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Paper No. 45
Entered: July 19, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.
and MYLAN LABORATORIES LIMITED,
Petitioner,

v.

UCB PHARMA GMBH,
Patent Owner.

Case IPR2016-00510[1]
Patent 6,858,650 B1

Before KRISTINA M. KALAN, ROBERT A. POLLOCK, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges*.

ANKENBRAND, *Administrative Patent Judge.*

FINAL WRITTEN DECISION

Finding Claims 1–5 and 21–24 Not Unpatentable
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Dismissing as Moot Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Granting Joint Motion to Seal and Entering Default Protective Order
37 C.F.R. § 42.54

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[1] Petitioners Alembic Pharmaceuticals Limited from IPR2016-01596, Torrent Pharmaceuticals Limited from IPR2016-01636, and Amerigen Pharmaceuticals Limited from IPR2016-01665 have been joined as Petitioners to this proceeding.

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–5 and 21–24 (collectively, "the challenged claims") of U.S. Patent No. 6,858,650 B1 (Ex. 1001, "the '650 patent"). We have jurisdiction under 35 U.S.C. § 6. For the reasons that follow, we determine that Petitioner does not demonstrate, by a preponderance of the evidence, that claims 1–5 and 21–24 are unpatentable.

A. Procedural History

Mylan Pharmaceuticals Inc. and Mylan Laboratories Limited ("Mylan") filed a Corrected Petition (Paper 5, "Pet.") requesting an *inter partes* review pursuant to 35 U.S.C. § 311.[2] On July 20, 2016, we instituted trial to determine (1) whether claims 1–5 and 21–24 are unpatentable under 35 U.S.C. § 103(a) over the combination of Postlind,[3] "Bundgaard

[2] In support of the Corrected Petition, Petitioner filed the declaration of its technical expert, Steven E. Patterson, Ph.D. (Ex. 1003), and the declaration of DeForest McDuff, Ph.D. (Ex. 1033) with respect to lack of commercial success.

[3] Postlind et al., *Tolterodine, A New Muscarinic Receptor Antagonist, is Metabolized by Cytochromes P450 2D6 and 3A in Human Liver Microsomes*, 26(4) DRUG METABOLISM & DISPOSITION 289–293 (1998) (Ex. 1010).

publications,"[4,5,6] Detrol Label,[7] and Berge;[8] and (2) whether claims 1–5 and 21–24 are unpatentable under 35 U.S.C. § 103(a) over the combination of Brynne,[9] Bundgaard publications, and Johansson.[10] Paper 12 ("Institution Decision" or "Inst. Dec.").

After the Institution Decision, Alembic Pharmaceuticals Limited ("Alembic"), Torrent Pharmaceuticals Limited ("Torrent"), and Amerigen Pharmaceuticals Limited ("Amerigen") were each joined as petitioners to the proceeding. *See* Case IPR2016-01596, Paper 8; Case IPR2016-01636, Paper 10; Case IPR2016-01665, Paper 8. Accordingly, we refer to Mylan, Alembic, Torrent, and Amerigen collectively as "Petitioner."

During trial, UCB Pharma GmbH ("Patent Owner") filed a Response (Paper 20, "Resp."),[11] and Petitioner filed a Corrected Reply (Paper 28, "Reply"). Patent Owner filed a Motion to Exclude, which is fully briefed.

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[4] In the Institution Decision, we interpreted Petitioner's reference to "Bundgaard publications" as referring to Exhibits 1012 and 1020. Inst. Dec. 5 n.3. We discuss those Exhibits individually in our analysis herein, and also reference the Bundgaard publications collectively.
[5] Bundgaard, Design of Prodrugs, Elsevier (1985) (Ex. 1012, "Bundgaard").
[6] WO 92/08459, published May 29, 1992 (Ex. 1020, "Bundgaard PCT").
[7] Detrol™ (tolterodine tartrate tablets) prescribing information (1998) (Ex. 1009).
[8] Berge et al., *Pharmaceutical Salts*, 66(1) J. PHARM. SCI. 1–19 (1977) (Ex. 1013).
[9] Brynne et al., *Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine*, 63(5) CLIN. PHARMACOL. & THERAPEUTICS 529–539 (1998) (Ex. 1011).
[10] WO 94/11337, published May 26, 1994 (Ex. 1005).
[11] With the Response, Patent Owner filed the declarations of Hans Maag, Sc.D. (Ex. 2021), William R. Roush, Ph.D. (Ex. 2022), Scott A. MacDiarmid, M.D., FRCPSC (Ex. 2023), Leonard J. Chyall, Ph.D. (Ex. 2024), and Claus O. Meese, Ph.D. (Ex. 2025).

Paper 37 (Motion); Paper 39 (Response); Paper 40 (Reply). The parties also filed a Joint Motion to Seal and for Entry of a Protective Order. Paper 34. The record further includes a transcript of the final oral hearing conducted on April 5, 2017. Paper 43 ("Tr.").

B. Related Proceedings

Patent Owner asserts that

> [Patent Owner] and Pfizer Inc. ("Pfizer"), the exclusive licensee of the '650 patent, have sued Mylan Pharmaceuticals Inc. for infringement of the '650 patent in the following actions: *Pfizer, Inc. and UCB Pharma GMBH v. Mylan Pharmaceuticals, Inc.*, No. 1:15-cv-00079-GMS (D. Del.) and *Pfizer Inc. and UCB Pharma GMBH v. Mylan Pharmaceuticals Inc*., Case No. 1:15-cv-00013-IMK (N.D.W.Va.).

Paper 7, 2; *see* Pet. 1–2 (noting that Pfizer is the NDA filer).

The '650 patent also is asserted in *Pfizer, Inc. v. Sandoz, Inc.*, No. 1:13-cv-01110-GMS (D. Del.),[12] and was asserted in the now-dismissed action, *Pfizer, Inc. v. Dr. Reddy's Laboratories, Ltd.*, No. 1:15-cv-01067-GMS (D. Del.). Paper 7, 2.

In addition to the case before us, we instituted an *inter partes* review in the following matters involving patents generally directed to 3,3-diphenylpropylamine compounds: Case IPR2016-00512 (U.S. Patent No. 7,384,980 B2) ("the '980 patent"); Case IPR2016-00514 (U.S. Patent

[12] Patent Owner provides, as Exhibit 2001, the District Court's Memorandum finding that the defendants in that proceeding "failed to present a prima facie case that the asserted claims of the patents-in-suit are invalid as obvious." Ex. 2001, 19. The district court reached that determination on a different record and applied different standards, but the arguments and references applied overlap with those before us. *See* Ex. 2001. Accordingly, although we are not bound by those findings, we find the district court's analysis informative.

No. 7,855,230 B2); Case IPR2016-00516 (U.S. Patent No. 8,338,478 B2), and Case IPR2016-00517 (U.S. Patent No. 7,985,772 B2).

Patent Owner updated its mandatory notices on February 16, 2017, to reflect that Case No. 1:15-cv-00079-GMS concluded with a general verdict in favor of Plaintiffs, and that Patent Owner and Pfizer filed suit against Torrent and Torrent Pharma Incorporated for infringement of the '650 patent, as well as the patents challenged in Case IPR2016-00512, Case IPR2016-00514, Case IPR2016-00516, and Case IPR2016-00517. Paper 33, 2. That action is captioned *Pfizer, Inc. v. Torrent Pharm. Ltd.*, No. 1:17-cv-00112-GMS (D. Del.). *Id.*

C. The '650 Patent

The '650 patent, titled "Stable Salts of Novel Derivatives of 3,3-diphenylpropylamines," issued on February 22, 2005. Ex. 1001. The '650 patent generally is directed to "highly pure, crystalline stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for the[ir] manufacture[,] and highly pure, stable intermediate products." *Id.* at Abstract, 1:10–14.

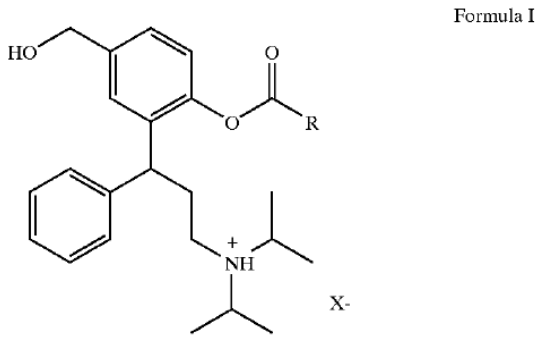
The specification discloses that the compounds "are valuable prodrug[s] for the treatment of urinary incontinence and other spasmodic complaints" that "overcome the disadvantage[s] of the active substances available to date." *Id.* at 1:17–20. Those disadvantages include "inadequate absorption of the active substance by biological membranes or the unfavoura[b]le metabolism of [the active substance]." *Id.* at 1:20–22. According to the specification, the compounds also "have improved pharmacokinetic characteristics compared with Oxybutynin and

Tolterodin[e]," two muscarinic receptor antagonists used to treat patients with overactive bladder. *Id.* at 1:23–25; Ex. 1009, 2; Ex. 1014, 528.

D. Illustrative Claim

Of the challenged claims, claim 1 is independent and recites:

1. Compounds of general formula I



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

Id. at 23:15–32.

Claims 2 and 3 narrow claim 1 by specifying that X^- is an acid ester chosen from an enumerated list of acids, including hydrochloric acid and fumaric acid, and requiring that the compounds have specific chirality (i.e., the (R) enantiomer), respectively. *Id.* at 23:33–65. Claims 4 and 5 depend from claim 3 and, therefore, inherit the chirality limitation of claim 3. Like claim 2, claim 4 specifies that X^- is an acid ester chosen from an enumerated list of acids, including hydrochloric acid and fumaric acid. *Id.* at 23:66–24:13. Claim 5 further narrows the compounds to the fumarate or hydrochloride salts. *Id.* at 24:14–19. Claims 21–23 recite methods of treating urinary incontinence disorder using the compounds of claims 1, 3, and 5, respectively. *Id.* at 30:30–41. Claim 24 recites the method of any one

of claims 21–23 and limits the urinary incontinence disorder to urge incontinence. *Id.* at 30:42–43.

