UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. AND APOTEX CORP.,
Petitioners

v.

AUSPEX PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2021-01507
U.S. Patent No. 8,524,733
Issued: September 3, 2013

Title:
BENZOQUINOLINE INHIBITORS OF VESICULAR MONOAMINE TRANSPORTER 2

PETITIONER'S REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE

LIST OF EXHIBITS

Exhibit No.	Description
1004	Naicker, S. et al., U.S. Patent No. 6,503,921, "Deuterated rapamycin compounds, methods and uses thereof" ("Naicker '921")
1005	Kohl, B. et al., Int'l. Pub. No. WO 2007/012650, "Isotopically Substituted Proton Pump Inhibitors" ("Kohl")
1006	Foster A.B. et al., *Isotope effects in O- and N-demethylations mediated by rat liver microsomes: An application of direct insertion electron impact mass spectrometry*, CHEM.-BIOL. INTERACTIONS, 9:327-340 (1974) ("Foster AB")
1009	Gant, T.G. et al., U.S. Pat. Pub. No. 2008/0280991, "Substituted Naphthalenes" ("Gant '991")
1027	Excerpts of the Application File History for the '733 Patent, U.S. App. No. 12/562,621 (the "FH Excerpts")

Apotex replies to two arguments[1] in Patent Owner's ("PO's) preliminary response, which seeks denial of Apotex's petition asserting that PO's patent claims to deuterated tetrabenazine are unpatentable. As to § 325(d), there is no evidence the Examiner specifically considered teachings or arguments relating to the many expected benefits of deuterating methoxy groups. So it is no surprise that she erred in accepting PO's evidence of "unexpected" results arising from deuterating tetrabenazine's methoxy groups. As to secondary considerations, they fail for lack of nexus or factual support. The Board should thus institute *inter partes* review.[2]

INSTITUTION SHOULD NOT BE DENIED UNDER § 325(D)

First, PO argues that the substance of Apotex's references and arguments were before the Examiner. POPR 2, 16-24. But there is no evidence that she specifically considered teachings or arguments relating to expected benefits of deuterating methoxy groups. Apotex's combination references teaching those benefits, Naicker '921, Kohl, Foster AB, and Gant '991, were ***not*** before the Examiner, and ***no*** arguments were made regarding those teachings. PO asserts that Foster AB is discussed in Foster 1985, a reference she considered in a rejection.

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[1] Apotex disagrees with PO's other arguments, resting on its Petition for them.

[2] Out of desperation, PO makes an outlandish allegation of extortion. POPR 33. But Apotex did ***not*** seek money; it sought a license to market a generic product.

POPR 20 (citing EX1027 at 51-53). But there is no evidence that she analyzed that portion of the disclosure. Her discussion of Foster 1985 focused ***solely*** on how it would have motivated a POSA to deuterate tetrabenazine to improve metabolic stability; notably, the word "methoxy" never appears. The only reasonable conclusion is that she overlooked that disclosure. PO also discounts Naicker '921, Kohl, Foster AB, and Gant '991 as cumulative. POPR 21. But those disclosures provide unique teachings and/or experimental data about the numerous benefits of deuterating methoxy groups. If the Examiner had specifically considered those teachings, she would have rejected PO's evidence of "unexpected" results.

Second, relying largely on attorney argument unsupported by any expert, PO argues that the Examiner correctly allowed the claims based on PO's evidence of unexpected results. POPR 25-33. But as explained in Apotex's petition, the Examiner initially, and correctly, rejected PO's results as "expected and not unexpected," as they were fully disclosed in the prior art. Pet. 36-40, 47-49, 59-60. The Examiner inexplicably erred in not maintaining her position.[3] Attempting to

[3] In short, the Examiner rejected PO's *in vitro* and *in vivo* data submitted in a first declaration as "quite expected." EX1027 at 26-32, 53-54. PO submitted side effect data in a second declaration, and she allowed the claims. *Id.* at 63-71, 126. This was inexplicable, as those data were expected ***and*** had no nexus. *See infra*.

justify this error, PO makes two basic assertions: (1) that Apotex improperly relies upon the teachings of references such as Naicker '921, Kohl, and Foster AB and (2) that Apotex's arguments should be rejected because they rely upon *in vitro* data instead of *in vivo* data. POPR 27-31. Both assertions are without merit.

As an initial matter, Apotex properly relied upon those references, as each teaches what *in vivo* ***and*** *in vitro* results a POSA would expect upon deuterating methoxy groups, ***including the results PO submitted to the Examiner***. As for Naicker '921, it teaches that deuterating such groups "alters the pharmacokinetic parameters of the drug," as well as increases potency and stability while reducing toxicity and clearance. EX1004 at 4:28-30, 32-36; *id.* at 4:30-32 ("Lower rates of oxidation, metabolism and clearance result in greater and more sustained biological activity."). Consistent with Naicker '921, Kohl used a predictive human liver microsome model, reporting that methoxy group deuteration reduced metabolism by 50%. EX1005 at Exs. 1 & 2 (synthesis), Table 1 (microsome data). This is ***the same result PO obtained*** in microsomes and submitted to the Examiner. EX1027 at 17, 31-32 (at least 50% metabolite reduction). Foster AB used a rat liver microsome model, reporting that methoxy group deuteration resulted in "[i]sotope effects of ~2." EX1006 at 327. ***This was predictive of the doubled half-life obtained*** in PO's *in vivo* study and submitted to the Examiner. EX1027 at 18, 32.

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