UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VIII, LLC,
Petitioner,

v.

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,
Patent Owner.

Case IPR2015-01836
Patent 7,832,268 B2

PATENT OWNER'S REPLY IN SUPPORT OF MOTION TO AMEND UNDER 37 C.F.R. § 42.121

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I. INTRODUCTION

The only disputed issue is whether the proposed substitute claims are patentable. Petitioner has failed to demonstrate that they are not.[1] Petitioner's new 6-way combination of alleged obviousness references—devoid of ***any*** human pharmacokinetic ("PK") or pharmacodynamic ("PD") data about lomitapide—fails to teach or suggest every limitation of the substitute claims, let alone provide any motivation to treat humans with lomitapide in the first place—a compound that failed in the clinic due to toxicities and was abandoned by the company that discovered it. Even assuming that a skilled person would be motivated to develop a treatment regimen in humans with lomitapide—notwithstanding its known toxicities—nothing in the prior art provided a motivation to use the claimed titration regimen. Further, a skilled artisan would not have had a reasonable expectation of success given the "dose-dependent" nature of the hepatic side effects associated with lomitapide (*i.e.*, worsened as the dose increased).

First, the prior art contains no information regarding the dose effect of lomitapide in humans. No human PK data. No human PD data. No human data at

[1] Congress has made clear that Petitioner "shall have" the burden on any "proposition of unpatentability" in this proceeding—regardless of whether the proposition pertains to an issued or a substitute claim. 35 U.S.C. § 316(e). In any event, Patent Owner has demonstrated that the claims are patentable.

all. Indeed, all a skilled artisan in 2004 would know about lomitapide's effect in humans was that it reduced cholesterol, but had been deemed too dangerous for further investigation because of dose-dependent hepatic side effects. Petitioner cites but fails to explain how a single two-week rabbit study disclosed in a paper ("Wetterau") that ***pre-dated*** the withdrawal of lomitapide from the clinic would motivate a person of ordinary skill in the art ("POSA") to resume clinical study of lomitapide, foregoing other known MTP inhibitors that had ***not*** been withdrawn. Wetterau itself could not provide the motivation—the reference makes no mention of side effects with lomitapide, let alone how to dose lomitapide effectively in humans without causing them. A POSA would know that the animal study in Wetterau—written by scientists at BMS—would contain far ***less*** information about the safety and efficacy of lomitapide in humans than the clinical trials that led to BMS's decision to discontinue the drug.

Second, nothing in the prior art suggested that the liver toxicities associated with lomitapide—known to ***increase*** with larger doses and to accumulate over time—could be mitigated by administering two-fold increasing doses of the drug over three intervals as short as a week. Nothing in the generic titration references upon which Petitioner relies, suggests that administering a drug with known toxicity in rapidly escalating doses would be safe, let alone mitigate toxicity.

In short, Petitioner's obviousness claim impermissibly relies upon selective

reading and the use of hindsight—as exemplified by the need to stitch together six different references (half of which do not even refer to lomitapide).

II. THE PROPOSED SUBSTITUTE CLAIMS ARE PATENTABLE

A. The Claims are Patentable Over Petitioner's 6-Way Combination

1. No Motivation to Use Lomitapide Over Other MTP Inhibitors

By 2004, it was well known in the art that Bristol-Myers Squibb ("BMS") discontinued further development of lomitapide after Phase II trials because of hepatotoxicity issues. (Ex. 2011; Ex. 1015 at 6.) Wetterau, a pre-clinical rabbit study that ***pre-dates*** BMS's decision to withdraw lomitapide from the clinic, would not have sufficiently motivated a POSA to revive study of the drug in humans. Whatever motivations a POSA might have drawn from Wetterau would have been dampened, if not completely extinguished, upon learning that BMS had pulled the compound from the clinic because of toxicity concerns that had ***not*** been reported in Wetterau (because they had yet to be observed). (Ex. 2305 at ¶¶ 12, 21-23, 38.) In fact, the Wetterau authors were from BMS. (Ex. 1018 at 1.) Petitioner's suggestion that others of skill in the art would have nonetheless been motivated to continue developing lomitapide based on Wetterau, when not even BMS (*i.e.*, the author of Wetterau) was motivated to do so, is classic hindsight.

To have been motivated to re-start investigation with lomitapide, a POSA would have required human *in vivo* information concerning the drug, including PK and PD data. (Ex. 2305 at ¶¶ 12, 21-23, 34, 38-39; Ex. 2024 at ¶¶ 80, 95, 113,

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