Trials@uspto.gov
571-272-7822

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

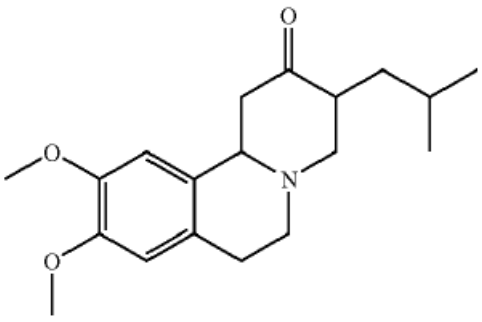
Petitioner states it is unaware of any related matters. Pet. 6. In a section of its Mandatory Notices titled "Related Matters," Patent Owner identifies two U.S. patent applications, one expired and one abandoned, as well as "a patent infringement lawsuit filed in the District of New Jersey in Civil Action 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

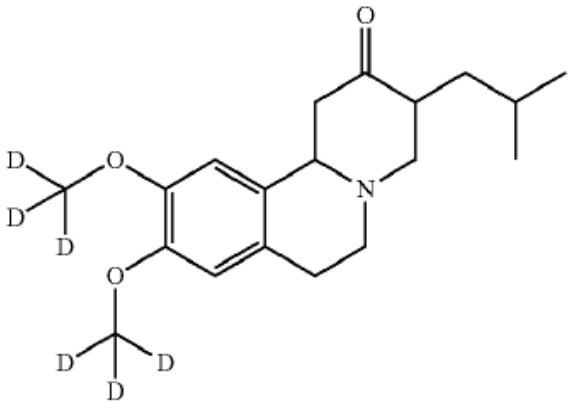
molecule have "deuterium enrichment of no less than about 90%." *Id.* at 50:57 (claim 1); *see id.* at 50:59–61 (claim 2, requiring "deuteration enrichment of no less than about 98%" at those same six positions).

To be clear, the challenged claims are directed to a *specific* deuteration pattern in tetrabenazine that involves O-demethylation of both methoxy groups but does not involve deuteration of the carbon-hydrogen bonds of the carbonyl group, the isopropyl group, or any other carbon-hydrogen position in the molecule. *Id.* at 50:40–64 (claims 1–3). That becomes critically important to our analysis, because as explained in detail below, no reference presented to the Examiner, and no reference asserted in the Petition, discloses deuteration – in *any* pattern – for tetrabenazine or any other drug in its class of benzoquinoline inhibitors.

B. Challenged Claims

Petitioner challenges claims 1–3 of the '733 patent. Pet. 7. Claim 1, which we reproduce below, is illustrative of the claimed subject matter.

1. A compound having the structural formula:



or a salt thereof, wherein each position represented as D has deuterium enrichment of no less than about 90%.

Ex. 1001, 50:41–58. Claim 2 depends from claim 1 and requires that "each position represented as D has deuterium enrichment of no less than

about 98%." *Id*. at 50:59–61. Claim 3 specifies "[a] pharmaceutical composition" that includes "a compound as recited in claim 1 together with a pharmaceutically acceptable carrier." *Id*. at 50:62–64.

C. Asserted Grounds of Unpatentability

Petitioner asserts three grounds under 35 U.S.C. § 103[2], as follows:

Ground	Claims Challenged	References
1	1–3	Zheng[3], Naicker[4], Kohl[5]
2	1–3	Zheng, Foster AB[6], Kohl
3	1–3	Gano[7], Schwartz[8], Gant[9]

[2] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284 (September 16, 2011), includes revisions to Section 103 that became effective on March 16, 2013. Petitioner argues, and Patent Owner does not contest, that the pre-AIA statutory provisions apply in this case. Pet. 1. Neither party indicates the result would change, however, based on which version of the statute the Board applies for purposes of deciding whether to institute review.

[3] Zheng, G. et al., V*esicular Monoamine Transporter 2: Role as a Novel Target for Drug Development*, THE AAPS JOURNAL, 8(4):E682-E692 (2006) (Ex. 1003).

[4] US Patent No. 6,503,921, issued Jan. 7, 2003 (Ex. 1004).

[5] WO 2007/012650, published Feb. 1, 2007 (Ex. 1005).

[6] 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) (Ex. 1006).

[7] US Patent No. 8,039,627, issued Oct. 18, 2011 (Ex. 1007).

[8] Schwartz, D.E. et al., *Metabolic studies of tetrabenazine, a psychotropic drug in animals and man*, BIOCHEMICAL PHARMACOLOGY, 15:645-655 (1966) (Ex. 1008).

[9] U.S. Pat. Pub. 2008/0280991, published Nov. 13, 2008 (Ex. 1009). Patent Owner states that it "does not dispute that Gant is prior art" for purposes of trial institution, "but in the event of institution," Patent Owner will show that Gant is not prior art "pursuant to 35 U.S.C. § 103(c)." Prelim. Resp. 15 n.4.

Pet. 21. The Petition is supported by the Declaration of Dr. Jeffrey P. Jones. Ex. 1002.

III. DENIAL UNDER SECTION 325(d)

We have authority to institute an *inter partes* review only where "there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2018). The Board, however, is "never compelled" to institute a review. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016). The Board has discretion to "take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d).

Patent Owner requests that we exercise our discretion and enter a denial of review under Section 325(d). Prelim. Resp. 8–23. We assess that request based solely on the information presented in the Petition, Preliminary Response, Reply, and Sur-reply. The findings and conclusions set forth in this Decision are provided for the exclusive purpose of explaining our reasons for exercising our discretion under Section 325(d).

A. Overview of the Prior Art

As a preface to our overview of the prior art, we highlight that the Examiner was well aware of "[m]any references" that "teach deuteration of known pharmaceutical drugs." Ex. 1027, 13 (prosecution history).[10] The challenges set forth in the Petition advance four allegedly new references that, according to Petitioner, teach deuteration of known pharmaceutical

[10] When citing the prosecution history, we refer to page numbers added by Petitioner (Ex. 1027) or Patent Owner (Ex. 2025).

compounds; but, as it was before the Examiner, we are directed to *no* reference that discusses *any* deuteration pattern specifically in tetrabenazine or *any* other compound in its class. Pet. 25–62.

