is addressed in that context in the Petition or Dr. Thirman’s Declaration.

Further, with respect to Drach, Petitioner contends that we disregarded our own finding that Drach was “stronger evidence” of obviousness than the references relied on during prosecution. Req. Reh’g 6. Petitioner contends “Drach discloses a crucial teaching concerning the use of lenalidomide to treat MCL, namely that ‘thalidomide 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 interactions) [i.e. MCL].” *Id.* (citing Ex. 1003, 10).

Again, Petitioner’s argument is unpersuasive. In the Decision, we acknowledged that Petitioner additionally relied on Drach’s “explicit suggestion for using lenalidomide in MCL treatment.” Inst. Dec. 23. Although we had reservations about whether Drach “makes an ‘explicit’ suggestion to use lenalidomide to treat MCL,” we agreed that it would be “a logical inference, given Drach’s particular focus on treatment of mantle cell lymphoma.” *Id.* We did not disregard our finding that Drach provided “somewhat stronger evidence” of obviousness than the references relied on during prosecution. *Id.* Rather, we agreed with Petitioner that Drach and Zeldis would have provided a reason for one of ordinary skill in the art to administer lenalidomide to patients with relapsed and/or refractory MCL. Similarly, we agreed with the Examiner’s determination that the combined teachings of Zeldis, Damaj, Wilson, and Kaufmann would have provided a reason to do so. Nevertheless, a reason to modify a reference in the manner required by the claims is only one aspect of the ultimate conclusion on obviousness—which brings us to Petitioner’s contentions regarding the impact of unexpected results on the ultimate conclusion of obviousness.

Petitioner contends that its witness, Dr. Thirman, “squarely disagreed with the declaration of Dr. Zhang, which was submitted by Patent Owner during prosecution, on the issue of unexpected results” as well as “many factual assertions of Patent Owner in its Preliminary Response regarding

reasonable expectation of success and unexpected results.” *Id.* Petitioner contends “[s]uch factual disputes should have been viewed in a light most favorable to the Petitioner and should ultimately be resolved at trial.” *Id.*

As we explained in the Decision, Petitioner bears the burden of proving unpatentability in an *inter partes* review, but in this case, Petitioner “ha[d] neither sufficiently pointed out how the Examiner erred, nor provided additional evidence or facts that warrant reconsideration of the Examiner’s decision.” Inst. Dec. 26. Although Dr. Thirman expressed disagreement with the Examiner and Dr. Zhang on the issue of unexpected results, he did not explain how the Examiner erred, nor did he point to any particular “factual assertions of Patent Owner” that were in error, or address Dr. Zhang’s Declaration and supporting evidence in any substantive way.

Essentially, Dr. Thirman summarized the teachings of Zeldis and Drach (Ex. 1002 ¶¶ 62–82), and stated that those teachings “would have provided a clear guidance/motivation for a [person of skill in the art] to use, or substitute thalidomide with, lenalidomide as a treatment for relapsed and/or refractory MCL with a reasonable expectation of success” (*id.* ¶ 77). Again, on this particular point, we agree with Petitioner and Dr. Thirman.

On the subject of unexpected results, Petitioner relied on the following testimony of Dr. 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 [sic], Celgene Press Release).

Ex. 1002 ¶ 109. “Thus,” according to Dr. Thirman, “the alleged unexpected properties would have been expected.” Ex. 1002 ¶ 110.

As we explained in the Decision, however, the Examiner maintained during prosecution that 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—particularly the 28% overall response rate in patients with relapsed and/or refractory mantle cell lymphoma. Inst. Dec. 17 & n.11, 18. As we further explained, 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, but Drach is no more informative as to unexpected results than the references the Examiner relied on in making out a *prima facie* case of obviousness. *Id.* at 25.

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. Nevertheless, neither Petitioner nor Dr. Thirman advanced any argument or evidence tending to establish that the Examiner erred in evaluating or balancing the evidence of unexpected results. We maintain, as we did in the Decision on Institution, that Petitioner neither sufficiently pointed out how the Examiner erred, nor provided additional evidence or facts that warrant reconsideration of the Examiner's decision. Dec. Inst. 26.

IV. CONCLUSION

For the foregoing reasons, Petitioner has not demonstrated that we abused our discretion in declining to institute an *inter partes* review of claims 1–4, 8, 9, 15, and 20 of the '929 patent.

V. ORDER

Accordingly, it is ORDERED that the Request for Rehearing is *denied*.

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