The compositions of claims 1–5 encompass fesoterodine fumarate (R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate)) distributed by Pfizer Labs under the brand Toviaz. *See* Pet. 5; Ex. 1024, 8, 19.

II. DISCUSSION

Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). Below, we explain why Petitioner has not met its burden with respect to the challenged claims.

A. Level of Ordinary Skill in the Art

We begin our analysis by addressing the level of ordinary skill in the art. For the purpose of this decision, we accept Petitioner's undisputed contention that:

> [a] person of ordinary skill in the art would have a Ph.D. in chemistry, medicinal chemistry, pharmacology, or a related field, and at least one year of industrial exposure to drug discovery, drug design, and synthesis. In lieu of an advanced degree, the individual may have additional years of industry experience, including, for example, in drug discovery, drug synthesis, and structure-activity work.

Pet. 6 (citing Ex. 1003 ¶ 23); *see* Resp. 6.

Based on our review of the '650 patent, the types of problems and solutions described in the '650 patent and cited prior art, we adopt

Petitioner's definition of a person of ordinary skill in the art at the time of the claimed invention. We note that the applied prior art also reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

B. Claim Construction

The Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S.Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard); 37 C.F.R. § 42.100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only those terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

Petitioner submits that the "claims in the '650 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language." Pet. 6. Patent Owner "does not dispute Petitioner's position that no claim terms require construction, which the Board also accepted for purposes of institution." Resp. 7 (citing Pet. 6; Inst. Dec. 7). In our Institution Decision, we determined that "no claim term requires express construction." Inst. Dec. 7. After reviewing the entire record developed during trial, we affirm our

determination from the Institution Decision that no claim term requires express construction to resolve the parties' dispute.

C. Legal Standards

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Obviousness is resolved based on underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A decision on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis "should be made explicit" and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418. We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

D. Overview of Asserted References

We begin our discussion with a brief summary of the asserted references.[13]

[13] Unless otherwise noted, we refer to the original page numbers in each reference, and not the page numbers Petitioner has added to the document.

1. Postlind (Ex. 1010)

Postlind investigates the metabolism of tolterodine in human liver microsomes having varying P450 cytochrome activities. Ex. 1010, Abstract. Postlind illustrates the results of these studies in Figure 1, reproduced below.

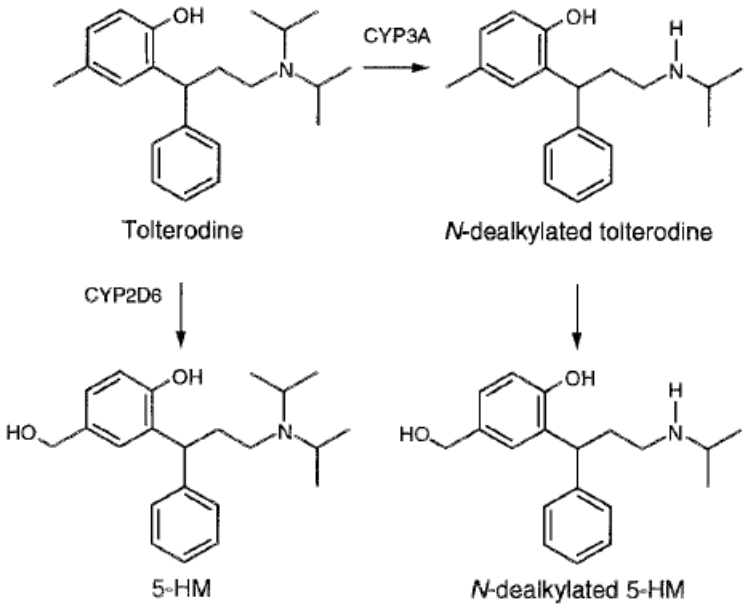


FIG. 1. *Main metabolic pathways of tolterodine in human liver microsomes.*

Figure 1 illustrates that "[m]etabolites are formed via two pathways: oxidation of the 5-methyl group to a 5-hydroxymethyl derivative (5-HM) [i.e., 5-HMT]" by cytochrome P450 2D6 ("CYP2D6" or "2D6") "and dealkylation of the nitrogen" by cytochrome P450 CYP3A4 ("CYP3A4"). *Id*. at 289; *see also id.* at 292 (concluding that the dealkylation reaction "is predominantly catalyzed by CYP3A4 in human liver microsomes.")[14]

[14] Petitioner's technical expert, Dr. Patterson, emphasizes that 5-HMT is also N-dealkylated by CYP3A4. Ex. 1003 ¶ 111; *see id*. ¶¶ 45–47 (citing Brynne et al., *Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity*, 35(7) INT'L J. CLIN. PHARMACOL. THERAP. 287–295 (1997) (Ex. 1007, "Brynne 1997")); Ex. 1007, 291 Fig. 2.

Postlind notes that "[c]linical studies have demonstrated that individuals with reduced CYP2D6-mediated metabolism represent a high-risk group in the population with a propensity to develop adverse drug effects" and a "number of drugs [have been] identified as being affected by CYP2D6 polymorphism. . . ." *Id.* at 292. Accordingly, "[t]he possibility of clinical drug interaction at the enzyme level [] exists, especially if tolterodine is administered at the same time as a compound that is preferentially metabolized by CYP2D6 or to individuals associated with the CYP2D6 poor metabolizer phenotype." *Id.*

Postlind further notes that CYP3A enzymes (e.g., CYP3A4) also have been associated with adverse drug interactions; "[h]owever, the large amount of CYP3A in the liver and the fact that tolterodine is predominantly eliminated via oxidation by CYP2D6 makes it less likely that clinically significant drug-drug interactions would occur with CYP3A substrates in individuals with the CYP2D6 extensive metabolizer phenotype." *Id.*

2. Brynne (Ex. 1011)

Brynne investigates the effect of CYP2D6 heterogeneity on the pharmacokinetics of tolterodine, as well as potential differences in selected pharmacodynamic properties (heart rate, visual accommodation, and salivation) of tolterodine as compared to 5-HMT. *See* Ex. 1011, Abstract. Brynne's study involved "[s]ixteen male subjects (eight extensive metabolizers and eight poor metabolizers) [who] received 4 mg tolterodine by mouth twice a day for 8 days followed by a single intravenous infusion of 1.8 mg tolterodine for 30 minutes after a washout period." *Id.*

With respect to the muscarinic side effect dry mouth, Brynne reports that "[a] distinct drug effect was [] obtained for four of eight extensive

metabolizers and most of the poor metabolizers after oral administration. For extensive metabolizers, the effect was equally pronounced after intravenous compared with oral administration, whereas salivation was less affected among poor metabolizers after the infusion." *Id*. at 535. In considering the relation between the severity of dry mouth and unbound serum levels of the two compounds, Brynne reports that "[t]here was a weak correlation between tolterodine concentration and effect on salivation. A stronger correlation was seen with [5-HMT] and effect." *Id*. at 536. Nevertheless, "[o]nly minor differences in pharmacodynamic effects after tolterodine dosage were observed between the groups. Tolterodine caused a similar decrease in salivation in both panels. The decrease occurred when the concentration of unbound tolterodine and 5-hydroxymethyl metabolite among extensive metabolizers was comparable with that of tolterodine among poor metabolizers." *Id.*, Abstract. Brynne suggests that "the similarity in salivary effects between the two phenotypic groups" may be explained by the 10-fold greater serum protein binding of tolterodine as compared to 5-HMT. *Id.* at 535–536.

Brynne also notes a shift in the effect curve with respect to visual accommodation with five of the poor metabolizers reporting abnormal visual accommodation. *Id.* at 536, 538. The authors posit that "the most likely explanation is the physicochemical differences between tolterodine and [5-HMT]. Tolterodine is tenfold more lipophilic than [5-HMT], and consequently tolterodine penetrates membranes more rapidly." *Id.* at 538. Brynne concludes that:

> Despite the influence of CYP2D6 polymorphism on the pharmacokinetics of tolterodine, this does not appear to be of great pharmacodynamic importance. This is because either high

> concentrations of the parent compound are mainly responsible for the effect among poor metabolizers or substantial concentrations of the active metabolite [5-HMT] are responsible for the effect among extensive metabolizers.

Id.; *see id.* at Abstract.

3. Detrol Label (Ex. 1009)

Detrol Label discusses the structural formula, pharmacokinetics, and pharmacology of tolterodine, provided as tolterodine tartrate "for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence." Ex. 1009, 5.[15] The reference states that:

> Tolterodine is extensively metabolized by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 and leads to the formation of a pharmacologically active 5-hydroxymethyl metabolite [i.e., 5-HMT]. Further metabolism leads to formation of the 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51% ± 14% and 29% ± 6.3% of the metabolites recovered in the urine, respectively.

Id. at 2. Detrol Label notes that about 7% of the population lack cytochrome P450 2D6 activity and are designated "poor metabolizers" as compared to the general population ("extensive metabolizers"). *Id.* Pharmacologic studies reveal that tolterodine is metabolized at a slower rate in poor metabolizers resulting in "significantly higher serum concentrations of tolterodine and negligible concentrations of [5-HMT]." *Id*. But "[b]ecause of differences in the protein-binding characteristics of tolterodine and [5-HMT], the sum of unbound serum concentrations of tolterodine and

[15] Because the Detrol Label does not include any page numbers, we refer to the page numbers Petitioner added to the document.

[5-HMT] is similar in [both populations]." *Id.* Moreover, "[s]ince tolterodine and [5-HMT] have similar antimuscarinic effects, the net activity of DETROL Tablets is expected to be similar in extensive and poor metabolizers." *Id.*

In addressing potential drug-drug interactions related to 2D6 heterogeneity, Detrol Label states that "[t]olterodine is not expected to influence the pharmacokinetics of drugs that are metabolized by cytochrome P450 2D6." *Id.* at 3. The reference further discloses that fluoxetine is a potent inhibitor of cytochrome P450 2D6 activity and has been shown to significantly inhibit the metabolism of tolterodine to 5-HMT such that the pharmacokinetics of the drug in extensive metabolizers resembles that of poor metabolizers. *Id*. The reference, nevertheless, states that "[n]o dose adjustment is required when DETROL and fluoxetine are coadministered." *Id*. Although Detrol Label does not suggest altering tolterodine dosages for 2D6 poor metabolizers, because a substantial portion of the drug is N-dealkylated by cytochrome P450 3A4, it recommends dose reduction for patients taking drugs that inhibit 3A4. *Id.* at 2, 5, 7.