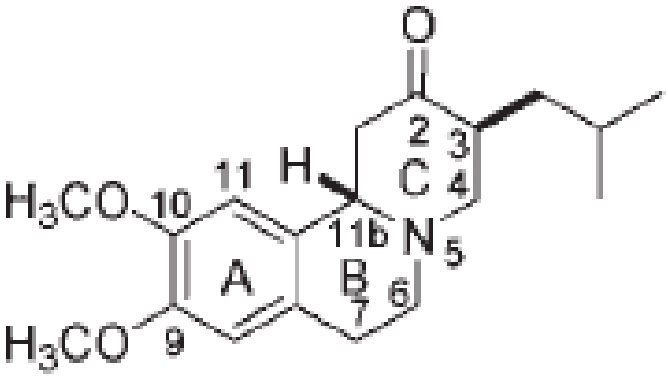
Petitioner advances three references—Zheng, Schwartz, and Gano (i.e., the "tetrabenazine references")—that discuss the metabolic pathways of tetrabenazine, each of which admittedly "was cited during prosecution." *Id.* at 26, 51. In fact, the '733 patent contains a section that expressly cites Zheng and Schwartz and discusses the known metabolic pathways and side effects of tetrabenazine as disclosed in those references. Ex. 1001, 1:34–46. Petitioner also advances four allegedly new references—Naicker, Kohl, Foster AB, and Gant (i.e., the "deuteration references")—that discuss a wide array of deuteration patterns in pharmaceutical compounds outside of tetrabenazine's drug class, which are relied upon to show that "[t]he prior art provided a narrow, straight-line path for arriving at" the *specific* deuteration pattern in tetrabenazine that is required by the claims. Pet. 1; *see id.* at 30, 32, 44, 55 (Petitioner's illustrations, purporting to show the structures of the deuterated compounds disclosed in Naicker, Kohl, Foster AB, and Gant).

In the following subparts, we discuss in greater detail each reference asserted in the patentability challenges, addressing first the tetrabenazine references that were before the Examiner then turning to the deuteration references.

(1) Zheng (Ex. 1003)

Zheng was before the Examiner and a focus of examination. Ex. 1027, 11–13, 51. Zheng relates to tetrabenazine but does not discuss deuteration of any compound. *See generally* Ex. 1003.

Zheng teaches that tetrabenazine was known "to treat hyperkinetic movement disorders, such as chorea associated with Huntington's disease." Ex. 1003, E683. In particular, according to Zheng, tetrabenazine depletes "cerebral monoamines . . . by reversibly inhibiting" vesicular monoamine transporter 2. *Id*. Zheng describes known side effects associated with such treatment, including "sedation, depression, akathisia, and parkinsonism." *Id*. We reproduce below Zheng's Figure 1.



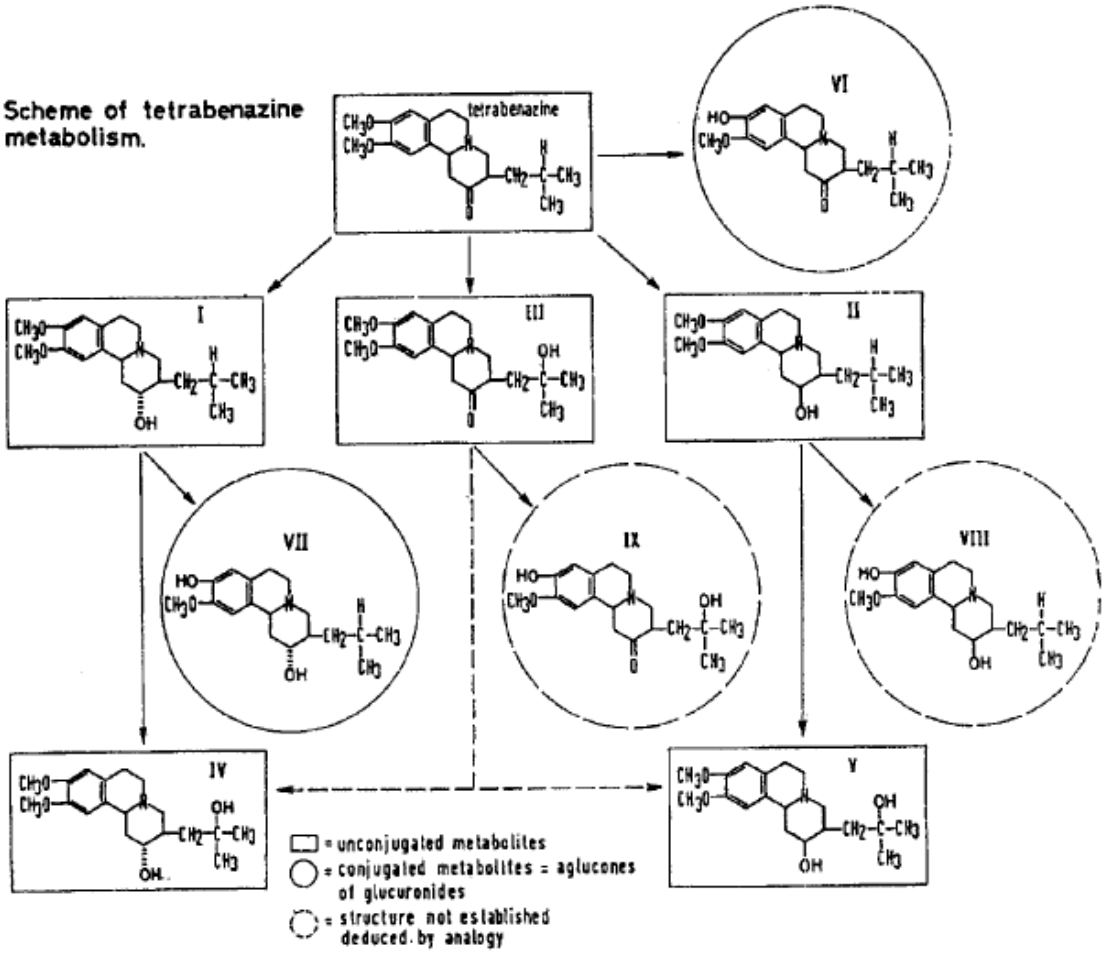
Ex. 1003, Fig. 1. Figure 1 illustrates the structure of tetrabenazine with relevant carbon atoms numbered. The three carbon rings of tetrabenazine are labeled A, B, and C in Figure 1. Throughout this Decision, we refer to the carbon atoms in tetrabenazine by reference to the numbers assigned in Zheng's Figure 1.

Zheng indicates that the carbonyl group at position 2 in Figure 1 "is rapidly and extensively metabolized to its reduced form," which "theoretically" may "exist as 4 possible stereoisomers." *Id*. at E684. Zheng further indicates that the "methoxy groups at positions 9 and 10 appear to be essential" for dopamine-depleting activity. *Id*. at E685.

(2) Schwartz (Ex. 1008)

Schwartz, like Zheng, was before the Examiner and a focus of examination. Ex. 1027, 11–13, 51. Schwartz relates to tetrabenazine but does not discuss deuteration of any compound. *See generally* Ex. 1008.

Schwartz illustrates the scheme of tetrabenazine metabolism, which we reproduce below.



Ex. 1008, 650 (Figure). The above Figure illustrates the scheme of tetrabenazine metabolism as disclosed in Schwartz. The scheme illustrates the structure of nine metabolites of tetrabenazine labeled I through IX. Metabolites III, IV, V, and IX show aliphatic hydroxylation of the isobutyl group at position 3. Metabolites I, II, IV, V, VII, and VIII show reduction of

the carbonyl group at position 2. Metabolites VI, VII, VIII, and IX show demethylation of the methoxy group at position 9. The scheme indicates that demethylation of the methoxy group does not occur at position 10.

