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Paper 89
Entered: December 2, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC. and AMNEAL PHARMACEUTICALS LLC,
Petitioners,

v.

YEDA RESEARCH & DEVELOPMENT CO. LTD.,
Patent Owner.

Case IPR2015-00643
Patent 8,232,250 B2[1]

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and TINA E. HULSE, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Granting-in-Part Patent Owner's Request for Rehearing
37 C.F.R. § 42.71

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[1] Case IPR2015-01976 has been joined with Case IPR2015-00643.

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition (Paper 1), seeking an *inter partes* review of claims 1–20 of U.S. Patent No. 8,232,250 B2 ("the '250 patent," Ex. 1001). The Board instituted trial to review whether the combination of Pinchasi[2] and the 1996 SBOA,[3] or the combination of Pinchasi and Flechter,[4] renders the challenged claims obvious. Paper 13. In the Final Written Decision, we held that Petitioner had shown by a preponderance of the evidence that the challenged claims are unpatentable. Paper 85 ("Dec."). Yeda Research & Development Co. Ltd. ("Patent Owner") requests that we reconsider the Final Decision. (Paper 87, "Reh'g Req.").

For the following reasons, Patent Owner's request is *granted-in-part*.

II. STANDARD OF REVIEW

A rehearing request for a final decision is governed by 37 C.F.R. § 42.71 (d), which requires the party requesting rehearing to "specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply."

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[2] Irit Pinchasi, WO 2007/081975 A2, published July 19, 2007 (Ex. 1005).
[3] Summary Basis of Approval ("SBOA") for the New Drug Application for 20 mg daily Copaxone ® (NDA #20-622) (Ex. 1007).
[4] S. Flechter et al., *Copolymer 1 (Glatiramer Acetate) in Relapsing Forms of Multiple Sclerosis: Open Multicenter Study of Alternate-Day Administration*, 25 CLINICAL NEUROPHARM. 11–15 (2002) (Ex. 1008).

III. ANALYSIS

In the Request for Rehearing, Petitioner argues that we misapprehended and overlooked the prior art teachings that both reducing the frequency of dosing to less than daily, and increasing the dosage to 40 mg glatiramer acetate ("GA"), would have been expected to decrease tolerability. Reh'q Req. 5–6.

A. Evidence Relating to Decreased Dosing Frequency

Patent Owner first asserts that we "misconstrued data in Flechter illustrating that alternate day dosing was as effective as daily dosing and found instead that the data taught that less-frequent-than-daily administration would have been more tolerable than daily administration." Reh'g Req. 7 (citing Dec. 32). Upon review of the Decision, we agree. *See* Dec. 32–33. Accordingly, we grant this portion of Patent Owner's Request for Reconsideration and retract our reliance on the efficacy data of Flechter in Section II.F of the Decision as the basis for rejecting Patent Owner's argument regarding the lack of motivation to combine Pinchasi and Flechter. We concurrently issue a modified Final Written Decision (Paper 90) to reflect this change.

Nevertheless, we are not persuaded by Patent Owner's argument that Flechter shows that less frequent injections were less tolerable than daily injections. *See* Reh'g Req. 8. In particular, Patent Owner and its declarant, Dr. Tjalf Ziemssen, compare the data reporting adverse events in patients in Flechter, who were treated with alternate-day administration of GA, with

those in a different cohort of patients in Meiner,[5] who were treated with daily administration of GA. *Id.*; PO Resp. 35–36; Ex. 2135 ¶ 89. From that comparison, Patent Owner contends that Flechter shows alternate-day administration is less tolerable than daily administration. PO Resp. 35–36; Reh'g Req. 8.

Dr. Ziemssen, however, qualifies this comparison and explains that a person of ordinary skill in the art "generally would not view this type of cross-study comparison between different study populations as a basis for drawing any comparative conclusions." Ex. 2135 ¶ 87. We agree. As a result, we are unpersuaded by the conclusion drawn from the *ad hoc* comparison of the data in Flechter with those in Meiner. This is especially so in view of Flechter's conclusion that alternate-day administration of glatiramer acetate was "well tolerated, comparing favorably with the effects of daily injections of Copolymer 1 in patients with relapsing MS." Ex. 1008, 1; *see also id.* at 5 ("The results of this trial suggest that alternate-day treatment with Copolymer 1 is safe, well tolerated, and probably as effective as daily Copolymer 1 in reducing relapse rate and slowing neurologic deterioration.").