4. Bundgaard (Ex. 1012)

Bundgaard describes prodrug design for drug delivery. Ex. 1012, v. According to Bundgaard, "[a] prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule." *Id.* Bundgaard explains that prodrugs bridge the gap between drug action and efficient delivery to a desired target site:

> A molecule with optimal structural configuration and physicochemical properties for eliciting the desired therapeutic

> response at its target site does not necessarily possess the best molecular form and properties for its delivery to its point of ultimate action. Usually, only a minor fraction of doses administered reaches the target area and, since most agents interact with non-target sites as well, an inefficient delivery may result in undesirable side effects. This fact of differences in transport and in situ effect characteristics for many drug molecules is the basic reason why bioreversible chemical derivatization of drugs, i.e., prodrug formation, is a means by which a substantial improvement in the overall efficacy of drugs can often be achieved.

Id.

Bundgaard teaches that esters are popularly used in the design of prodrugs because the body contains numerous, widely distributed esterases that can cleave such prodrugs to their active forms. *Id.* at 3–4. With respect to parent drugs containing a hydroxyl moiety, exemplary prodrugs have employed, for example, carboxylate, carbonate, phosphate, diacetyl, amino acid, ditoluyl, dipivaloyl, aromatic, and hemisuccinate esters. *See id*. at 3, Table 2.

Bundgaard further teaches that "[e]ster formation has long been recognized as an effective means of increasing the aqueous solubility of drugs containing a hydroxyl group, with the aim of developing prodrug preparations suitable for parenteral administration." *Id.* at 7. This approach makes it "feasible to obtain derivatives with almost any desirable hydrophilicity or lipophilicity as well as in vivo lability." *Id.* at 4. "The most commonly used esters for increasing aqueous solubility of alcoholic drugs are hemisuccinates, phosphates, dialkylaminoacetates and amino acid esters." *Id*. at 8.

5. Bundgaard PCT (Ex. 1020)

Bundgaard PCT describes ester and diester prodrug derivatives of morphine for transdermal delivery. Ex. 1020, 1–5, 7–8, 10, 15. In contrast to morphine, "the morphine esters [were] more lipophilic than the parent drug in terms of octanol-aqueous buffer partition coefficients" and "the 3-hexanoyl, 3,6-dihexanoyl and other 3,6-dipropionyl morphine esters readily penetrated human skin." *Id*. at 9–10.

6. Berge (Ex. 1013)

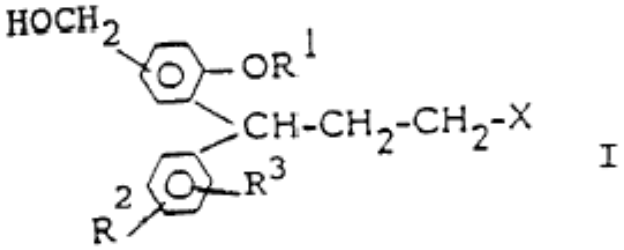
In a review of pharmaceutical formulation salts, Berge states that:

> The chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form. Choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to the parent compound.
>
> Salt-forming agents are often chosen empirically. Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists primarily on a practical basis: cost of raw materials, ease of crystallization, and percent yield. Other basic considerations include stability, hygroscopicity, and flowability of the resulting bulk drug. Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility and formulation profiles.

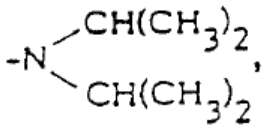
Ex. 1013, 1. Berge Table I is a list of FDA-approved, commercially marketed salts, along with an indication of how frequently those salts were used in the pharmaceutics industry as of 1974. *Id.* at 2. Table I indicates that fumarate salts were used 0.25% of the time. *Id.*

7. Johansson (Ex. 1005)

Johansson discloses compounds of the general formula I reproduced below:



Ex. 1005, 1:18–2:4. General formula I represents a class of 3,3-diphenylpropylamines. *Id.* at Abstract. In formula I, "R_1 signifies hydrogen or methyl, R_2 and R_3 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group." *Id.* at 1:27–30. Johansson further discloses that preferred tertiary amino groups of formula I include the group reproduced below:



Id. at 2:26–3:5. Johansson teaches that such compounds "can form salts with physiologically acceptable acids . . . . Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like." *Id.* at 2:5–10. According to Dr. Patterson, Johansson's general formula encompasses 5-HMT (Ex. 1003 ¶¶ 133–136), which Patent Owner does not contest (*see* Resp. 60 (referencing "Johansson's disclosure of potential salts of 5-HMT")).

E. Analysis of Alleged Obviousness over Postlind, Bundgaard Publications, Detrol Label, and Berge (Ground I)

Petitioner asserts that the combination of Postlind, Bundgaard, Bundgaard PCT, Detrol Label, and Berge would have rendered the subject matter of claims 1–5 and 21–24 obvious to a person of ordinary skill in the art. *See* Pet. 3, 21–43. In particular, Petitioner argues that it would have been obvious for one of ordinary skill in the art to (1) identify 5-HMT as a lead compound for drug development; (2) recognize that 5-HMT could have adverse effects due to its metabolism and poor oral bioavailability due to its lipophilicity profile; (3) address such concerns regarding adverse effects and poor oral bioavailability by esterifying 5-HMT to create a prodrug having increased lipophilicity and, subsequently, optimizing the ester moiety to arrive at a compound having a short-chain mono-ester derivative at only the 5-hydroxyl position; and (4) select an acid-addition salt that provides the desired product stability. *Id.* at 21–38. Further, with regard to claims 3–5, 22, and 23,[16] which require compounds having a specific chirality, Petitioner argues that the ordinarily skilled artisan would have been led to the (R) enantiomer of fesoterodine. *Id.* at 37, 38, 41, 42. Petitioner also argues that it would have been obvious for one of ordinary skill in the art to treat a patient suffering from urinary incontinence generally (claims 21–23), and urge incontinence specifically (claim 24), with the compounds of claims 1, 3, and/or 5, as recited in claims 21–24. *Id.* at 38–43.

A determination of whether a new chemical compound would have been obvious over the prior art typically follows a two prong inquiry

[16] Claim 24 alternatively depends from any one of claims 21–23 and, therefore, does not require a specific chirality.

considering first, whether one of ordinary skill would have selected one or more lead compounds for further development and, second, whether the prior art would have supplied sufficient motivation to modify a lead compound to arrive at the compound claimed with a reasonable expectation of success. *See Otsuka Pharm. Co., Ltd., v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012).

Based on our review of the arguments and evidence of record, we determine that Petitioner does not demonstrate, by a preponderance of the evidence, that the combination of Postlind, Bundgaard, Bundgaard PCT, Detrol Label, and Berge would have rendered obvious the subject matter of claims 1–5 and 21–24.

1. Identification of 5-HMT as a Lead Compound

In the first step of our analysis, we determine "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id*. at 1291. A lead compound comprises "a natural choice for further development efforts," *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009), i.e., a prior art compound "that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity," *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). "In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties." *Otsuka Pharm.*, 678 F.3d at 1292; *see also Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (stating that even "post-*KSR*, a prima facie case of

obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound").

Petitioner begins with the proposition that, in light of Postlind and the pharmacodynamic information in the Detrol Label, one of ordinary skill in the art would recognize that tolterodine was metabolized to an active metabolite, 5-HMT, having beneficial properties as compared to the parent compound. Pet. 22–24; *see* Ex. 1003 ¶¶ 40–43, 95–102. Petitioner argues that because the references disclose that tolterodine is metabolized to 5-HMT by cytochrome CYP2D6, one of ordinary skill in the art would have elected to begin with the 5-HMT metabolite in order to avoid the potential for 2D6 drug-drug interactions, or the propensity of 2D6 poor metabolizers to develop adverse side effects when using drugs subject to this pathway. Pet. 23–24. In particular, Petitioner relies on Postlind, which provides the general caution that "[c]linical studies have demonstrated that individuals with reduced CYP2D6-mediated metabolism represent a high-risk group in the population with a propensity to develop adverse drug effects" and states that a "number of drugs" have been identified as "being affected by CYP2D6 polymorphism." Ex. 1010, 292. In light of that experience with other drugs metabolized via the 2D6 pathway, Postlind suggests that for tolterodine, "[t]he possibility of clinical drug interaction at the enzyme level [] exists, especially if tolterodine is administered at the same time as a compound that is preferentially metabolized by CYP2D6 or to individuals associated with the poor CYP2D6 poor metabolizer phenotype." *Id.*

Petitioner further asserts that, for the treatment of overactive bladder ("OAB"), "tolterodine and its metabolite 5-HMT had advantages in tolerability and efficacy compared to other antimuscarinic therapies such as

oxybutynin, as well as to other classes of compounds such as calcium antagonists." Reply 3–4 (citing Pet. 16–17; Ex. 1003, ¶¶ 85–102; Ex. 1008,[17] 53; Ex. 1016,[18] 53 [sic]). Petitioner argues that, unlike its active metabolite, 5-HMT, tolterodine may be associated with certain side effects, and is subject to CYP2D6 metabolism, which raises the risk of drug-drug interactions, as well as potentially increased side effects and enhanced N-dealkylation via the CYP3A4 pathway in poor CYP2D6 metabolizers. *See generally* Pet. 7–9, 14–15, 22–24; Reply 4–9; Tr. 13:35–16:11. Accordingly, Petitioner asserts, one of ordinary skill in the art would have had reason "to focus on 5-HMT instead of tolterodine to avoid the complication of dosing two active moieties, complications from CYP2D6 metabolism, and undesirable side effects, all of which were associated with tolterodine, but not [with] 5-HMT." Reply 9.