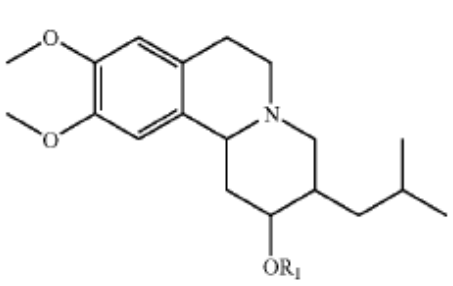
Significantly, for purposes of this Decision, we find, on this record, that tetrabenazine metabolism occurs by aliphatic hydroxylation of the isobutyl group at position 3, reduction of the carbonyl group at position 2, and demethylation at the methoxy group at position 9. Ex. 1008, 650 (Figure). This finding is consistent with disclosures in the written description of the '733 patent. Ex. 1001, 1:20–40 (citing Schwartz), 3:16–18 (referring to "discoveries made in our laboratory, as well as . . . the literature").

(3) Gano (Ex. 1007)

For purposes of this Decision, we accept Petitioner's assertion that Gano was before the Examiner during patent prosecution but never substantively discussed in any Office action. Pet. 51. Gano addresses tetrabenazine but does not discuss deuteration of any compound. *See generally* Ex. 1007.

Gano describes tetrabenazine as a drug "used for decades" as "a potent, reversible inhibitor of catecholamine uptake by vesicular monoamine transporter-2." Ex. 1007, 1:24–28. Similar to Zheng, Gano reports that "[s]ide effects associated with" tetrabenazine "include sedation, depression, akathisia, and parkinsonism." *Id*. at 1:32–33; *see* Ex. 1003, E683 (Zheng's similar disclosure). Gano identifies "a need for analogs of tetrabenazine that exhibit a longer half-life than tetrabenazine." *Id*. at 1:58–59.

Gano further states, "The compounds of this invention have the following structure (I):"



(I)

Ex. 1007, 3:2–15. Structure (I) illustrates an analog of tetrabenazine in which the carbonyl group at position 2 is replaced with an ester functional group. None of the structures illustrated in Gano indicates demethylation of either the position 9 or 10 methoxy group. *See generally id*. (all figures) (positions 2, 9, and 10 are relative to Zheng's Figure 1, *supra* 10).

Gano indicates that its solution for extending the half-life of tetrabenazine involves replacing the carbonyl group at position 2 with an ester functional group, which according to Gano, "may be particularly beneficial because it may allow an administration regimen that requires fewer doses per day than tetrabenazine." *Id*. at 7:64–66. In particular, "because of the unexpectedly longer duration of action afforded by these compounds, once daily dosing may be attainable." *Id*. at 8:3–5.

(4) Naicker (Ex. 1004)

Naicker was not before the Examiner during patent prosecution. Naicker relates to the deuteration of rapamycin, a pharmaceutical compound useful, for example, in "inducing immunosuppression" and treating "transplantation rejection." Ex. 1004, code (57) (Abstract). Naicker does not discuss tetrabenazine or any other benzoquinoline compound. *See generally* Ex. 1004. Petitioner advances Naicker's Figure 1 (annotated) as follows.

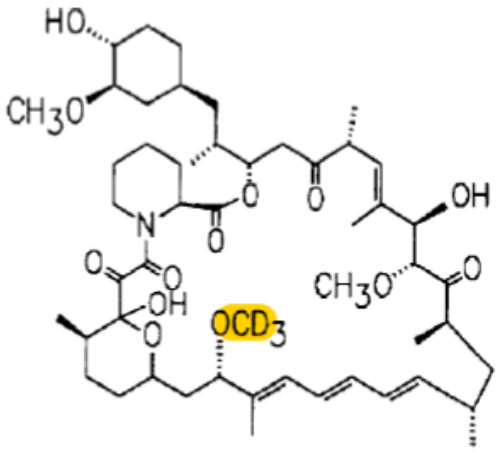


FIG. 1

Pet. 30 (reproducing Ex. 1004, Fig. 1). Figure 1 of Naicker illustrates the chemical structure of 7-deuteromethyl rapamycin. *Id*. at 4:39–40. Petitioner annotates Figure 1 to highlight the cite of deuteration taught by Naicker, which involves O-demethylation of one methoxy group.

Figure 1 shows that Naicker selects one of three methoxy groups of rapamycin for deuteration. *Id*. at Fig. 1. Naicker states, "Deuteration of the rapamycin molecule results in altered physicochemical and pharmacokinetic properties which enhance its usefulness in the treatment of transplantation rejection, host vs. graft disease, graft vs. host disease, leukemia/lymphoma, hyperproliferative vascular disorders, autoimmune diseases, diseases of inflammation, solid tumors, and fungal infections." *Id*. at 4:11–17.

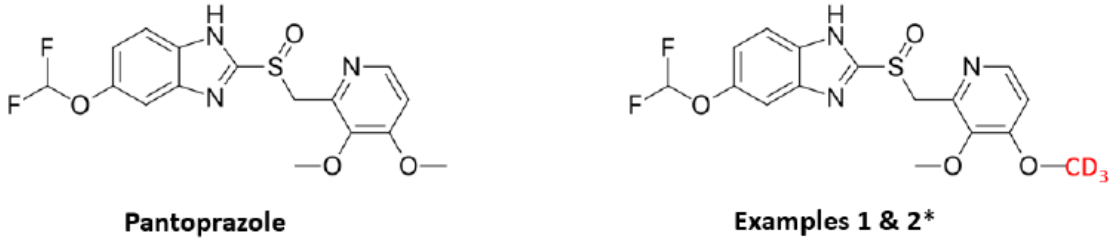
Rapamycin is metabolized "to at least six metabolites." *Id*. at 2:14–15. "In rapamycin, demethylation of methoxy group at C-7 Carbon will lead to the change in the conformation of the" molecule "due to the interaction of the released C-7 hydroxyl group with the neighbouring pyran ring system which is in equilibrium with the open form of the ring system." *Id*. at 2:19–24. "The C-7 hydroxyl group will also interact with the triene system and

possibly alter the immunosuppressive activity of rapamycin." *Id*. at 2:24–26. According to Naicker, "This accounts for the degradation of rapamycin molecule and its altered activity." *Id*. at 2:26–27. "Deuteration is targeted at various sites of the rapamycin molecule to increase the potency of [the] drug," among other benefits. *Id*. at 4:32–36.

(5) Kohl (Ex. 1005)

Kohl was not before the Examiner during patent prosecution. Kohl "relates to isotopically substituted proton pump inhibitors," such as pantoprazole, which "are of considerable importance in the therapy of disorders associated with an increased secretion of gastric acid." Ex. 1005, 1; *see* Pet. 55 (identifying pantoprazole as a compound of interest). We are directed to no information that Kohl mentions tetrabenazine or any other benzoquinoline compound. *See generally* Ex. 1005.

