

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN LIMITED,
Petitioner,

v.

VERTEX PHARMACEUTICALS INCORPORATED,
Patent Owner.

Case IPR2015-00405
Patent 6,436,989 B1

Before LORA M. GREEN, SHERIDAN K. SNEDDEN, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION
Denying Petitioner's Request for Rehearing
37 C.F.R. § 42.71

I. INTRODUCTION

An *inter partes* review was instituted in the above referenced case. Paper 13 (“Decision”). Lupin Limited (“Petitioner”) requested rehearing of our Decision. Paper 15 (“Request”). Vertex Pharmaceuticals Incorporated (“Patent Owner”) filed a response. Paper 21 (“Response”). Petitioner filed a reply. Paper 22 (“Reply”).

In its Petition, Petitioner challenged claims 1–12 of U.S. Patent No. 6,436,989 B1 (Ex. 1001; “the ’989 Patent”) on the following grounds. Paper 7, 7–8 (“Pet.”).

Ground	Reference[s]	Basis	Claims challenged
1	Roy and Grobelny	§ 103(a)	1–2
2	Roy, Grobelny, and Bighley	§ 103(a)	3–12
3	Roy II and Grobelny	§ 103(a)	1–2
4	Roy II, Grobelny, and Bighley	§ 103(a)	3–12

In rendering the decision to institute, we instituted an *inter partes* review as to claims 1 and 4–9 of U.S. Patent No. 6,436,989 B1 (Ex. 1001; “the ’989 Patent”) for the following proposed grounds of unpatentability:

- (i) claim 1 of the ’989 Patent as unpatentable under 35 U.S.C. § 103 over the combination of Roy and Grobelny; and
- (ii) claims 4–9 of the ’989 Patent as unpatentable under 35 U.S.C. § 103 over the combination of Roy, Grobelny, and Bighley.

Decision 25. We also determined that Petitioner failed to demonstrate a reasonable likelihood of prevailing on its challenge of claims 2, 3, and

10–12 on any ground asserted in the Petition. *Id.*

In its Request, Petitioner contends that the Board should reconsider its decision not to institute on Ground 1 as to claim 2; Ground 2 as to claims 3, 10–12; and Grounds 3–4 as to claims 1–12. Request 1.

For the reasons set forth below, Petitioner’s request for rehearing is denied.

II. STANDARD OF REVIEW

When rehearing a decision, the Board reviews the decision for an abuse of discretion. *See* 37 C.F.R. § 42.71(c). An abuse of discretion occurs when a “decision [i]s 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). “The burden of showing that a decision should be modified lies with the party challenging the decision.” Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,768 (Aug. 14, 2012). In its request for rehearing, the dissatisfied party must (1) “specifically identify all matters the party believes the Board misapprehended or overlooked” and (2) identify the place “where each matter was previously addressed.” 37 C.F.R. § 42.71(d); Office Patent Trial Practice Guide, 77 Fed. Reg. at 48,768. We address Petitioner’s arguments with these principles in mind.

III. ANALYSIS

A. Grounds 1 and 2

In deciding whether to institute, we considered the Petition (Paper 7) and the Preliminary Response (Paper 11). Based on the evidence of record at that time, we determined that Petitioner had failed to demonstrate a

reasonable likelihood of prevailing on Ground 1 as to claim 2 or Ground 2 as to claims 3 and 10–12. 35 U.S.C. § 314(a).

In our Decision, we determined that the evidence of record showed “that fosamprenavir, and in particular fosamprenavir calcium, has improved pharmacokinetics, reduced gastrointestinal side effects, and different resistance profile as compared to its parent drug, amprenavir.” Decision 22. Petitioner challenges these findings and contends that our Decision is not supported by “substantial evidence.” Request 3–11. In particular, Petitioner argues that

- 1) Wood (Ex. 2013) shows that fosamprenavir’s pharmacokinetics are equivalent to amprenavir, not improved (*id.* at 3–6);
- 2) Wood shows that drug-related adverse events were generally evenly distributed between patients administered amprenavir group than the two fosamprenavir (*id.* at 6–8); and
- 3) the finding of a different resistant profile for fosamprenavir is based on studies testing the combination of fosamprenavir and ritonavir, and not fosamprenavir alone (*id.* at 8–11).

We disagree with Petitioner’s contention that our Decision was not supported by evidence of record. First, with regard to fosamprenavir’s pharmacokinetics, Petitioner does not dispute our finding that Wood discloses that fosamprenavir delivers the same amount of amprenavir over time (AUC) in a manner that achieves a lower maximum concentration ($C_{\max}$) and a higher minimum concentration ($C_{\min}$). Dec. 18. Rather, Petitioner merely argues that Wood discloses that the pharmacokinetics of amprenavir and fosamprenavir are the same because Wood discloses that fosamprenavir delivers equivalent plasma values as amprenavir. Request 5.

This argument is unpersuasive, however, as it fails to address Wood's disclosure that not only does fosamprenavir achieve the equivalent overall plasma levels of aprenavir, but it does so with a higher $C_{\min}$ and lower $C_{\max}$. Dec. 18; Paper 11, 33. Such results are relevant as they impact tolerability of the drug, and potentially explain the decrease in the incidence of gastrointestinal adverse drug effects suggested in the study disclosed by Wood. Dec. 18; Paper 11, 33; Ex. 2013, 122.