Patent Owner responds that tolterodine—and, thus its 5-HMT metabolite—did not "stand out as a lead compound" from other compounds taught or suggested for the treatment of OAB. Resp. 16–18. Patent Owner further argues that the art was moving away from the use of non-specific muscarinic inhibitors such as tolterodine. *See id*. at 17–18; Tr. 51:19–56:21. According to Dr. Maag, for example,

> [a]lthough tolterodine was reported to have a selective effect on the bladder muscle over the salivary glands, a lack of selectivity for the bladder in OAB drugs remained a problem even after its launch, with researchers targeting drugs that were selective for

[17] Thomas et al., *Concentration dependent cardiotoxicity of terodiline in patients treated for urinary incontinence*, 74 BR. HEART J. 53–56 (1995).
[18] DeMaagd & Davenport, *Management of Urinary Incontinence*, 37(6) P&T 345–361H (2012).

> muscarinic receptor subtypes in hopes that they would yield a better therapeutic index.

Ex. 2021 ¶ 48. In contrast to such potential treatments, however, tolterodine (Detrol) was already approved and marketed for use in treating OAB. *See* Ex. 1009. Accordingly, we find that one of ordinary skill in the art seeking to improve upon OAB therapy would have reasonably looked to tolterodine.

With respect to then selecting the tolterodine metabolite 5-HMT as a lead compound, Patent Owner argues that there is insufficient evidence of record that side effects associated with Detrol could be reduced by administering 5-HMT alone, or that variations in CYP2D6 metabolism had any significant effect on patient outcome. Resp. 18–25; Tr. 56:35–63:29. Although both parties present well-reasoned positions, for the reasons discussed above, we agree with Petitioner that one of ordinary skill in the art would have focused on 5-HMT "to reduce the number of metabolic steps and variables in pharmacology," and avoid potential 2D6 drug-drug interactions or the propensity of 2D6 poor metabolizers to develop adverse side effects. *See, e.g.*, Reply 6; Ex. 1003 ¶¶ 95–102 (Dr. Patterson explaining, with citations to supporting evidence, why the ordinarily skilled artisan would have chosen 5-HMT); Ex. 1010, 292. Accordingly, we find that one of ordinary skill in the art would have reasonably selected 5-HMT as a lead compound.

2. Reason to Modify 5-HMT

In the second stage of our analysis, we analyze whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Otsuka Pharm.*, 678 F.3d at 1292; *see also Eisai*, 533 F.3d at 1357 ("Obviousness based on structural similarity [] can be proved by identification of some motivation that would have led one

of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound."). We first address a preliminary argument Petitioner raises regarding a prior patent, then turn to the parties arguments regarding whether there existed a reason to modify 5-HMT with a reasonable expectation of success in achieving the claimed compounds.

a. Prior patent

In footnote 4 of the Petition, Petitioner asserts that because "the patent to the 5-HMT compound was available as of November 1997, this is an additional reason that a person of skill in the art in 1998 would have been motivated to research and investigate a different compound." Pet. 45 n.4. Referencing this footnote in the Reply, Petitioner argues that the alleged prior disclosure of the 5-HMT compound would have discouraged one of ordinary skill in the art "from seeking to use orally-administered 5-HMT." Reply 9–10 (citing Pet. 45 n.4; Ex. 1003 ¶ 136). Then, at oral hearing, Petitioner argued that dosing 5-HMT directly was a "nonstarter" because "part of what drives drug development and drug design is at the end of the day being able to have a commercially viable product" and "[i]f you don't have patent protection in the West, you cannot have a commercially viable product." Tr. 28:11–29.

Petitioner's arguments in the Reply and at oral hearing appear to be, at best, a variation on a nominal position taken in footnote 4 of the Petition which provides: "Because the patent to the 5-HMT compound was available as of November 1997 . . . a person of skill in the art in 1998 would have been motivated to research and investigate a different compound." Pet. 45 n.4 (citing Ex. 1003 ¶ 136). Footnote 4, however, was part of Petitioner's

Ground II argument that Johansson and its divisional application make it "more predictable that the prodrug of 5-HMT in a fumarate salt would be successfully achieved." *Id.* But in the Reply, and at oral hearing, Petitioner leverages this footnote into a new argument that the *oral administration* of 5-HMT would have been discouraged by the existence of a prior patent disclosing the compound. Reply 9–10; Tr. 28:13–29. Such a shift in position "is foreclosed by the statute, [Federal Circuit] precedent, and Board guidelines." *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1286–87 (Fed. Cir. 2017). Additionally, we are not made aware of any authority supporting Petitioner's argument that one of ordinary skill in the art would not have pursued oral administration of 5-HMT due to the existence of a patent on the 5-HMT compound. *See also* Tr. 65:23–29 (Patent Owner's assertion that there was "no case law suggesting that persons of ordinary skill are focused on patents in deciding which steps to make").

Considering the untimely development of Petitioner's position, the absence of factual underpinnings,[19] and the lack of legal precedent, we are unpersuaded that we need to give considerable weight to Petitioner's argument regarding the prior patent.

[19] Paragraph 136 of Dr. Patterson's Declaration, relied on to support footnote 4 of the Petition, consists of the bald assertion that "[b]ecause the 5-HMT compound would have been covered by this patent and its U.S. counterpart, a skilled drug designer and developer would recognize the need to make some changes to avoid the patent." Ex. 1003 ¶ 136. We accord little to no weight to Dr. Patterson's conclusory statement. *See* 37 C.F.R. §42.65(a).

b. Metabolism

With respect to a reason to modify 5-HMT, Petitioner states that Postlind "would have motivated a person of ordinary skill to modify 5-HMT to a compound that avoided CYP2D6 metabolism as known to occur with tolterodine." Pet. 23 (citing Ex. 1010, 292); *id.* at 24 ("[A] person of ordinary skill in the art would have appreciated the 5-HMT compound was a great candidate for overactive bladder treatment and sought to modify the [5-HMT] compound to avoid CYP2D6 metabolism and the risk of drug interaction and adverse effect associated with administering tolterodine." (citing Ex. 1003 ¶¶ 95–102)). Petitioner argues that Postlind would have informed one of ordinary skill in the art that "various factors, such as polymorphism and/or inhibition of CYP2D6 by concurrently administered drugs, may result in decreased metabolism of tolterodine to 5-HMT and an increased incidence in adverse side effects in the affected subpopulation." *Id.* at 24 (citing Ex. 1003 ¶¶ 40–43).

Petitioner, however, fails to point to any evidence that 5-HMT is metabolized through the CYP2D6 pathway, or that administering 5-HMT would have resulted in the same risks of drug interaction and adverse effects that Petitioner contends are the result of administering tolterodine. *See* Pet. 22–24 (describing alleged problems associated with tolterodine, not 5-HMT); Ex. 1003 ¶¶ 95–100 (Dr. Patterson's testimony regarding the drawbacks of tolterodine). Indeed, such an argument appears to undermine Petitioner's position, discussed in Section II.E.1 *supra*, that one of ordinary skill in the art would have selected 5-HMT as a lead compound over tolterodine to avoid the CYP2D6 metabolic pathway, and Dr. Patterson's testimony that the prior art collectively "indicated to a skilled drug designer

interested in overactive bladder treatment that 5-HMT would avoid the issues associated with dosing [] tolterodine." Ex. 1003 ¶ 101. Petitioner's argument also is contradicted by Dr. Patterson's testimony that "5-HMT is not metabolized by both CYP2D6 and CYP3A4, but only by CYP3A4." *Id.* ¶ 111; *see also* Ex. 1010, 289 (Postlind indicating that 5-HMT is not a CYP2D6 substrate).

Petitioner also argues that the Detrol Label's dose reduction recommendation for "patients with significantly reduced hepatic function or who are currently taking drugs that are inhibitors of cytochrome P450 3A4" confirms the cytochrome polymorphism interaction by requiring a dose adjustment to prevent adverse effects in certain patients. Pet. 24 (citing Ex. 1009, 7).

Patent Owner responds that Petitioner's argument regarding the Detrol Label's requirement of a dose adjustment related to inhibition of P450 3A4 "confuses the issue because the cytochrome relevant to tolterodine metabolism is cytochrome is P450 *2D6* [i.e., CYP2D6]." Resp. 21. Patent Owner further notes that the absence of a warning in the Detrol Label related to CYP2D6 "indicates that there was *no* polymorphism concern." *Id.* at 22 (citing Ex. 2021 ¶¶ 74, 79). Petitioner replies, in a footnote, that Patent Owner's position is contradicted by the Detrol Label and Postlind, which discuss that the "identified pathway of metabolism for . . . poor metabolizers[] is dealkylation via cytochrome P450 3A4." Reply 5 n.3 (citing Ex. 1009, 2; Ex. 1010, 292).

We agree with Petitioner that the Detrol Label and Postlind discuss two alternative metabolic pathways for tolterodine. Petitioner, however, does not provide a sufficient reason why such information would have been

meaningful to one of ordinary skill in the art in the context of Petitioner's arguments regarding modification of 5-HMT. For instance, although tolterodine and 5-HMT are both P450 3A4 substrates (*see supra* § II.D.1), Petitioner directs our attention only to what it contends were known problems associated with the oral administration of tolterodine, not 5-HMT. *See, e.g.*, Tr. 14:17–25 ("So at the time the art didn't really suggest that clearing 5-HMT through [P450] 3A4 was a problem, but it did suggest that for tolterodine."). Accordingly we remain unpersuaded that Petitioner has adequately explained its position that Postlind's concerns regarding CYP2D metabolism of tolterodine or the Detrol Label's concerns relating to the P450 3A4 substrate profile of tolterodine would have motivated one of ordinary skill in the art to modify 5-HMT.

c. Lipophilicity and bioavailability

Petitioner also relies on paragraphs 116 and 118 of Dr. Patterson's declaration in asserting that "a person of ordinary skill in the art would have appreciated that 5-HMT was too lipophilic and needed to be modified in a way to improve bioavailability." Pet. 26. Addressing this statement in the Reply, Petitioner contends that it "inadvertently stated that 5-HMT was 'too lipophilic,' when [it] intended to say 'too hydrophilic.'" Reply 11 n.5; *see also* Pet. 10 (asserting that 5-HMT was known to have "poor lipophilicity").

Relevant to Ground I, Dr. Patterson testifies that

> [w]hen the skilled artisan would have looked at 5-HMT, it would have seen that the presence of two hydroxyl groups around the left most aromatic ring . . . would have created a product likely to have decreased oral bioavailability compared to tolterodine because of its hydrophilicity and thus lower than acceptable lipophilicity.