Petitioner advances Kohl for the proposition that the reference "provides additional motivation with its biological data demonstrating the benefits of deuterating at a methoxy group." Pet. 32. Specifically, Petitioner alleges that Kohl discloses the following examples of deuteration in pantoprazole:

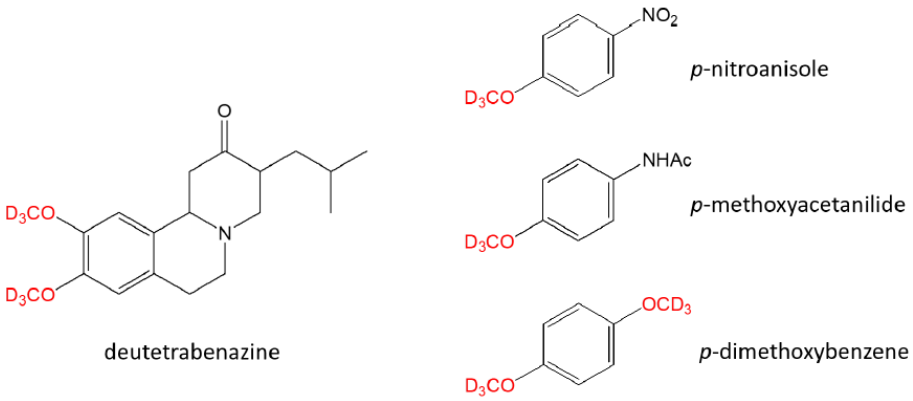


Pet. 32 (citing Ex. 1005, 13–14, 40). Petitioner's figure compares the structure of pantoprazole (on the left) to the structure of two examples of deuterated analogs of pantoprazole (on the right) where the examples "are

identical except for the stereochemistry (not shown)." *Id*. (citing Ex. 1002 ¶ 81). Petitioner annotates the examples to highlight (in red) that one of two adjacent methoxy groups is deuterated. *Id*.

(6) Foster AB (Ex. 1006)

Foster AB was not before the Examiner during patent prosecution. Foster AB is an article that relates to methoxy-deuteration of *p*-nitroanisole, *p*-methoxyacetanilide, and *p*-dimethoxybenzene, and respective trideutero-methyl derivatives. Ex. 1006, 327. Petitioner generates a comparison illustration pertaining to Foster AB, which we reproduce below.



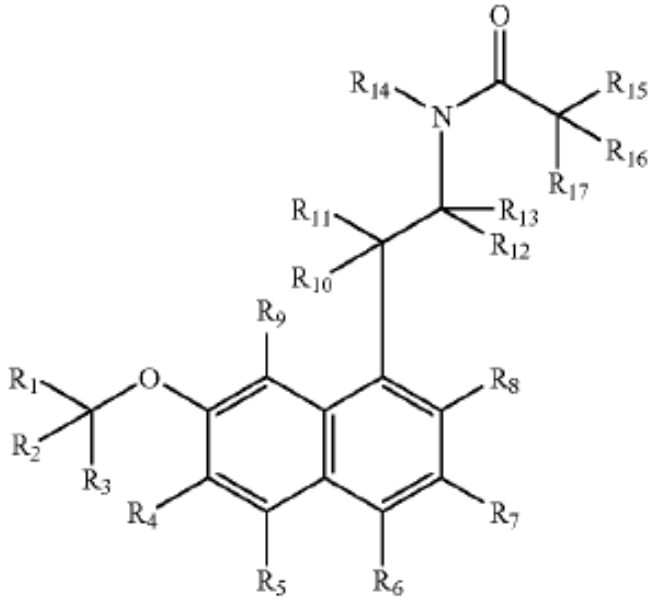
Pet. 44 (citing Ex. 1002 ¶ 99). The above illustration shows the structure of the deutetrabenazine compound specified in the challenged claims (on the left) and Petitioner's renditions of structures of deuterated compounds allegedly disclosed in Foster AB (on the right). Petitioner highlights (in red) that every methoxy group of each compound is fully deuterated.

Foster AB does not discuss tetrabenazine or any other benzoquinoline compound. *See generally* Ex. 1006.

(7) Gant (Ex. 1009)

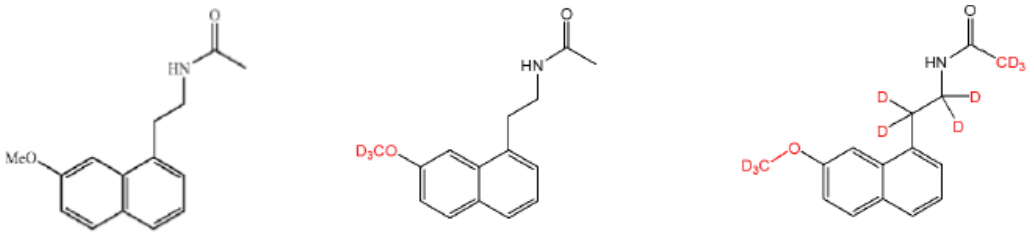
Gant was not before the Examiner during patent prosecution. Gant discloses deuteration patterns for agomelatine and discloses a broad range of deuteration patterns at every position of the molecule, reproduced below.

Formula I



Ex. 1009, code (57), ¶¶ 3–5. The above illustration shows the structure of Gant's Formula I, which includes fifteen hydrogen atoms at positions R1 through R15. Gant discloses deuteration of one, all, or any combination of hydrogen positions R1 through R15. *See id.* ¶¶ 6–7, 93–95, 97, 100, 246, 289, 292, 315, 318, 325, 328, 335; *see especially id.* ¶¶ 338, 346 (illustrating and claiming a broad spectrum of deuteration patterns). Only some include deuteration of the positions R1–R3 of the methoxy group. *Id.* ¶¶ 338, 346.

From the broad spectrum of deuteration patterns disclosed in Gant (*see id.*), Petitioner selects two as illustrating that Gant "discloses deuteration of a methoxy group." Pet. 55. Petitioner acknowledges, however, that Gant subjects "other positions" to deuteration. *Id.* Petitioner generates a comparison illustration pertaining to Gant, which we reproduce below.



Agomelatine | **Example 4** (deuterated methoxy group) | **Example 9** (deuterated methoxy and other aliphatic positions)

Pet. 55 (citing Ex. 1002 ¶ 118). The above illustration shows the structure of agomelatine (on the left), the structure of Gant's Example 4 compound (in center), and the structure of Gant's Example 9 compound (on the right). Petitioner labels Example 4 as "deuterated methoxy group" and Example 9 as "deuterated methoxy and other aliphatic positions." Petitioner highlights (in red) the sole methoxy group, which is deuterated, in Gant's Example 4 compound (that is, deuteration occurs at positions R1–R3 in Formula I) and further highlights (in red) seven additional positions that are deuterated in Gant's Example 9 (that is, positions R1–R3 of the methoxy group as well as positions R10–13 and R15–R17 in Formula 1).

Gant discloses, illustrates, and claims a broad spectrum of deuteration patterns for agomelatine in which the sole methoxy group sometimes, but not always, is deuterated. *Id.* ¶¶ 4–7, 338, 346. Gant also sometimes, but not always, deuterates every other hydrogen position in the molecule. *Id.*

Gant does not discuss tetrabenazine or any other benzoquinoline compound. *See generally* Ex. 1009.

