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Paper 9
Date: March 9, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC. AND APOTEX CORP.,

Petitioner,

v.

AUSPEX PHARMACEUTICALS, INC.,

Patent Owner.

IPR2021-01507
Patent 8,524,733 B2

Before GRACE KARAFFA OBERMANN, JOHN G. NEW, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

OBERMANN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 325(d)

I. INTRODUCTION

Apotex Inc. and Apotex Corp. (collectively, "Petitioner") filed a Petition (Paper 2, "Pet.") for institution of an *inter partes* review of claims 1–3 of U.S. Patent No. 8,524,733 B2 (Ex. 1001, "the '733 patent"). Auspex Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp."). With Board authorization, Petitioner filed a Reply (Paper 7) and Patent Owner filed a Sur-reply (Paper 8) limited to addressing three issues, including whether we should exercise discretion and deny review under 35 U.S.C. § 325(d) ("Section 325(d)"). Ex. 3001.

A. Real Parties-in-Interest

The Petition indicates that Apotex Inc., Apotex Corp., Apotex Pharmaceutical Holdings Inc., and Aposherm Delaware Holdings Corp. are real parties-in-interest. Pet. 6. Patent Owner's Mandatory Notice indicates that Auspex Pharmaceuticals "is the real party-in-interest," however, "[o]ut of an abundance of caution," Patent Owner identifies also "Teva Branded Pharmaceutical Productions R&D, Inc. as a real party-in-interest for the purposes of providing notice in this" proceeding. Paper 4, 1.

B. Related Matters

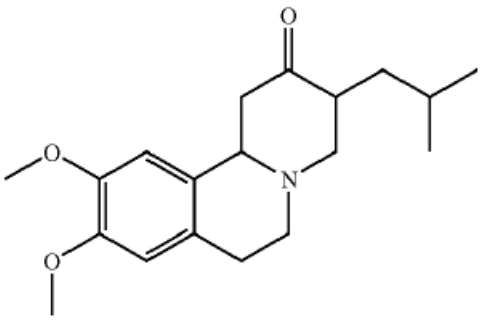
Petitioner states it is unaware of any related matters. Pet. 6. In a section of its Mandatory Notices titled "Related Matters," Patent Owner identifies two U.S. patent applications, one expired and one abandoned, as well as "a patent infringement lawsuit filed in the District of New Jersey in Civil Action No. 3:21-cv-13240, *Teva Branded Pharm. Products R&D, Inc. et al. v. Aurobindo Pharma Ltd. et al*." Patent Owner, however, "does not concede that any of" these matters "would affect, or be affected by, a decision in the present proceeding." Paper 4, 1–2.

II. BACKGROUND

A. The '733 Patent (Ex. 1001)

The '733 patent is titled "Benzoquinoline Inhibitors of Vesicular Monoamine Transporter 2." Ex. 1001, code (54). The '733 patent claims priority to a provisional application filed on September 18, 2008. *Id.* at code (60), 1:4–7. The invention of the '733 patent relates to "new benzoquinoline compounds" and "pharmaceutical compositions made thereof" that inhibit vesicular monoamine transporter 2 activity and, thereby, are useful "for the treatment of chronic hyperkinetic movement disorders." *Id.* at 1:8–12; *see id.* at code (57) (Abstract).

Tetrabenazine was a known and "commonly prescribed" benzoquinoline compound for treating Huntington's disease, one of several "chronic hyperkinetic movement disorders." *Id.* at 1:13–19, 6:56–67. The structure of tetrabenazine follows:



Tetrabenazine

Ex. 1001, 1:13–32. The above illustration shows the structure of "Tetrabenazine (Nitoman, Zenazine, Ro 1-9569), 1,3,4,6,7,1 1b-Hexahydro-9,10-dimethyoxy-3-(2-methylporpyl)-2H-benzo[a]quinoline," which "is a vesicular monoamine transporter 2" inhibitor. *Id.* at 1:13–16.

At the time of the invention, an ordinarily skilled artisan would have had a basic understanding of the *in vivo* metabolic pathways of

tetrabenazine and adverse side effects associated with its administration. *Id.* at 1:36–46. That artisan would have known that the body expresses enzymes to eliminate foreign substances, including therapeutic agents, in metabolic reactions that frequently involve the oxidation of a carbon-hydrogen bond. *Id.* at 1:48–56. "The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds." *Id.* at 1:56–60.

The ordinarily skilled artisan further would have been aware that deuterium[1] forms a stronger bond with carbon than hydrogen (*id.* at 2:14–16) and that, therefore, its substitution for hydrogen in the carbon-hydrogen bond of pharmaceutical compounds produces a kinetic isotope effect that "will cause a decrease in the reaction rate" (*id.* at 2: 19–20). At the time of the invention, "[d]euteration of pharmaceuticals" was known "to improve pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles" and had "been demonstrated previously with some classes of drugs." *Id.* at 2:53–55. For example, deuteration had been used successfully "to decrease the hepatotoxicity of halothane, presumably by limiting the production of reactive species such as trifluoroacetyl chloride." *Id.* at 2:55–57.

It was known also that, due to "the promiscuous nature of many metabolic reactions" and, in particular, the phenomenon of "metabolic switching," deuteration "may not be applicable to all drug classes." *Id.* at 2:57–65. "Metabolic switching occurs when xenogens, sequestered by Phase I enzymes, bind transiently and re-bind in a variety of conformations

[1] Deuterium (D) is a heavier isotope of hydrogen with one additional neutron. Ex. 1004, 2:28–30; Ex. 1027, 10.

prior to the chemical reaction (e.g., oxidation)." *Id*. at 2:60–63. The effects of deuteration may result in a "new metabolic profile" for any particular class of drugs that imparts "more or less toxicity." *Id*. at 3:1. The '733 patent states, "Such pitfalls are non-obvious and are not predictable *a priori* for any drug class." *Id*. at 3:2–3.

The claims are directed to a specific deuteration pattern for tetrabenazine in which each hydrogen in adjacent methoxy groups, but no other hydrogen position, is deuterated. *Id*. at 50:40–64 (claims 1–3). "Based on discoveries made in our laboratory, as well as considering the literature," the inventors of the '733 patent assert they discovered that "tetrabenazine is metabolized in humans at the isobutyl and methoxy groups." *Id*. at 3:16–18. Taking account of that discovery, the invention allegedly limits production of certain metabolites by employing "deuteration patterns" having "strong potential to slow the metabolism of tetrabenazine and attenuate interpatient variability." *Id*. at 3:16–43.

The '733 patent discloses:

> In certain embodiments, the deuterated compounds disclosed herein maintain the beneficial aspects of the corresponding non-isotopically enriched molecules while substantially increasing the maximum tolerated dose, decreasing toxicity, increasing the half-life ($T_{1/2}$), lowering the maximum plasma concentration (C_{max}) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.

Id. at 4:44–52. "The carbon-hydrogen bonds of tetrabenazine contain a naturally occurring distribution of hydrogen isotopes," including deuterium in a range of "about 0.0156%." *Id*. at 3:4–7. The claimed compound requires that six carbon-hydrogen bond positions in the tetrabenazine

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