Accordingly, we are not persuaded that a person of ordinary skill in the art considering combining a higher dose of GA with the alternate-day dosing schedule in Flechter would, as Patent Owner asserts, conclude that

[5] Meiner et al., *Copolymer 1 in Relapsing-Remitting Multiple Sclerosis: a Multi-Centre Trial, in Frontiers in Multiple Sclerosis: Clinical Research and Therapy* (Abramsky et al. eds., 1997) (Ex. 1009).

such a regimen would likely exacerbate the frequency of injection site reactions. *See* PO Resp. 36.

B. Evidence Relating to Increased Dosage

Patent Owner further argues that we overlooked evidence that a 40 mg dose of GA would have been expected to result in decreased tolerability when compared to 20 mg GA. Reh'g Req. 10–12. Patent Owner cites Cohen,[6] which compares the occurrence of different categories of adverse events when administering 40 mg GA daily versus 20 mg GA daily. *Id.* at 10–11 (citing Ex. 1006, Table 3). Patent Owner complains that we did not discuss Cohen in our Final Written Decision. *Id.*

As an initial matter, we considered all admissible evidence presented by both parties. We, however, did not address each and every piece of evidence in our Decision, particularly if it was cumulative of other evidence. In our Decision, we noted that in the FORTE trial, "the higher [40 mg] dose maintained the favorable safety and tolerability profile of COPAXONE® 20 mg." Dec. 12 (quoting Ex. 2001, 1). Thus, we were not persuaded by Patent Owner's argument that a person of ordinary skill in the art would not have used 40 mg GA because it was associated with more frequent adverse events. *Id.*

Cohen does not add to our discussion of FORTE. According to Patent Owner, the FORTE trial "was a large Phase III study that followed up on the Phase II study reported by Cohen." PO Resp. 17. Thus, we did not

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[6] J.A. Cohen et al., *Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS*, 68 NEUROLOGY 939–44 (2007) (Ex. 1006).

expressly discuss Cohen because it is cumulative of the FORTE trial. Indeed, Cohen concludes that the 40 mg dose was "safe and well tolerated." Ex. 1006, 1 (Abstract). Although certain aspects of injection site reactions were more common with the higher dose and the injections seemed to be more painful, Cohen states that "the overall incidence of injection site reactions was similar." *Id.* at 6. Thus, we are not persuaded that, as Patent Owner asserts, Cohen shows decreased tolerability for 40 mg GA.

Patent Owner also cites the FORTE study as showing a "statistically significant increase in treatment discontinuation due to injection site reactions" for the 40 mg dose compared with the 20 mg dose. Reh'g Req. 11–12 (citing PO Resp. 18; Ex. 2028, 5; Ex. 2135 ¶ 100). According to Patent Owner, this is the "only statistically significant finding from the study reported in the prior art." *Id.* at 12.

We did not overlook or misapprehend this argument regarding the FORTE study; we simply found it unpersuasive. Although the Comi slides,[7] which reflect the results of the FORTE study, state that the difference in adverse events between 20 mg GA and 40 mg GA was statistically significant and "mainly due to Injection Site Reactions," that statistically significant difference is only among the patients who terminated the study early. Ex. 2028, 5 (Slide 14). The slides are silent as to any statistical significance for the injection site reactions across the entire patient population for the entire study. *Id.* at 9 (Slide 25). Indeed, the percentage of

[7] Giancarlo Comi, *FORTE: Results from a Phase III, 1-Year Randomized, Double-Blind, Parallel-Group, Dose-Comparison Study with Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis* (Ex. 2028).

patients who reported injection site reactions was 55.6% for 20 mg GA and 58% for 40 mg GA. *Id.* And Patent Owner's declarant, Dr. Edward J. Fox, testified that he was "not certain of the statistical significance of those two numbers as reported on Slide 25." Ex. 2146, 141:4–142:19. Moreover, Slide 25 states "both doses were well-tolerated," and Slide 26 concluded there was "[g]ood safety and tolerability profile; no unexpected adverse effect with the high dose." Ex. 2028, 9. Thus, given the art as a whole repeatedly states 40 mg GA is well tolerated, we are not persuaded that, as Patent Owner asserts, the art suggested a 40 mg dose of GA was less tolerable than 20 mg GA.