B. Overview of the Prosecution History

Zheng and Schwartz were a focus of examination and are central to Petitioner's challenges. Pet. 26, 51; Ex. 1027, 9, 11–14, 51. Gano was cited

to the Examiner but not discussed substantively in any Office action. Pet. 51. The examination, however, focused on a textbook identified by both parties in this proceeding as "Foster 1985." Prelim. Resp. 20 (citing Ex. 2001[11]); Reply 2; *see* Ex. 1027, 8, 19, 21, 51–53 (applying Foster 1985).

Foster 1985 contains a section devoted to known benefits and disadvantages of deuteration of methoxy groups in drugs. Ex. 2001, 1, 19–21. That section of Foster 1985, which undeniably was presented to the Examiner, cites both Foster AB and Mitoma[12], which Petitioner advances in this proceeding as allegedly new references that would have provided information about the deuteration of methoxy groups in unrelated drug classes sufficient to change the trajectory of the examination. Ex. 2001, 19; *see, e.g.*, Pet. 4 (reproducing figures from both references).

The prosecution history demonstrates that the Examiner possessed a firm understanding of the known technical principles bearing on the deuteration of methoxy groups in unrelated classes of drugs. The Examiner twice rejected the challenged claims as obvious, citing, for example, Zheng, Schwartz, and Foster 1985, based on the argument that deuteration of the methoxy groups of tetrabenazine would have been known to slow down metabolism of the molecule, reduce its side effects, and improve its activity. Ex. 1027, 9–14, 51–54.

---

[11] Foster, A., *Deuterium Isotope Effects in the Metabolism of Drug and Xenobiotics: Implication for Drug Design*, ADVANCES IN DRUG RESEARCH vol. 14 (1985).

[12] Mitoma, C. et al., *Effect of deuteration of the O-CH3 group on the enzymic demethylation of o-nitroanisole*, BIOCHEM. BIOPHYS. ACTA, 136:556–567 (1967) (Ex. 1012).

In an initial Office action, the Examiner observed, "[D]euteration of drugs is a well known technique to obtain enhanced pharmaceutical properties." *Id*. at 10. The Examiner also observed that the known metabolic pathways of tetrabenazine involve rapid and extensive reduction of the carbonyl group (citing Zheng) and "O-demethylation of the methoxy groups, as well as hydroxylation of the isobutyl group" (citing Schwartz). *Id*. at 11. Given that Zheng and Schwartz "teach that the methoxy group is in the metabolite," the Examiner reasoned, an ordinarily skilled artisan would have been prompted "to replace specific H's with deuterium to see if it had any effect on toxicity, lipophilic effect or in general" would "improve or change the activity of the compound." *Id*. at 12–13. The Examiner further emphasized, "Many references teach deuteration of known pharmaceutical drugs." *Id*. at 13. "In the absence of a showing of unexpected results," the Examiner reasoned, "it cannot be seen how the claims can be patentable." *Id*.

Patent Owner responded to this Office action by participating in a first interview with the Examiner and submitting a First Declaration of Dr. Margaret Bradbury, indicating that "one of skill in the art would not be able to predict whether deuteration at any particular site in a molecule would cause a net increase in metabolic stability of that molecule." *Id*. at 20. Dr. Bradbury explained why "the effect of deuterium substitution on the *in vitro* or the *in vivo* stability of compounds cannot be reasonably predicted based on the structure of the compound, the site at which deuterium is installed, or prior knowledge of the metabolic pathways of the compound." *Id*. at 21 (quoting *id*. at 30–31 (First Bradbury Declaration ¶ 6)).

Dr. Bradbury supported her opinions with experimental results that included data from a randomized, double blind Phase I clinical study in

human subjects, which compared the effects of the claimed d_6-deutetrabenazine compound to a non-deuterated dosage form of tetrabenazine. Ex. 1027, 33–48. Patent Owner argued to the Examiner that the teachings "of Zheng and Schwartz that tetrabenazine is metabolized at the O-methyl groups does not support a conclusion that deuteration of those specific positions would be expected by [a] skilled artisan to result in a compound with increased overall metabolic stability." *Id*. at 22. Patent Owner also pointed out that Foster 1985 "describes the phenomenon of metabolic switching, which compensates for a reduced rate of metabolism at one site in a molecule by increasing the rate of metabolism at a different site," which "typically results in no significant net effect on the overall metabolism of a compound." *Id*. (citing Ex. 2001, 6–8). Patent Owner argued, "[T]he prior art examples relating to the deuterium isotope effect on metabolic stability show mixed and unpredictable results." *Id*. at 24.

By way of support, Patent Owner quoted Foster 1985, which states, "It is now becoming clear that the scope for using" deuterium isotope effects "effectively in drug design to block adverse metabolism or to deflect metabolism away from toxic products (metabolic switching) is very limited." Ex. 2001, 35; Ex. 1027, 19, 21 (Patent Owner, twice quoting this portion of Foster 1985). In some studies, "a deuterium isotope effect (DIE) was observed at the site of metabolism near the deuterium substitution," Patent Owner argued, but "[t]he fact that a DIE is observed in a compound cannot be extrapolated to a conclusion that the deuterated version of the compound will demonstrate increased net stability." *Id*. at 19. "This is due in large part to the phenomenon of metabolic switching." *Id*. (citing Foster 1985 (Ex. 2001, 6–8)).

The Examiner acknowledged that Foster 1985 teaches "several different pathways and switching of the pathway[s]," but nonetheless determined that "this does not take away from the teaching that deuterated drugs would have a retarded metabolic reaction" as compared to the non-deuterated drug. Ex. 1027, 53. Thus, the Examiner reasoned, "The motivation to try is clearly presented in" Foster 1985. *Id*. On that basis, the Examiner finally rejected the claims. *Id*. at 54.

Patent Owner thereafter participated in a second interview with the Examiner (*id*. at 67) and submitted a Second Declaration of Dr. Bradbury (*id*. at 63–71) directed to "(1) increases in half-life and AUC [area under curve] for the claimed compound as compared to tetrabenazine, with small changes in C_{mzx} and T_{max}; and (2) additional clinical data showing reduced adverse effects" (*id*. at 60). Significantly, Patent Owner highlighted for the Examiner that the clinical trial data advanced in the First Bradbury Declaration compared a 15mg extended release dosage form of the claimed compound with a 25mg immediate release dosage form of tetrabenazine. *Id*. at 61. Patent Owner asserts, without contest from Petitioner, that "[t]he Examiner initiated an interview to discuss this precise topic of reconciling the differences in dosages between deutetrabenazine and tetrabenazine" in the data presented by Dr. Bradbury. Prelim. Resp. 31 (citing Ex. 1027, 124 (record of second interview); *see generally* Reply (not contesting that assertion).