Ex. 1003 ¶ 112; *see also id.* ¶ 115 ("[E]xamination of the structure of 5-HMT would have suggested that 5-HMT could have significantly less bioavailability than its parent, tolterodine. Confirming this would be a matter of routine experimentation.").

Regarding the lipophilicity and bioavailability of 5-HMT, we note Dr. Patterson testifies that Brynne (asserted in the Petition with respect to Ground II) "specifically informed the field that tolterodine 'is tenfold more lipophilic than 5-HM[T], and consequently tolterodine penetrates membranes more rapidly.'" Ex. 1003 ¶ 116 (quoting Ex. 1011, 538). Accordingly, Petitioner argues that "a person of ordinary skill in the art would have appreciated that 5-HMT was [too hydrophilic] and needed to be modified in a way to improve bioavailability" and, thus, "preparing an ester prodrug would have been an obvious choice to modify 5-HMT." Pet. 26 (citing Ex. 1003 ¶¶ 116, 118).

Patent Owner argues that Petitioner's own prior art proves that there was no expectation that 5-HMT would have had insufficient absorption or bioavailability. Resp. 26. Patent Owner contends that (1) Petitioner does not cite a single prior art reference that discloses the oral bioavailability of 5-HMT (*id.*); (2) 5-HMT, as of the critical date, "had never been directly orally administered to a patient and thus the oral absorption and bioavailability properties of 5-HMT were entirely unknown" (*id.* (citing Ex. 2020, 133:13–20, 209:18–23; Ex. 2026, 60:4–61:8; Ex. 2022 ¶¶ 52–58, 75)); and (3) even if "a person of skill had considered 5-HMT to be less lipophilic than tolterodine, a compound known to be bioavailable and well-absorbed, it does not follow that 5-HMT – a close structural analog – would

necessarily have a bioavailability or absorption problem" (*id.* at 27 (citing Ex. 2022 ¶¶ 52–59)).

Petitioner, in its Reply, maintains its position that the prior art suggested that 5-HMT may have had bioavailability concerns. Reply 9. Specifically, Petitioner restates its citation to Brynne in support of the proposition that "[t]olterodine is tenfold more lipophilic than 5-HM[T], and consequently tolterodine penetrates membranes more rapidly." *Id.* at 10 (citing Ex. 1011, 538). Petitioner also states that no actual oral bioavailability data would have been necessary for a skilled artisan to understand bioavailability, arguing that Brynne would have taught a skilled artisan to be concerned about 5-HMT's bioavailability, because a compound's lipophilicity was an important predictor of its bioavailability. *Id.* at 12.

In addressing bioavailability, both parties' experts discuss the "Rule of 5" set forth in the Lipinski reference.[20] For example, Dr. Patterson explains Lipinski teaches "that poor absorption is more likely where there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight is greater than 500 and the calculated Log P is greater than 5," and asserts that "[t]hese principles were widely applied at the time of [the] invention." Ex. 1003 ¶ 121. Dr. Roush testifies that Lipinski "provides guiding principles for gauging whether a compound will have poor absorption" but that the "Lipinski 'rules' are not absolute and serve only as guidelines of

[20] Lipinski et al., *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings*, 23 ADV. DRUG DELIVERY REV. 3–25 (1997) (Ex. 1019, "Lipinski").

properties above which absorption is potentially problematic." Ex. 2022 ¶ 56.

According to Dr. Patterson, one of ordinary skill in the art would have applied Lipinski's rules in the design of derivative esters of 5-HMT. *See* Ex. 1003 ¶¶ 122–123, 129. But neither Petitioner nor Dr. Patterson provides such an analysis for 5-HMT itself. In contrast, Dr. Roush calculates that 5-HMT does not "violate" any of the Lipinski rules and, thus, concludes that one of ordinary skill in the art would have had "no reason to suspect that 5-HMT would possess poor oral absorption." Ex. 2022 ¶¶ 57–58.

In reply, Petitioner asserts that the "Rule of 5" "is not a strict threshold of bioavailability; instead, it only identifies a class of compounds at risk for having poor absorption." Reply 13. Petitioner maintains that Dr. Patterson based his opinion of the bioavailability of 5-HMT on an examination of its structure, and faults Patent Owner for failing to address Dr. Patterson's opinion that 5-HMT's structure "would have suggested that 5-HMT could have significantly less bioavailability than its parent." *Id.* (citing Ex. 1003 ¶¶ 110–15, 121–22).

On the complete record before us, we are unpersuaded that Petitioner carries its burden of demonstrating that 5-HMT has a bioavailability problem that would have motivated one of ordinary skill in the art to modify its structure.

Regarding the lipophilicity profile of 5-HMT, Petitioner does not provide, or attempt to provide, any actual (as opposed to relative) data concerning the bioavailability of 5-HMT. *Cf. supra* § II.D.2 (Brynne comparing lipophilicity of tolterodine to lipophilicity of 5-HMT). Although data is not required, and although we do not find that absence of data alone

to be fatal to Petitioner's position on this issue, the absence of any data concerning the actual bioavailability of 5-HMT leaves Petitioner's argument solely supported by expert testimony. We now turn to the contradictory statements of the parties' experts.

Following our weighing of the experts' testimony, we find that Dr. Roush's testimony better addresses the issue at hand and we credit that testimony over Dr. Patterson's testimony. Dr. Patterson opines generally that the "presence of two hydroxyl groups around the left most aromatic ring . . . would have created a product likely to have decreased oral bioavailability compared to tolterodine because of its hydrophilicity and thus lower than acceptable lipophilicity" (Ex. 1003 ¶ 112), and that it "would [have been] a matter of routine experimentation" to confirm that 5-HMT could have significantly less bioavailability than its parent, tolterodine" (Ex. 1003 ¶ 115). Dr. Patterson, however, did not perform any experiments to confirm 5-HMT's oral bioavailability, and cites to no further evidence to support his opinions. *See* Ex. 2022 ¶ 92; *compare* Brynne (Ex. 1011) discussed *supra* § II.D.1.

Dr. Roush, on the other hand, conducts an analysis of the compound under the "Rule of 5" to determine that "*5-HMT does not meet a single factor, much less two, of the rule*" thus teaching the skilled artisan "away from concluding that 5-HMT had an oral absorption problem." Resp. 28–29 (citing Ex. 2022 ¶¶ 56–58, 87, 92). At oral hearing, Patent Owner restated that the analysis under the Rule of 5 indicates that 5-HMT was "not even close to being a problem . . . for all four of these properties, 5-HMT says there's no red flags; there's no problem," and that "Dr. Patterson admitted in

his deposition, 5-HMT does not violate the Rule of Five." Tr. 67:35–68:3; 68:17–21; *see* Ex. 2020, 180:14–181:14.

Regarding Petitioner's reliance on the statement in Brynne that "[t]olterodine is tenfold more lipophilic than 5-HM[T], and consequently tolterodine penetrates membranes more rapidly," Patent Owner does not appear to dispute the substance of that statement. Although such a statement illustrates a relative relationship between the lipophilicity of 5-HMT and tolterodine, it does not demonstrate that the lipophilicity of 5-HMT would have presented an absorption problem that would have led one of ordinary skill in the art to modify 5-HMT. Even if 5-HMT were considered by one of ordinary skill in the art to be less lipophilic than tolterodine, and thereby less rapidly absorbed, the record lacks sufficient evidence regarding the actual properties of 5-HMT for us to conclude that 5-HMT's lipophilicity would have presented a bioavailability problem.[21] For these reasons, Petitioner's assertion that 5-HMT "may have bioavailability concerns" that would have prompted one of ordinary skill in the art to modify 5-HMT is unpersuasive. Reply 13.

We find, on the complete record before us, that Petitioner fails to demonstrate by a preponderance of the evidence that one of ordinary skill in the art would have recognized from the lipophilicity profile of 5-HMT,

[21] To the contrary, in light of Dr. Patterson's assertion that "5-HMT would be less likely to generate neurological adverse events compared to tolterodine" because "[a]n increase in lipophilicity results in an increase in the likelihood of passive blood brain barrier penetration" (Ex. 1003 ¶117), we do not see why one of ordinary skill in the art would have wanted to increase the lipophilicity of 5-HMT, and thereby risk the neurological adverse events associated with passive blood brain barrier penetration.

and/or the Brynne reference, that 5-HMT would have poor oral bioavailability and/or absorption.

3. Using a Prodrug Approach to Arrive at the (R) Enantiomer of a Short-chain Mono-ester Derivative at the 2-position Carbon

Building on its lipophilicity and bioavailability arguments, Petitioner next contends that the person of ordinary skill in the art would have modified 5-HMT to arrive at the claimed compounds by using a prodrug approach, which Petitioner contends "was a matter of routine optimization" for "active compounds with hydroxyl groups," such as 5-HMT. Pet. 18. Petitioner relies on Bundgaard as teaching "that esterification of a compound containing a hydroxyl group makes it 'feasible to obtain derivatives with almost any desirable hydrophilicity or hydrophobicity as well as in vivo lability.'" *Id.* at 26–27 (citing Ex. 1012, 4). Petitioner also relies on Dr. Patterson's testimony that, in light of the Bundgaard publications, and applying the Rule of 5, one of ordinary skill in the art would have begun experimenting with 2 to 6 carbon mono-ester derivatives of 5-HMT. *Id.* at 27–29 (citing Ex. 1003 ¶¶ 116–120, 124–130); *see also* Ex. 1003 ¶ 16 ("[A] person of ordinary skill in the art . . . would have immediately recognized the desirability of making a prodrug of the known active metabolite of tolterodine – 5-HMT."). According to Dr. Patterson, in designing a better-absorbed prodrug of 5-HMT, the skilled artisan would have rejected 2, 5 diesters (i.e., modifications to the hydroxyl group on both the 2- and 5-positions of 5-HMT's methylated phenolic ring) as "overly lipophilic" and sought to modify only the 2-position hydroxyl group to avoid transesterification. Ex. 1003 ¶¶ 123, 126–127. Dr. Patterson further opines that determining "the stability and requisite lipophilicity of those esterified

5-HMT compounds would have been a matter of routine testing and optimization." *Id*. ¶ 129.

a. Prodrug approach

Patent Owner responds that even if one of ordinary skill in the art would have found that 5-HMT had an absorption issue, such a person would have applied a prodrug approach "only as a last resort." Resp. 31–33 (citing Ex. 2021 ¶¶ 82–85; Ex. 2022 ¶¶ 41–49). Patent Owner relies on Dr. Roush's testimony to argue that "a skilled artisan would have considered numerous other possibilities to address an alleged oral absorption issue, such as structural analogs, formulations, micronizations, and polymorphs." *Id.* at 31–32 (citing Ex. 2022 ¶¶ 60–65); *see also* Ex. 2001, 16 ("The limited information about 5-HMT's properties, the risks associated with prodrug development, and the existence of more straightforward optimization techniques all indicate that a prodrug approach would not have been obvious.").