C. Prior Art as a Whole

Patent Owner argues that, when considered as a whole, "the prior art taught that decreased frequency of injection and increased dosage amount per injection were expected to decrease the tolerability of GA treatment." Reh'g Req. 12–13. Patent Owner further contends that a person of ordinary skill in the art "thus would not have been motivated to develop the claimed treatment regimen in an effort to increase tolerability of GA treatment." *Id.* at 13. We note that none of the claims, other than claims 15–18, recite any limitation regarding tolerability. And regarding claims 15–18, as stated in the Decision, we credited the testimony of Dr. Green that prior art shows, compared with daily dosing, every-other-day dosing decreases the injection related side effects. Dec. 23–24 (citing Ex. 1004 ¶¶ 117–18; Exs. 1010, 1011).

Patent Owner also criticizes our reliance on the Khan 2008[8] and Caon 2008[9] abstracts because the references neither contain any data nor involve the 40 mg dose. Reh'g Req. 13. According to Patent Owner, "reported data found in the prior art as a whole clearly suggested that decreased tolerability would result from a 40 mg, three times per week regimen and the Board's decision erred in finding otherwise." *Id.* As explained above, we were not persuaded that the prior art suggested decreased tolerability. Instead, in light of the prior art references each stating that the dosage regimens were well tolerated, we were, and remain, persuaded that a person of ordinary skill in the art would have had a reason to combine the asserted references to reach the claimed dosing regimen with a reasonable expectation of success.

D. Evidence Relating to Secondary Considerations

Finally, Patent Owner asserts that the Board overlooked evidence regarding the expected decrease in tolerability in our discussion of secondary considerations. Reh'g Req. 14–15. Patent Owner argues that our "finding that Patent Owner failed to provide any evidence of improved tolerability over the Pinchasi reference (FWD at 26) is also incorrect." *Id.* at 14. We did not state that Patent Owner failed to provide *any* evidence of improved tolerability—we stated that Patent Owner provided "*insufficient*

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[8] Khan et al., *Randomized, Prospective, Rater-Blinded, Four-Year, Pilot Study to Compare the Effect of Daily Versus Every-Other-Day Glatiramer Acetate 20 mg Subcutaneous Injections in Relapsing-Remitting Multiple Sclerosis*, 14 MULTIPLE SCLEROSIS S296 (2008) (EX. 1010).

[9] Caon et al., *Randomized, Prospective, Rater-Blinded, Four-Year, Pilot Study to Compare the Effect of Daily Versus Every-Other-Day Glatiramer Acetate 20 mg Subcutaneous Injections in RRMS*, 72 NEUROLOGY A317 (Mar. 17, 2009) (Ex. 1011).

evidence of record showing any unexpected benefit between the claimed three-times-weekly as compared to the prior art every-other-day dosing." Dec. 26 (emphasis added). Substantively, as explained above, we find Patent Owner's characterizations of the prior art, including Cohen, unpersuasive. As a result, we were not, and remain not, persuaded that the nonobviousness of the challenged claims is supported by evidence of unexpected results.

IV. CONCLUSION

For the foregoing reasons, Patent Owner has demonstrated that we misapprehended the evidence and argument regarding the combination of Pinchasi and Flechter. We, therefore, grant Patent Owner's Request for Rehearing as to this issue, and modify Section II.F of the Final Written Decision to include our analysis above in Section III.A. Patent Owner, however, has not demonstrated we misapprehended any other evidence and argument. We, therefore, deny Patent Owner's Request for Rehearing as to the remaining issues.

V. ORDER

Accordingly, it is ORDERED that Patent Owner's Request for Rehearing is *Granted-In-Part*;

FURTHER ORDERED that the Final Written Decision issued on August 24, 2016 (Paper 85) is *vacated*; and

FURTHER ORDERED that a modified Final Written Decision is entered concurrently with this Order.

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