Patent Owner's assertion is supported by the prosecution history, which indicates that this second interview was focused on explaining why the clinical study data introduced with the First Bradbury Declaration was credible and persuasive, notwithstanding the differences in doses and dosage

forms. On that point, the information submitted by Dr. Bradbury persuaded the Examiner that, "because the AUC and CMax was higher" for the claimed compound as compared to tetrabenazine, the clinical study data showed that "a lower" dose of d_6-deutetrabenazine "gave the same effect" as the non-deuterated dosage form and the side effect "of sleepiness was reduced as was dizziness, not to the same extent but nevertheless was reduced." Ex. 1027, 124; *see id*. at 64–70 (Second Bradbury Declaration ¶ 4).

The Examiner subsequently withdrew the rejection and allowed the claims to issue. *Id*. at 125–126, 130.

C. Overview of Applicable Caselaw

Patent Owner requests that we exercise our discretion and deny institution of review under Section 325(d). Prelim. Resp. 15–34.[13] We resolve Patent Owner's request under a two-part framework. First, we assess whether the Examiner considered the same or substantially the same prior art or arguments asserted in the Petition and, if so, we resolve whether Petitioner shows sufficiently that the Examiner erred in a manner material to the patentability of the challenged claims. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

In applying the two-part framework articulated in *Advanced Bionics*, we consider several non-exclusive factors, including:

(a) the similarities and material differences between the asserted art and the prior art involved during examination;

[13] We need not, and do not, reach Patent Owner's additional request, embedded within its arguments pertaining to Section 325(d), that we deny review under 35 U.S.C. § 314(a) based on Petitioner's alleged attempt "to extort Patent Owner with a meritless challenge." Prelim. Resp. 33.

(b) the cumulative nature of the asserted art and the prior art evaluated during examination;

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;

(e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) ("*Becton, Dickinson*").

Becton, Dickinson factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 10. Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of the prior art or arguments. *Id.* In general, only if the same, or substantially the same, art or arguments previously were presented to the Office, do we turn to whether Petitioner has established a material error. *Id.* "At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9.

D. Same or Substantially the Same Prior Art

The grounds of unpatentability set forth in the Petition rely on Zheng, Schwartz, Gano, Naicker, Kohl, Foster AB, and Gant. *See* Pet. 7 (grounds

chart). We assess below whether those references are the same as, or cumulative to, references presented to the Examiner during prosecution.

(1) Zheng, Schwartz, and Gano

Petitioner admits that Zheng[14] and Schwartz were "cited during prosecution and considered by the Examiner." Pet. 26, 51, 61. In fact, these references were a focus of examination. Ex. 1027, 9–14, 51–54.

Petitioner acknowledges that Gano also "was cited during prosecution," but argues, Gano was "***not substantively considered by the Examiner***." Pet. 51 (Petitioner's emphasis). A reference submitted, but not substantively discussed during prosecution, nonetheless qualifies as prior art previously presented to the Office. As the precedential decision in *Advanced Bionics* makes clear, "Previously presented art includes art made of record by the Examiner, and art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent." *Advanced Bionics*, Paper 6 at 7–8.

In any event, we agree with Patent Owner that Petitioner relies on Gano for information similar to that disclosed in other references that were a focus of examination. Prelim. Resp. 17 (citing Pet. 61). For example, Petitioner advances Gano to show "that tetrabenazine 'is currently used in the treatment of various hyperkinetic movement disorders' but 'had a number of drawbacks,' related to its side effects and half-life.'" *Id*. (quoting

[14] References to "Zhang" and "Zang" in the prosecution history refer to Zheng (Ex. 1003) and references to "Swartz" refer to Schwartz (Ex. 1008). Prelim. Resp. 17 n.5; *see, e.g.*, Ex. 1027, 12 ("Zang and Swartz teach that the methoxy group is in the metabolite" of tetrabenazine).

Pet. 52). But as Patent Owner observes, "These disclosures all appear in Zheng." *Id*. (citing Ex. 1003, E683–E684).

On this record, we determine that Zheng, Schwartz, and Gano are the same or substantially the same as references previously presented to the Office during examination.

(2) Naicker, Kohl, Foster AB, and Gant

Petitioner's challenges raise four other references, which "all relate to the deuteration of non-tetrabenazine compounds." Prelim. Resp. 18; *see supra* 13–18 (overview of the disclosures, explaining that none pertains to deuteration of tetrabenazine). It is undisputed that Naicker, Kohl, Foster AB, and Gant were not before the Examiner. Petitioner and Patent Owner, however, dispute whether Naicker, Kohl, Foster AB, and Gant are cumulative of the references presented to the Examiner. Pet. 26, 42, 51–52.; Reply 1–4; Prelim. Resp. 18–22; Sur-reply 1–4.

The claims require a *specific* deuteration pattern in tetrabenazine, in which both of two adjacent methoxy groups—but no other hydrogen positions—are deuterated. Ex. 1001, 50:41–64. The claims specifically exclude deuteration patterns in which the carbonyl group, the aliphatic isobutyl group, or any aromatic hydrogen position is deuterated. *Id*.

As an initial matter, we find unpersuasive Petitioner's assertion that the Examiner did not "substantively" consider "***any*** reference disclosing the benefits of deuteration at methoxy groups." Pet. 40–41, 50 (Petitioner's emphasis). To the contrary, the Examiner was presented with and considered Foster 1985, a textbook that contains "an entire section" on the benefits and drawbacks of deuteration of methoxy groups in drugs. Prelim. Resp. 20

(citing Ex. 2001, 19–21); *see* Ex. 1027, 9, 19, 21, 51–53 (prosecution history). Indeed, Foster 1985 was a focus of examination. *Id.*

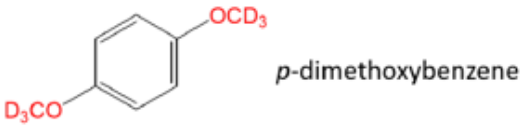
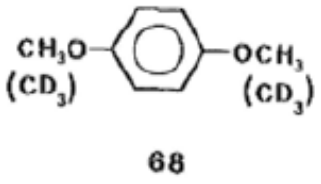
In the Reply, Petitioner shifts position, arguing the Examiner must have "overlooked that disclosure" in Foster 1985, because the section that discusses deuteration of methoxy groups was not specifically cited in any Office action. Reply 2. Under the specific circumstances at hand, we reject that assertion. The Examiner focused extensively on Foster 1985 (Ex. 1027, 9, 19, 21, 51–53) and initialed the reference to indicate that the substance of its disclosure was "considered" (Ex. 2025, 5, 11). Standing alone, those facts support a finding that the Examiner fully considered Foster 1985's disclosure. Prelim. Resp. 1 (and cases cited therein).

Foster 1985 discusses "metabolic switching" in metabolites of methoxy compounds and informs that this phenomenon introduces a level of unpredictability that makes deuteration a "very limited" tool. Ex. 2001, 20, 35. The Examiner demonstrated an awareness that metabolic switching affects the metabolites of methoxy groups, and remarked that "switching of the pathway" affects metabolites of the methoxy groups of tetrabenazine in particular. Ex. 1027, 53. Those remarks from the Examiner further bolster a finding that the Examiner was aware of, and considered, the information in the section of Foster 1985 that discusses deuteration of methoxy groups.