Petitioner next argues that we made an error relying on data from Wood "selectively presented" by Vertex regarding gastrointestinal side effects. Request 6–8. We disagree. Wood discloses that patients taking fosamprenavir experienced reduced side effects for diarrhea, nausea and abdominal pain compared with the patients taking amprenavir. Ex. 2013, 120 121, 122 (Table 5). This data is suggestive of an improved GI sided effect profile affecting patient compliance. Dec. 19–20; *cf.* Ex. 2018, 551 ("early PI [protease inhibitor] therapy posed a number of challenges to clinicians and patients. The first marketed PIs were generally large pills with high pill burden that required frequent dosing. They were frequently associated with significant gastrointestinal side effects, including diarrhea, nausea and vomiting"). Further, as stated by Patent Owner, "[t]hat Wood shows the remaining side effects may be evenly distributed between the fosamprenavir and amprenavir patient populations does not diminish the suggestion made by the improved GI side effect distribution." Response, 8–9.

With regard to the resistance profile for fosamprenavir, Petitioner contends that we erred by being persuaded that fosamprenavir has a different resistance profile, namely a reduced selection for the I50V mutation.

Request 8–11. In our Decision, we relied, in part, on the teachings set forth in Ex. 2014 and Ex. 2017 disclosing that the I50V mutation is associated with the highest levels of amprenavir resistance, and on the teachings of Ex. 2030 and Ex. 2031 suggesting that the I50V is absent in certain fosamprenavir therapy. Dec. 19 (citing Ex. 2014, 112; Ex. 2017, 84; Ex. 2030 (Abstract No. 598); Ex. 2031, 652). Petitioner argues that Exs. 2030 and 2031 relate to resistance profiles for fosamprenavir administered with another active agent, ritonavir, and not fosamprenavir administered alone. Request 9–10. Petitioner supports this new argument with reference to Ex. 1047, which discloses that the I50V mutation is observed with unboosted fosamprenavir. *Id.*

We are not persuaded by Petitioner’s argument that a clear error was made based on the record at the time of our Decision. First, we note that these arguments are being made for the first time in the Request, and as such, cannot be the basis for rehearing. The Board cannot have misapprehended or overlooked an argument that was not presented earlier. Second, Lupin arguments are supported by new evidence and fail to comply with 37 C.F.R. § 42.71(d). It would be inappropriate for us to consider Ex. 1047 in a request for rehearing.

Petitioner further argues that we

fundamentally misapprehended Ex. 2026 in finding that development of HIV protease inhibitors was not predictable, because of an inaccurate comparison to ritonavir and lopinavir, which are structurally dissimilar from amprenavir (see Ex. 1002, contrast ritonavir structure in ¶ 43, to VX-478 and DG35 structures in ¶ 93). The better comparator is the parent compound of the ’269 publication, which, as shown in Dr. Fisher’s declaration, has structural features near the phosphate

ester that are highly analogous to those of amprenavir. *Id.* Thus, Ex. 2026 is less probative of unpredictability than is the '269 publication; it is not a reasonable comparator.

Request, 11–12. Petitioner added that the data in Grobelny (Ex. 1022) supports a reasonable expectation of success in making an orally bioavailable phosphate ester prodrug of amprenavir. Request, 12–14.

Here, Petitioner continues to advocate its position and expresses disagreement with our decision, but does not persuade us that we misapprehended or overlooked any matter. In our Decision, we determined that “[t]he data presented in the Grobelny application, showing that the prodrug of Grobelny did not deliver the parent compound consistently,” supporting the conclusion that “the complexity of *in vivo* conversion renders the treatment with prodrugs unpredictable.” Dec. 24. In this regard, we note that Petitioner does not dispute that Ex. 2015, for example, shows variable delivery of the parent compound in rats ranging from “0% to greater than 35%”, suggesting that certain rats received 0% of the active ingredient in their system.

Moreover, in its Petition, Petitioner failed to identify guidance in the prior art disclosing to a person of ordinary skill in the art which specific modifications of a prior art compound would result in a predictably bioavailable compound. In contrast, the Patent Owner provided evidence of unpredictably demonstrating that the mere production of a compound does not predict whether the compound would be bioavailable, that is, convert from prodrug to drug. *See e.g.*, Ex. 2026, 2965 (Table 1) (discussing the importance of structural features in the vicinity of the phosphate ester on the rate at which prodrug reverted to back to parent drug). As such, we disagree

with Petitioner's contention that our Decision was not supported by evidence of record, and, thus, clearly erroneous.

In view of the above, we conclude that the evidence of record submitted by Petitioner and Patent Owner was considered in our Decision to Institute and, when considered in light of the Petition and Dr. Fisher's declaration, found to be insufficient to establish a reasonable likelihood of unpatentability. We did not misapprehend or overlook the evidence or arguments now raised by Petitioner.

B. Grounds 3 and 4

Patent Owner confirms that it will not rely on 35 U.S.C. § 103(c) to remove Roy I as prior art, thus mooted those grounds in Petitioner's rehearing request. Response 15.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's request for rehearing is *denied*.

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