Petitioner disagrees that prodrugs were generally disfavored and a difficult approach to drug development, pointing to the testimony of Dr. Roush and Dr. Maag, who Petitioner asserts "both admitted that prodrug development, and in particular ester prodrugs were within the capabilities of a skilled artisan." Reply 14–15 (citing Ex. 1073, 110:20–111:7, 112:7–113:7; Ex. 1074, 102:6–103:6).

On this record, and under our standard for final decisions in an *inter partes* review, we are unpersuaded by Petitioner's argument. Regardless of whether prodrugs generally were known in the art, or were part of an ordinarily skilled artisan's arsenal at the time of the invention, Petitioner does not establish that such an ordinarily skilled artisan would have

embarked on a prodrug approach to modify 5-HMT. As we have discussed above, Petitioner does not establish that bioavailability of 5-HMT was a problem and, therefore, Petitioner cannot reasonably establish that one of ordinary skill in the art would have turned to prodrug development to solve an undefined problem. As Patent Owner points out, and as we agree, "prodrug development requires monitoring the toxicity, bioavailability, receptor affinity, pharmacokinetics, and pharmacodynamics of not only one, but two, compounds – the prodrug and the desired active compound – making the development process even more complex, time consuming, and expensive." Resp. 32 (citing Ex. 2021 ¶¶ 82–85; Ex. 2022 ¶¶ 41–49). Moreover, the possible variations in prodrug structure due to the number of substitutions, locations on the compound, and combinations can lead to millions of possible variations. *Id.* at 32–33; Ex. 2022 ¶ 48. On this record, we find that such known deterrents to prodrug development would have counseled one of ordinary skill in the art to try alternative approaches, such as those Dr. Roush identifies, before trying a prodrug approach. *See* Ex. 2022 ¶¶ 60–65.

i. Prodrug must be inactive

Patent Owner also notes that Bundgaard defines a prodrug as "a pharmacologically *inactive derivative* of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug," arguing that Petitioner has not identified any prior art suggesting that a person of ordinary skill in the art would have expected derivatives of 5-HMT to have been inactive. Resp. 34 (citing Ex. 1012, 5).

Petitioner replies that "nothing in the prior art taught a skilled artisan that a *prodrug* of 5-HMT might exhibit its own pharmacological activity, or

that such would be desirable." Reply 16 (citing Ex. 1074, 64:24–65:13, 78:2–7 (Dr. Maag testifying that it would be a "very rare occurrence" for a prodrug to exhibit any level of activity)).

We consider this argument as part of our determination whether one of ordinary skill in the art would have attempted to develop a prodrug of 5-HMT. The definition of a prodrug as a pharmacologically inactive derivative of a parent drug molecule, we determine, would have led one of ordinary skill in the art to seek some degree of certainty that a prodrug of a particular molecule would be inactive before embarking on the process of attempting to create the prodrug. No such certainty is provided here. The testimony and evidence Petitioner cites appears to relate to prodrugs in general, but not to prodrugs of 5-HMT, which we must consider in the case before us. Petitioner, which bears the burden of proof in this proceeding, neither explains adequately why one of ordinary skill in the art would have desired a pharmacologically inactive derivative of 5-HMT, nor presents evidence that "if you put esters on [5-HMT and tolterodine] they will be inactive." Tr. 75:11–15.

ii. No prodrug teaching existed

Patent Owner further argues that prodrug design would have been disfavored because no prodrug examples analogous to 5-HMT existed—for example, Petitioner points to no prodrugs "in the same chemical class (diphenylpropylamines), or with the same mechanism of action (antimuscarinics), or for use in the same field of treatment (overactive bladder)." Resp. 34–35. Patent Owner faults Petitioner for failing to provide evidence that any person other than the inventors ever considered a

prodrug of an antimuscarinic or any sort of overactive bladder drug. *Id.* at 35.

As with the immediately preceding issue, we look to Petitioner to bear its burden of proof on issues relevant to its case. Although Petitioner does not have to demonstrate explicitly that there were prodrug examples analogous to 5-HMT, without such a showing, Petitioner has not provided factual support for the argument that one of ordinary skill in the art, in the absence of a roadmap of similar or exemplary prodrugs from which to analogize, would have considered prodrugs desirable for antimuscarinic activity, or for the treatment of overactive bladder. On that point, Petitioner contends that tolterodine acts like a prodrug, but concedes that tolterodine "was not developed as a prodrug" and that, unlike a prodrug, tolterodine is pharmacologically active. Reply 16; *compare* Pet. 7 ("Artisans also knew tolterodine possessed its own activity separate from the 5-HMT metabolite."), *with* Ex. 1012, v (defining a prodrug as "a pharmacologically inactive derivative of a parent drug molecule"). Petitioner also does not identify "any other prodrugs for 5-HMT or prodrugs for overactive bladder use." Tr. 33:3–34:5. Patent Owner argues persuasively, and we find, there is no evidence that anyone other than the inventors considered a prodrug of an antimuscarinic or any sort of overactive bladder drug. Resp. 35 (citing Ex. 2022 ¶ 65).

b. Specific molecular modifications

Patent Owner also argues that the prior art fails to suggest making the specific molecular modifications of the claimed invention. Resp. 35–49. Patent Owner takes issue with Petitioner's contention that it would have been obvious to "(1) synthesize and test a limited number of ester prodrugs

of 5-HMT, and (2) modify only the 2-position hydroxyl group of 5-HMT, rather than both hydroxyls or only the 5-position hydroxyl group." *Id.* at 36.

i. Not a limited number of simple substituents

A showing of obviousness requires "that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention,'" and a reasonable expectation of success in doing so. *Takeda*, 492 F.3d at 1356 (quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)) (emphasis added).

Patent Owner argues that "Petitioner's suggestion to 'optimize' the prodrug substituents from a group of compounds to arrive at fesoterodine is a jarring concession that Petitioner cannot identify prior art teaching the 'specific molecular modifications' of the claimed compound, fesoterodine." Resp. 37. First, Patent Owner argues that persons of ordinary skill in the art, pursuing prodrugs, would not have limited themselves to ester prodrugs. *Id.* at 38 (citing Ex. 2022 ¶¶ 49, 78–84). Dr. Roush testifies, for example, that "[i]nstead of simply selecting an ester," one of ordinary skill in the art would have "considered a variety of factors, such as rate of conversion, ease of manufacture, ease of storage, level of uptake, and stability, before deciding which type of prodrug to pursue." Ex. 2022 ¶ 78. Dr. Roush continues that the skilled artisan then would have "considered a variety of potential prodrug substitutions, including esters, ethers, carbamates, carbonates, phosphate esters, Mannich bases, and macromolecular prodrugs. *See, e.g.*, Bundgaard (Ex. 1012)." *Id.* ¶ 79. Moreover,

> even if a person of ordinary skill in the art decided to select an ester, she would have recognized that there were many classes of ester prodrugs from which to choose, including, for example, carboxylate esters, carbonate esters, phosphate esters, aliphatic

> esters, aromatic esters, amino acid esters, and hemisuccinate esters.

Id. ¶ 81 (citing Ex. 1012, Table 2).

Even focusing only on alkyl ester prodrugs, Patent Owner argues, there were numerous classes of esters available to be substituted, individually or together, at the 2- and 5- position carbons. Resp. 38. By Patent Owner's "narrow, conservative estimate of substitutions with small chain esters up to six carbons," the result "is 86 possible monoesters at each position, 86 possibilities of homogenous diesters, and over 7,000 mixed diesters, with no expectation that any of them may succeed." *Id.* at 38–39.

Petitioner replies that Bundgaard "explicitly characterized ester prodrugs — particularly small chain esters — as one of the most commonly used and logical prodrug approaches." Reply 15 (citing Ex. 1012, 1–4). Petitioner further replies that "Patent Owner's assertion that arriving at fesoterodine from 5-HMT was one in 7,568 possibilities is meritless, and merely assumes the skilled artisan would mindlessly toil through synthesizing every permutation of monoesters and diesters at the [2- and 5-position] carbons of 5-HMT." *Id.* at 16. Rather, Petitioner argues that a skilled artisan would have (i) first ruled out diesters because they would create an overly lipophilic compound and require additional metabolic steps; (ii) then ruled out monoester modifications to the [5-position] carbon because of the possibility that would require more metabolic steps to release 5-HMT, or fail to release 5-HMT at all; and (iii) understood that modifying the [5-position] carbon raised the risk of incomplete inactivation. *Id.* at 16–17. Thereafter, arriving at fesoterodine from "the 86 possible phenolic monoesters at the [2-position] carbon would be a matter of routine optimization." *Id.* at 17.

Based on the complete record before us, we disagree with Petitioner. As a preliminary matter, we are not persuaded that Petitioner identifies the specific molecular modification necessary to achieve the claimed invention, simply by pointing to a proposed sequence of multiple steps that Petitioner asserts one of ordinary skill in the art would have taken to achieve the eventual specific molecular modification. There is inadequate evidence in the record that the prior art Petitioner cites would have suggested making the specific molecular modification necessary to achieve fesoterodine, namely, substitution of a mono-isobutyryl ester at the 2-position, and a reasonable expectation of success in doing so. The sheer number of possibilities available to the person of ordinary skill in the art at each stage of the process speaks to the nonobviousness of the final product.

