IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

| | | |
|---|---|---|
| PFIZER INC. and UCB PHARMA GMBH, | ) | |
| Plaintiffs, | ) | |
| v. | ) | C.A. No. 15-79-GMS |
| MYLAN PHARMACEUTICALS INC., | ) | |
| Defendant. | ) | |

**MEMORANDUM**

## I. INTRODUCTION

In this Hatch-Waxman patent infringement action, plaintiffs Pfizer Inc. and UCB Pharma GmbH (collectively, "Pfizer" or "Plaintiffs") allege that Mylan Pharmaceuticals Inc. ("Mylan" or "Defendant") infringes the asserted claims of the patents-in-suit. The court held a three-day bench trial in this matter beginning on January 23, 2017. Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the patents-in-suit, specifically whether the asserted claims are invalid as obvious under 35 U.S.C. § 103. (D.I. 80; D.I. 81.)

Pursuant to Federal Rule of Civil Procedure 52(a), having considered the entire record in this case and the applicable law, the court concludes that none of asserted claims of the patents-in-suit are invalid due to obviousness. These findings of fact and conclusions of law are set forth in further detail below.

## II. FINDINGS OF FACT[1]

### A. The Parties

1. Plaintiff Pfizer Inc. is a corporation organized and existing under the laws of Delaware, having a place of business at 235 East 42nd Street, New York, New York.

2. Plaintiff UCB Pharma GmbH is an entity organized and existing under the laws of Germany, having a place of business at Alfred-Nobel-Strasse 10, Monheim, Germany.

3. Defendant Mylan Pharmaceuticals Inc.") is a corporation organized and existing under the law of West Virginia, having principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505-4310.

4. The court has subject matter jurisdiction and personal jurisdiction over all parties.

### B. Background

5. Pfizer Inc. holds an approved New Drug Application ("NDA") No. 02-2030 under Section 505(a) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for fesoterodine fumarate extended-release tablets, in 4 and 8 mg dosage strengths, which Pfizer sells under the trade name Toviaz®.

6. Toviaz® was approved by the United States Food and Drug Administration ("FDA") in October 2008 for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

7. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, U.S. Patent Nos. 6,858,650 (the "'650 patent"), 7,384,980 (the "'980 patent"), 7,855,230 (the "'230 patent"), 7,985,772 (the "'772 patent), and 8,338,478 (the "'478 patent") (collectively, the "patents-in-suit") are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Toviaz®.

8. Mylan filed Abbreviated New Drug Application No. 20-6701 ("Mylan's ANDA") to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to market a generic version of fesoterodine fumarate extended release tablets in 4 and 8 mg dosage strengths.

9. Chemical names for fesoterodine fumarate include:

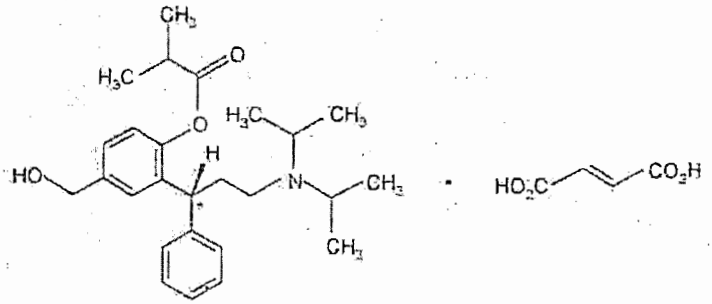
---

[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 75, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in Part III this opinion ("Discussion and Conclusions of Law"), preceded by the phrase "the court finds" or "the court concludes."

a. Isobutyricacid2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-hydroxymethylphenyl ester hydrogen fumarate;
b. R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate;
c. R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate;
d. R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate; and
e. R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester hydrogen fumarate.

10. The structural formula of fesoterodine fumarate is:




The asterisk (*) indicates the chiral carbon.

## C. The Patents-in-Suit

11. Collectively, the '980, '230, '772, and '478 patents may be referred to as the "Compound Patents."

12. The Compound Patents each issued from common parent applications, each of which ultimately claim priority to European Application No. 98108608.5, filed May 12, 1998.

13. The '980 patent issued on June 10, 2008 and is entitled "Derivatives of 3,3-Diphenylpropylamines." The '980 patent names Claus Meese and Bengt Sparf as inventors.

14. The '230 patent issued on December 21, 2010 and is entitled "Derivatives of 3,3-Diphenylpropylamines." The '230 patent names Claus Meese and Bengt Sparf as inventors.

15. The '772 patent issued on July 26, 2011 and is entitled "Derivatives of 3,3-Diphenylpropylamines." The '772 patent names Claus Meese and Bengt Sparf as inventors.

16. The '478 patent issued on December 25, 2012 and is entitled "Derivatives of 3,3-Diphenylpropylamines." The '478 patent names Claus Meese and Bengt Sparf as inventors.