Of the assertedly new references, only Foster AB even arguably discloses a deuteration pattern resembling the claimed deuteration pattern, which involves deuteration of both methoxy groups but no other hydrogen positions. Pet. 44 (citing Ex. 1002 ¶ 99). The disclosure of Foster AB, however, is essentially identical in all material respects to the disclosure of Foster 1985, which was before the Examiner. That is unsurprising, because

as Patent Owner observes, Foster 1985 (which was before the Examiner) cites and discusses the study reported in Foster AB (Petitioner's allegedly new reference). Prelim. Resp. 20; Ex. 2001, 19.

Neither reference, however, relates to tetrabenazine or any compound in its class, and neither discloses deuteration of two adjacent methoxy groups as required by the challenged claims. The following illustration compares the disclosures of Foster AB and Foster 1985.

Pet. 44; Ex. 2001, 19. The above comparison illustration shows, on the left, Petitioner's rendition of the structure of p-dimethoxybenzene as disclosed in Foster AB. Pet. 44. The illustration shows, on the right, the structure of p-dimethoxybenzene as disclosed in Foster 1985. Ex. 2001, 19. Both show a pattern of deuteration in which two non-adjacent methoxy groups, but no other hydrogen positions, are deuterated. *Cf.* Ex. 1001, 50:41–64 (claims).

The above comparison illustration shows that Foster AB suggests the claimed invention with no greater clarity than Foster 1985, which was before the Examiner. Ex. 1001, 50:41–64 (challenged claims, specifying deuteration of the two adjacent methoxy groups of tetrabenazine, but no other hydrogen position). Foster AB and Foster 1985 both discuss benefits and drawbacks of deuteration at methoxy groups in non-tetrabenazine compounds. Ex. 1006, 327–339 (Foster AB); Ex. 2001, 19–22 (Foster 1985).

Petitioner's own information persuades us that none of the other assertedly new references—Naicker, Kohl, and Gant—suggests the specific pattern of deuteration, required by the claims, with any greater clarity than Foster 1985. Pet. 28–34, 43–46, 54–57. Naicker deuterates one of three methoxy groups in rapamycin, where none is adjacent to another. Pet. 30 (citing Ex. 1004, 1). Kohl deuterates one, but not both, of two adjacent methoxy groups in pantoprazole. Pet. 32 (citing Ex. 1005, 13–14, 40). Gant discloses a spectrum of deuteration patterns in agomelatine, in which a single methoxy group sometimes, but not always, is deuterated, a carbonyl group sometimes, but not always, is deuterated, and none, all, or any combination of aliphatic and aromatic hydrogen positions is deuterated. Pet. 55; *see* Ex. 1009, code (57), ¶¶ 5, 338, 346 (disclosures in Gant).

For the above reasons, we find that Naicker, Foster AB, Kohl, and Gant are cumulative of Foster 1985, which was presented previously to the Office. Standing alone, that determination, along with the fact that Zheng, Schwartz, and Gano were previously presented during prosecution, warrants our assessment of the second part of the two-part framework articulated in *Advanced Bionics*, namely, whether Petitioner directs us to evidence sufficient to demonstrate a material Examiner error. *See Advanced Bionics*, Paper 6 at 8.

Before turning to that question, however, we address whether, and to what extent, Petitioner raises arguments that are the same or substantially the same as arguments previously presented to the Office. Our assessment of that issue provides an alternative rationale that independently warrants our consideration of the adequacy of Petitioner's information pertaining to material Examiner error. *See* Prelim. Resp. 15 (Patent Owner, arguing that

both the prior art *and* the arguments presented in the Petition are substantially the same as those presented to the Examiner).

E. Same or Substantially the Same Arguments

Patent Owner contends that the arguments raised in the Petition overlap with arguments made during prosecution. *See* Prelim. Resp. 22–24 (identification of overlapping arguments). When assessing a request for denial under Section 325(d), the Board focuses on "the extent of the overlap between" arguments made during examination and those presented in a petition for review. *Advanced Bionics*, Paper 6 at 9 n.10.

We take note of Petitioner's argument that Naicker, Foster AB, Kohl, and Gant "were ***not*** before the Examiner, and ***no*** arguments were made regarding those teachings." Reply 1 (Petitioner's emphasis). We further take account of Petitioner's view that "there is no evidence that" the Examiner "analyzed" the portion of Foster 1985 that cites and reviews the content of the study in Foster AB, which Petitioner advances in the patentability challenges. *Id*. at 2. Even if we accept that some of the arguments raised in the Petition concerning Naicker, Foster AB, Kohl, and Gant are new, however, the degree of overlap between the arguments raised in the Petition, and those considered by the Examiner, is significant.

Petitioner argues, "Zheng's disclosure regarding tetrabenazine's benefits and drawbacks would have motivated" an ordinarily skilled artisan "to select tetrabenazine as a compound to improve." Pet. 26–27. As Patent Owner points out, "The Examiner relied on Zheng and other references for exactly" that point. Prelim. Resp. 22 (citing Ex. 1027, 11–12).

Petitioner argues that Schwartz teaches that the methoxy groups of tetrabenazine were sites of metabolism. Pet. 10–11, 53. The Examiner

expressly relied on Schwartz, however, to find that the "metabolic pathways" of tetrabenazine "involve O-demethylation of the methoxy groups." Ex. 1027, 11; *see id*. at 13 (the Examiner, specifically arguing, and accepting, that Zheng and Schwartz "both show that" tetrabenazine is metabolized at "the methoxy group").

Petitioner argues that an ordinarily skilled artisan would have been prompted to "slow the O-demethylation metabolic pathways" of tetrabenazine through deuteration and, thereby, "reduce" its "side effects." Pet. 32–33, 60. The Examiner considered that same argument, finding "that deuterated compounds" were known to lower "some side effects," increase "bioavailability," and increase "the time of activity as it stays longer in the system." Ex. 1027, 12.

Petitioner argues that "[t]he deuteration path to therapeutic improvement was so well-trodden by the priority date that it had a 'paint by numbers' character." Pet. 2. That argument is substantially the same argument regarding the predictability of deuteration that was considered extensively by the Examiner. Ex. 1027, 9–14, 17–23, 26–32, 51–54, 57, 60–71, 124–127; *see id*. at 24 (Patent Owner, arguing that "the prior art examples relating to the deuterium isotope effect on metabolic stability show mixed and unpredictable results"). Petitioner addresses the question of the substantial similarity of these arguments inadequately, if at all, except to argue that the Examiner erred by resolving those arguments in favor of Patent Owner. *See generally*, Reply.

For these reasons, we find Petitioner raises the same or substantially the same arguments previously presented to the Office. That finding

provides an independent, alternative basis that warrants our consideration of the sufficiency of Petitioner's showing as to Examiner error.