Petitioner's argument that one of ordinary skill in the art would have ruled out diesters is countered effectively by Dr. Roush, who identifies the many other prodrug substitutions, as well as the many other esters that one of ordinary skill in the art would have considered. Ex. 2022 ¶¶ 79–81. Bundgaard, upon which Petitioner relies for its teaching of simple esters, also discloses "special double ester[s]" and prodrug design alternatives to esters. Resp. 40 (citing Ex. 1012, 4, 10–36). And Dr. Patterson admits that one of ordinary skill in the art could have tried additional esters, that Bundgaard teaches many alternatives that would have been available to the skilled artisan, and that Bundgaard does not specifically teach the isobutyryl ester characteristic of fesoterodine. Ex. 2020, 161:13–22, 164:25–165:8; 166:19–167:16, 173:6–13.

Even if we were persuaded that one of ordinary skill in the art would have whittled the choices down to 86 possible phenolic monoesters at the

2-position carbon, we are not persuaded that it would have been "routine optimization" to test all 86 possible phenolic esters, particularly in view of the inventors' testimony in the district court litigation that those experiments yielded unpredictable results (Ex. 2001, 18).

ii. Not obvious to modify 2-position carbon

Patent Owner argues (1) there are many potential locations to which a person of ordinary skill could have added the prodrug substituent, and the target would not necessarily be a hydroxyl group; (2) both hydroxyl groups (2- and 5-position), together or alone, are available for substitution; and (3) Bundgaard 1991,[22] the only prior art reference addressing phenolic substitutions, suggests to look elsewhere. Resp. 41–44.

Petitioner replies that one of ordinary skill in the art would have ruled out "monoester modifications to the [5-position] carbon because the prior art taught that the metabolism of tolterodine to 5-HMT via CYP2D6 involved changing a methyl at this position to a hydroxymethyl group, thereby raising the possibility that a [5-position] carbon ester would require more metabolic steps to release 5-HMT, or even fail to release active 5-HMT at all." Reply 17. Petitioner further replies that one of ordinary skill in the art "would have also understood that the inactivation pathway of 5-HMT into *N*-dealkylated 5-CM also involved the [5-position] carbon, but not the [2-position] carbon, such that modifying the [5-position] carbon raised the risk of incomplete inactivation." *Id.*

We are unpersuaded that one of ordinary skill in the art would have relied on such justifications to rule out modification at the 5-position carbon.

[22] Bundgaard, *Novel chemical approaches in prodrug design*, 16(5) DRUGS OF THE FUTURE 443–458 (1991) (Ex. 2015).

Patent Owner argues that Petitioner fails to cite any prior art in support of the "radical step" of ignoring the 5-position carbon. Resp. 42. In the absence of supporting prior art, Petitioner's argument that one of ordinary skill in the art would have ignored the 5-position carbon relies on Dr. Patterson's testimony. But, as Patent Owner points out, Dr. Patterson "does not discuss the CYP2D6 concern at all" in the portion of his Declaration that Petitioner cites. *Id.* at 42 n.17. Patent Owner also points out that Dr. Patterson fails to provide supporting facts or data upon which his opinion regarding transesterification is based. *Id.* at 43; *see also* Ex. 1003 ¶¶ 125–27. Having reviewed the relevant testimony regarding transesterification (*see also* Ex. 2020, 190:12–16, 193:16–20), we agree that Petitioner does not sufficiently establish the probability of transesterification as a problem. We find, as argued by Patent Owner, that the teachings of the relevant prior art on phenolic substitutions indicated that there were no preferred derivatives for substitution on the phenolic group (i.e., 2-position carbon) of drugs, and as such, even the inventors of the challenged patent initially modified the 5-position carbon of 5-HMT. *See* Resp. 43–44 (citing Ex. 2006, 49:12–21; Ex. 2015, 456).

iii. No motivation to use an isobutyryl ester/ no expectation of success

Patent Owner argues that Petitioner fails to explain why a person of ordinary skill would have selected the specific isobutyryl ester modification to 5-HMT. Resp. 44–45. Moreover, "Petitioner's suggestion of a finite number of possibilities does not withstand scrutiny," according to Patent Owner, because "fesoterodine was the result of an entirely new path – the first prodrug ever in the antimuscarinic or overactive bladder fields" and

"the substitution possibilities are not finite at all" based on Petitioner's prodrug references. *Id.* at 45–46.

With respect to the selection of esters alone, Dr. Roush opines that, "there is no scientific justification to limit the ester possibilities to six carbons or less as significantly larger carbon ester chains would be entirely reasonable and were known in the prior art"; moreover, there are 86 possible mono-ester substitutions having two to six carbons. Ex. 2022 ¶¶ 102–03. "In short, even if a person of ordinary skill in the art would have limited their efforts to ester prodrugs of six carbons or less, it would have been highly unpredictable which, if any, of the thousands of possibilities would achieve that delicate balance of properties." *Id.* ¶ 104; *see also* Ex. 2001, 18 (the district court finding, based on the record before it, that "the inventors' work involved a large amount of trial and error" and "yielded unpredictable results").

We credit Dr. Roush's testimony in this regard. Although we have considered Dr. Patterson's testimony, we disagree that his discounting of the many permutations available and the many steps needed to arrive at the finish line supports Petitioner's arguments. The sheer number of possibilities for substitution narrows the possibility that one of ordinary skill in the art readily could have arrived at the specific ester. Combined with the unpredictability of the properties of the substituted moiety, the likelihood of obviousness narrows further.

c. (R) enantiomer

Finally, Petitioner's claim chart relies on the teaching of Postlind to support its argument that the compound claimed is an (R) enantiomer. Pet. 36–38 (citing Ex. 1010, 289). Patent Owner responds that Petitioner

ignores that claims 3–5[23] recite the (R) or (+) enantiomer of fesoterodine. Resp. 49. Patent Owner further argues that Petitioner's reliance on the preferred enantiomer of tolterodine teaches nothing about determination of the preferred enantiomer of the claimed compound, fesoterodine. *Id.* at 49–50. In a footnote in the Reply, Petitioner argues again that the "prior art taught that tolterodine is an (R) enantiomer," that "5-HMT is also an (R) enantiomer" (citing Ex. 1075, 202:10–18), and because "5-HMT and tolterodine are (R) enantiomers, a skilled artisan would have no reason to develop anything other than an (R) enantiomer." Reply 9 n.4.

As noted in our Institution Decision, we are unpersuaded that Petitioner has ignored the requirement of the (R) or (+) enantiomer, because Petitioner expressly addresses it in the claim charts of its Petition. Inst. Dec. 24–25. In our Institution Decision, however, we indicated that Patent Owner raised "an issue of material fact regarding how an ordinarily skilled artisan would have viewed Postlind's disclosure of the (R) enantiomer of the parent tolterodine compound vis-à-vis chirality of the 5-HMT metabolite and, in turn, fesoterodine fumarate." *Id.* at 24. At this stage of the proceeding, after having considered the arguments in light of the entire record developed during trial, we are not persuaded that Petitioner has met its burden.

Petitioner's Reply footnote presents primarily attorney argument, and references a small portion of the deposition testimony of Dr. Maag in the companion district court case (1:15CV00079-GMS), in which Dr. Maag testified that the (R) enantiomer of tolterodine gets metabolized to 5-HMT, "which is the R-enantiomer." Ex. 1074, 202:10–18. Petitioner does not

[23] As explained above, claims 22 and 23 also require the (R) enantiomer.

present persuasive evidence or argument as to why that statement would have given the skilled artisan "no reason to develop anything other than an (R) enantiomer," let alone address the issue of how Postlind discloses the (R) enantiomer of fesoterodine by disclosing the (R) enantiomer of tolterodine.

Accordingly, we find that Petitioner does not demonstrate, by a preponderance of the evidence, that selecting a prodrug approach to arrive at the (R) enantiomer of a short-chain mono-ester derivative at the 2-position carbon of 5-HMT (e.g., fesoterodine), would have been routine or within the ordinary skill of one in the relevant art.

4. Selecting an Acid Addition Salt

The claims at issue in this proceeding encompass salts of 5-HMT derivatives. Petitioner contends that the claims encompass fumarate salts, and in light of Berge, "the disclosure of an acid addition salt does not render claims 1-5 non-obvious." Pet. 29–30 (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362–63 (Fed. Cir. 2007)). Petitioner appears to extend this argument to method claims 21–24 in its claim charts. *Id.* at 40–43. With respect to method claims 21–24, Petitioner also argues that the combination of Postlind, Bundgaard, Berge, and the Detrol Label would have made the methods of treatment and uses obvious. *Id.* at 38–40.

Patent Owner argues that Berge's general disclosure does not render the claimed salts of fesoterodine, especially the hydrogen fumarate salt form, obvious. Resp. 50; *see id.* at 55 (addressing claims 21–24, directed to methods of treatment with salts of fesoterodine). More particularly, Patent Owner argues that Petitioner fails to provide any evidence why a person of ordinary skill in the art would have even desired a salt form of fesoterodine,

i.e., where the art taught that the freebase form of fesoterodine would be unstable. Resp. 51. Additionally, Patent Owner takes issue with Petitioner's reliance on *Pfizer* and implication "that the Federal Circuit found the use of any previously FDA-approved salt to be *per se* obvious." *Id.* at 51–52. According to Patent Owner, Berge "actually teaches the difficulties of salt selection," and "provides no teaching or direction toward the hydrogen fumarate salt." *Id.* at 52–53.

Patent Owner further argues that the inventor of the '650 patent screened more than 70 salts of fesoterodine, leading "to the discovery of only two viable stable, pure, and crystalline salt forms – hydrogen fumarate and hydrochloride hydrate, a feat he considered to be 'serendipitous.'" *Id.* at 54 (citing Ex. 2025 ¶¶ 16–19); *see also* Tr. 85:11–25 ("one of the hydrochloride attempts was left on the shelf and it got some moisture in it, and just by serendipity they found it started to crystallize. And so based on that, they decided to try conditions where you would actually add water, which you would normally never do with hydrochloride salt form. And that's how they ended up with the hydrochloride hydrate form.") According to Patent Owner, such evidence supports its argument that one of ordinary skill in the art "would have had no reasonable expectation that fesoterodine fumarate would be an effective pharmaceutical, as is required by the method claims, particularly claim 23." Resp. 55.