F. Petitioner's Showing as to Examiner Error

Petitioner alleges that the Examiner made three material errors. First, Petitioner argues that the Examiner materially erred by failing to consider "***any*** reference disclosing the benefits of deuteration at methoxy groups like" Naicker, Foster AB, Kohl, or Gant. Pet. 40, 50, 61 (Petitioner's emphasis). As Patent Owner points out, however, that proposition is not supported on this record, given that Foster 1985 was "discussed extensively in prosecution" (Sur-Reply 1) and "includes an *entire section* discussing deuteration of methoxy groups" (Prelim. Resp. 20).

Against that backdrop, Petitioner shifts position in the Reply, arguing the Examiner must have "overlooked" the disclosure in Foster 1985 that is devoted to methoxy groups. Reply 2. For reasons discussed above, we reject that proposition because Foster 1985 was a focus of examination (Ex. 1027, 9, 19, 21, 51–53), the Examiner initialed the reference to indicate that its disclosure was "considered" (Ex. 2025, 5, 11), and the Examiner displayed a firm understanding of the metabolic pathways of tetrabenazine, the implications of metabolic switching, and the known benefits and drawbacks of deuteration at methoxy groups. Ex. 1027, 9–14, 17–48, 51–54. In other words, on this record, we find the Examiner possessed a firm understanding of Foster 1985 and its relevant subject matter. Petitioner does not show a material Examiner error in connection with Foster 1985 or the Examiner's understanding of the art pertaining to deuteration of methoxy groups.

Second, Petitioner contends the Examiner materially erred by "inexplicably" changing position after the first Office action, suggesting the

Examiner had no rational basis for reversing position on whether the "well known" benefits of deuteration in other classes of pharmaceutical compounds would have made obvious the claimed deuteration pattern in tetrabenazine. Pet. 21–22. In that same Office action, however, the Examiner explained, "*In the absence of a showing of unexpected results* it cannot be seen how the claims can be patentable." Ex. 1027, 13 (emphasis added). Patent Owner thereafter submitted evidence of unexpected results, including *in vitro* and *in vivo* data accompanying the First Bradbury Declaration, in response to the Examiner's guidance. Ex. 1027, 17–32.

Petitioner correctly points out that the Examiner initially rejected Dr. Bradbury's *in vitro* and *in vivo* data as reflecting what would have been expected in the art. Pet. 21–22; Ex. 1027, 54. But in response to the Examiner's concerns in that regard, Patent Owner submitted the Second Bradbury Declaration and addressed the specific issues of concern during a telephone interview initiated by the Examiner. Ex. 1027, 60–71, 117, 124, 126. The Second Bradbury Declaration and the telephone interview resolved the Examiner's concerns that the clinical trial data compared a 15mg extended release dosage form of the claimed compound to a 25mg immediate release dosage form of tetrabenazine. *Id*. On this record, Petitioner does not show that the Examiner "inexplicably" changed position about the "***same***" clinical trial data submitted by Dr. Bradbury. Pet. 21–22 (Petitioner's emphasis).

Third, and somewhat relatedly, Petitioner argues that "the new data supporting reduced side effects presented by" Patent Owner in support of unexpected results "are legally erroneous." *Id*. at 22. Petitioner challenges the Examiner's reasons for changing position, but raises the exact same issue

about the perceived discrepancies in dose and dosage forms that were the subject of the Examiner's concerns, the Examiner-initiated interview, and the Second Bradbury Declaration. *Id*. at 22–23, 39–40; Ex. 1027, 60–71, 117, 124, 126.

Patent Owner provides the same reasonable explanation here, as it did before the Examiner, that "the 15mg dose of deutetrabenazine yielded the most similar metabolite AUC to the 25mg tetrabenazine tablet, and it nevertheless resulted in far smaller QTcF prolongations (0.36 vs. 7.26) and fewer incidents of somnolence (3 vs. 6) and dizziness (0 vs. 1)." Prelim. Resp. 32. Patent Owner also effectively counters Dr. Jones's opinion, which was not before the Examiner, that the extended release formulation could have impacted the side-effect profile by showing that "deutetrabenazine improved the QTcF prolongation interval *even at the highest dose* (22.5mg), which yielded an AUC *and* C_{max} that was higher than that of tetrabenazine." *Id.* citing (Ex. 1027, 67). Against that backdrop, we are of the view that Patent Owner casts significant doubt on Petitioner's proposition that the Examiner erred by crediting Patent Owner's evidence of unexpected results. *See* Ex. 1027, 126 (Examiner, crediting Second Bradbury Declaration, which explains discrepancies in dose and release forms); *see also id*. at 63–71 (Second Bradbury Declaration, addressing with clarity those discrepancies).

In essence, Petitioner, in the Petition, asks the Board to second guess the Examiner's consideration of the prior art and the Bradbury Declarations that were submitted during prosecution. That is, in order for Petitioner to prevail on its challenges in this proceeding, we would need to credit Petitioner's declarant Dr. Jones over the contrary statements of Dr. Bradbury regarding the issue of unexpected results associated with deuteration of

tetrabenazine. We are not persuaded, however, that the declaration and arguments submitted with the Petition demonstrate sufficiently that the Examiner committed a material error in evaluating the Bradbury Declarations or the prior art during prosecution.

We understand that Petitioner disagrees with the Examiner's treatment of the prior art and the Bradbury Declarations in resolving the issue of the dose and dosage form discrepancies during patent prosecution. But in the absence of any showing that the Examiner relied upon materially false or incomplete statements during prosecution, or otherwise failed to properly apply the standard for assessing unexpected results, we find Petitioner's information insufficient to support a finding of material Examiner error. *See* Reply 1–4. Petitioner bears the burden of showing that the Office erred, for example, by "misapprehending or overlooking specific teachings of the relevant prior art whose teachings impact patentability of the challenged claims." *Advanced Bionics*, Paper 6 at 8. Significantly, we apply the principle that, "[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments" by the Examiner, then "it cannot be said that the Office erred in a manner material to patentability." Prelim. Resp. 25 (quoting *Advanced Bionics*, Paper 6 at 9). This is a case where, even "[i]f reasonable minds can disagree," our "commitment to defer to previous Office evaluations of the evidence of record unless material error is shown" tips the scale in favor of exercising our discretion to deny review under Section 325(d). *Advanced Bionics*, Paper 6 at 9.

IV. CONCLUSION

Taking a holistic view of the totality of the information presented, we determine that the challenges set forth in the Petition are based on the same

or substantially the same prior art or arguments previously presented to the Examiner. Moreover, Petitioner does not direct us to information sufficient to establish a material Examiner error. Accordingly, we exercise our discretion under Section 325(d) and do not institute an *inter partes* review.

V. ORDER

It is

ORDERED that the Petition is *denied* and no *inter partes* review is instituted.

For PETITIONER:

Vishal Gupta
John J. Molenda
Jordan P. Markham
STEPTOE & JOHNSON LLP
vgupta@steptoe.com
jmolenda@steptoe.com
jmarkham@steptoe.com

For PATENT OWNER:

David Berl
Thomas Fletcher
Shaun Mahaffy
WILLIAMS & CONNOLLY LLP
dberl@wc.com
tfletcher@wc.com
smahaffy@wc.com