Petitioner replies that "salt forms came from a limited genus of FDA approved salts," and "developing a salt form of a drug was a matter of routine experimentation as recognized by the Federal Circuit, and taught by the Berge reference." Reply 20. Accordingly, Petitioner argues, "selection

of a fumarate or hydrochloride salt was obvious as a matter of routine optimization." *Id.* at 22.

We are unpersuaded, as discussed above, that fesoterodine is prior art to the '650 patent and, thus, we are unpersuaded that Petitioner has shown that fesoterodine would have been obvious. Without proving that fesoterodine would have been obvious, Petitioner is hard-pressed to prove that a salt form of fesoterodine would have been obvious. The *Pfizer* case cited by Petitioner, although instructive, is distinguishable in that the prior art there disclosed the base compound and a number of its salt forms. 480 F.3d at 1362–63. Moreover, we are persuaded by Patent Owner's proffered testimony that testing and eventual determination of the acceptable salt form of fesoterodine was more than simply routine optimization. The serendipitous circumstances leading to the discovery of the eventual salt forms, as discussed above, underscore the Patent Owner's assertion that "there is *no reliable way of predicting* the influence of a particular salt species on the behavior of a parent compound." Resp. 52–53 (quoting Ex. 1013, 1).

Accordingly, we find that Petitioner fails to demonstrate, by a preponderance of the evidence, that one of ordinary skill in the art would have understood that selecting an acceptable salt form of the mono-ester derivatives of 5-HMT within the scope of the claims was a matter of routine experimentation.

5. Remaining claims

Petitioner's claim charts present separate entries for each of the method claims 21–24. Pet. 40–43. Those entries by and large incorporate the points made in relation to claims 1–5 to the remaining claims. *Id.* The

Petition also presents separate arguments relating to method claims 21–24, summarizing that "skilled artisans would have expected the use of the compound in claim 1 to be quickly metabolized to the active compound, 5-HMT, which was well known to be beneficial for the treatment of urinary incontinence," and urge incontinence. *Id.* at 39–40. Having considered the record before us, none of Petitioner's arguments overcome the shortcomings we have already discussed in the obviousness arguments with respect to the common issues in the context of claims 1–5.

In sum, we not are persuaded that Petitioner demonstrates, by a preponderance of the evidence, that the subject matter of any of challenged claims 1–5 and 21–24 of the '650 patent would have been obvious over the combination of Postlind, Bundgaard Publications, Detrol Label, and Berge.

F. Alleged Obviousness over Brynne, Bundgaard Publications, and Johansson

Petitioner asserts that claims 1–5 and 21–24 would have been obvious over the combination of Brynne, Bundgaard, and Johansson. Pet. 3, 43–53. Patent Owner opposes. Resp. 56–61. The parties' arguments are substantially the same as for Ground I, except with respect to the citation of Brynne in lieu of Postlind and Detrol Label, and Johansson instead of Berge.

Petitioner argues Brynne teaches that 5-HMT was the active metabolite of tolterodine metabolism via the CYP2D6 pathway, and that "a skilled person would have elected to begin with 5-HMT because of its known efficacy and ability to avoid administering tolterodine." Pet. 43–44 (citing Pet. § VII.A). Petitioner further argues that one of ordinary skill would have then sought to modify 5-HMT because Brynne teaches that tolterodine is tenfold more lipophilic than 5-HMT. *Id.*; *see supra* § II.E.2.c

(discussing Petitioner's lipophilicity and bioavailability arguments with respect to modifying 5-HMT).

Petitioner further argues that one of ordinary skill in the art would have selected 5-HMT in lieu of tolterodine because Brynne teaches that "'there was a correlation between tolterodine concentration and the effect on salivation . . . .' Ex. 1011, 538." Pet. 44. Our reading of Brynne fails to support Petitioner's contention. As discussed in Section II.D.2, above, Brynne reports "a weak correlation between tolterodine concentration and effect on salivation," whereas "[a] stronger correlation was seen with [5-HMT] and effect." Ex. 1011, 536; *see also id.* at 529 ("Tolterodine caused a similar decrease in salivation in [extensive and poor 2D6 metabolizer] panels."). Thus, to the extent Brynne suggests any difference in salivation, it teaches that the side effect is *worse* with respect to 5-HMT. *See* Resp. 57–58.

Petitioner relies on Johansson as teaching or suggesting a fumarate salt. Pet. 20, 45. As noted above, the claims at issue in this proceeding encompass salts of 5-HMT derivatives. *See supra* § II.E.4. Petitioner contends that the claims encompass fumarate and hydrochloride salts and, in light of Johansson, a person of ordinary skill in the art "would recognize that the fumarate and hydrochloric salts would obtain the desired stability of the product for administration and handling. Ex. 1003, ¶¶ 131–137." Pet. 21.

Patent Owner responds that Johansson "discloses a large genus of compounds that *does not* include fesoterodine, and therefore teaches nothing about the expected properties of a salt of fesoterodine." Resp. 59.

Petitioner also points to Johansson's disclosure of enantiomers of 3,3-diphenylpropylamines in asserting that the ordinarily skilled artisan would have been led to the (R) enantiomer of the compound. *E.g.*, Pet. 49.

Patent Owner argues that "Johansson *only* stands for the unremarkable proposition that enantiomers of 3,3-diphenylpropylamines were possible" and that this fact "has no bearing on which enantiomer may be preferred or effective, as it is not uncommon for one enantiomer to be active while the other is inactive." Resp. 58–59. Thus, "[t]he mere existence of enantiomers, without more, is not a specific teaching to the (R) enantiomer of fesoterodine, as the law requires." *Id.* at 59.

The issues in Ground I and Ground II are largely coextensive. As noted above with respect to Ground I, we are not persuaded by Petitioner's arguments with respect to the issues before us. *See supra* §§ II.E.2–4. Petitioner's arguments for Ground II are also unpersuasive for the reasons provided in Patent Owner's Response and as discussed above with respect to Ground I.

In sum, based on the arguments and evidence before us, we are not persuaded that Petitioner demonstrates, by a preponderance of the evidence, that the subject matter of any of claims 1–5 and 21–24 of the '650 patent would have been obvious over the combination of Brynne, Bundgaard Publications, and Johansson.

G. Motion to Exclude

We turn next to Patent Owner's Motion to Exclude. *See* Papers 37, 39, 40. Patent Owner seeks to exclude Exhibits 1033–34 and 1036–49 as irrelevant. Paper 37, 1–4. Patent Owner's motion also seeks to expunge

Exhibits 1050–72, which Petitioner filed as supplemental evidence, because they fail to resolve Patent Owner's objections. *Id.* at 4–6.

Petitioner responds that the exhibits sought to be excluded are commercial success evidence relevant to whether an unmet need has been met, and the specific information is relevant to Patent Owner's assertion of unmet need in the marketplace. Paper 39, 2–7. Petitioner further responds that Exhibits 1050–72 should not be expunged, noting that Patent Owner did not file an objection within five business days of the filing and service of those exhibits, but instead seeks to have them expunged in its Motion. *Id.* at 8–9 (citing 37 C.F.R. § 42.64).

Patent Owner replies that Petitioner identifies no precedent supporting its introduction of commercial success evidence. Paper 40, 1–3. Patent Owner also replies that commercial success evidence is not relevant to the nexus between the claimed invention and long-felt need. *Id.* at 3–4. Regarding the request to expunge Exhibits 1050–72, Patent Owner replies that no objection was necessary because Petitioner's supplemental evidence was filed improperly. *Id.* at 4.

We do not affirmatively rely upon Exhibits 1033–34, 1036–49, or 1050–72 in our present determination. Therefore, we need not decide Patent Owner's Motion to Exclude Exhibits 1033–34 and 1036–49 or Patent Owner's request to expunge Exhibits 1050–72, and we dismiss the motion and request as moot.

H. Motion to Seal

Pursuant to the Board's Order of February 16, 2017 (Paper 32), Petitioner filed two exhibits under seal (Exhibits 1073A and 1075A), and the parties filed a Joint Motion to Seal (Paper 34) and a protective order

(*id.* at Addendum). Our Order included the instruction that "[i]f the parties choose to propose a protective order deviating from the default protective order . . . . [a] marked-up comparison of the proposed and default protective orders should be presented as an additional exhibit to the motion, so that differences can be understood readily." Paper 32, 4. The parties did not file a marked-up copy of the proposed protective order for the Board's consideration.

Accordingly, the joint motion to seal is *granted* and the default protective order is *entered*.

There is an expectation that information will be made public where the information is identified in a final written decision, and that confidential information that is subject to a protective order ordinarily would become public 45 days after final judgment in a trial, unless a motion to expunge is granted. 37 C.F.R. § 42.56; Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,761 (Aug. 14, 2012). In rendering this Final Written Decision, it was not necessary to identify, nor discuss in detail, any confidential information. However, a party who is dissatisfied with this Final Written Decision may appeal the decision pursuant to 35 U.S.C. § 141(c), and has 63 days after the date of this decision to file a notice of appeal. 37 C.F.R. § 90.3(a). Thus, it remains necessary to maintain the record, as is, until resolution of an appeal, if any.

In view of the foregoing, the confidential documents filed in the instant proceeding will remain under seal, at least until the time period for filing a notice of appeal has expired or, if an appeal is taken, the appeal process has concluded. The record for the instant proceeding will be preserved in its entirety, and the confidential documents will not be

expunged or made public, pending appeal. Notwithstanding 37 C.F.R. § 42.56 and the Office Patent Trial Practice Guide, neither a motion to expunge confidential documents nor a motion to maintain these documents under seal is necessary or authorized at this time. *See* 37 C.F.R. § 42.5(b).

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner does not establish, by a preponderance of the evidence, that claims 1–5 and 21–24 of the '650 patent are unpatentable under 35 U.S.C. § 103.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner does not establish, by a preponderance of the evidence, that claims 1–5 and 21–24 of the '650 patent are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is *dismissed* as moot as to Exhibits 1033–34, 1036–49, and 1050–72;

FURTHER ORDERED that the parties' Joint Motion to Seal is *granted* and the Board's default protective order *entered*; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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