17. The '650 patent issued on February 22, 2005 and is entitled "Stable Salts of Novel Derivatives of 3,3-Diphenylpropylamines." The parties refer to the '650 patent as the "Salt

Patent." It claims priority to German Patent Application No. DE 199 55 190 filed November 16, 1999. The '650 patent names Claus Meese as the inventor. Schwarz Pharma AG holds title to the '650 patent, and has granted Pfizer Inc. an exclusive license to the patent.

**(1) The Asserted Claims**

18. Pfizer has asserted infringement of claims 1-5, and 21-24 of the '650 patent against Mylan.

19. Pfizer has asserted infringement of claims 1-16 of the '980 patent against Mylan.

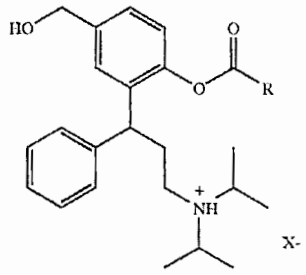
20. Pfizer has asserted infringement of claims 1-5 of the '230 patent against Mylan.

21. Pfizer has asserted infringement of claims 1, 3, 4, 6-8 of the '772 patent against Mylan.

22. Pfizer has asserted infringement of claims 1-3, 5-8, 10-12 of the '478 patent against Mylan.

*i. '650 Patent, Claim 1*

23. Claim 1 of the '650 patent claims: Compounds of general formula I




in which R denotes $C_1$-$C_6$-alkyl, $C_3$-$C_{10}$-cycloaklkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid" of claim 1 has its plain and ordinary meaning.

24. The term "[c]ompounds of general formula I in which R denotes $C_1$-$C_6$-alkyl, $C_3$-$C_{10}$-cycloaklkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid" of claim 1 has its plain and ordinary meaning. *Pfizer Inc. and UCB Pharma GmbH v. Alkem Labs. Ltd., et al.*, Civil Action No. 13-111-GMS (D.I. 168.)

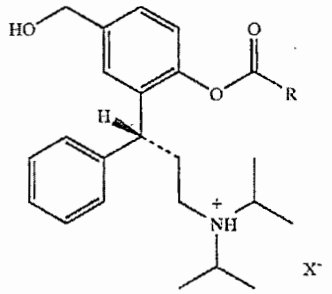
*ii. '650 patent, Claim 2*

25. Claim 2 of the '650 patent claims: Compounds in accordance with Claim 1, characterized in that X- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+) –tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)- glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid,

gallic acid, hippuric acid (N – benzoyl-glycine), aceturic acid (Naectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

*iii. '650 Patent, Claim 3*

26. Claim 3 of the '650 Patent claims: Compounds in accordance with claims [sic] 1, characterized in that they have general formula 2




in which R denotes C1-C6-alkyl, C3-C10-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

*iv. '650 Patent, Claim 4*

27. Claim 4 of the '650 Patent claims: Compounds 26. in accordance with Claim 3, characterized in that X- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+) -tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)- glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N -benzoyl-glycine), aceturic acid (Naectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

*v. '650 Patent, Claim 5*

28. Claim 5 of the '650 Patent claims: Compounds in accordance with claims [sic] 3, characterized in that they are R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate, R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate.

*vi. '650 Patent, Claim 21*

29. Claim 5 of the '650 Patent claims: Compounds in accordance with claims [sic] 3, characterized in that they are R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4 hydroxymethylphenylisobutyrate ester hydrogen fumarate, R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate.

30. Claim 21 of the '650 Patent claims: A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 1.

*vii. '650 Patent, Claim 22*

31. Claim 22 of the '650 Patent claims: A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 3.

*viii. '650 Patent, Claim 23*

32. Claim 23 of the '650 Patent claims: A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 5.

*ix. '650 Patent, Claim 24*

33. Claim 24 of the '650 Patent claims: The method of any one of claims 21-23, wherein the urinary incontinence disorder is urge incontinence."

*x. '980 Patent, Claim 1*

34. Claim 1 of the '980 patent claims: R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

*xi.* '980 Patent, Claim 2

35. Claim 2 of the '980 patent claims: A salt of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenyl propyl)-4-hydroxymethylphenyl ester with a physiologically acceptable acid.

*xii.* '980 Patent, Claim 3

36. Claim 3 of the '980 patent claims: A pharmaceutical composition comprising an effective amount of R-(+ )-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, or a salt thereof with a physiologically acceptable acid and a pharmaceutically acceptable carrier.

*xiii. '980 Patent, Claim 4*

37. Claim 4 of the '980 Patent claims: A method of antagonizing a muscarinic receptor in a patient in need thereof, the method comprising administering to the patient R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a salt thereof with a physiologically acceptable acid so as to result in contact of the muscarinic receptor with an effective amount of R -(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol.

*xiv. '980 Patent, Claim 5*

38. Claim 5 of the '980 Patent claims: A method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering to the mammal a pharmaceutical composition comprising an effective amount of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a salt thereof with a physiologically acceptable acid.

*xv. '980 Patent, Claim 6*

39. Claim 6 of the '980 Patent claims: The method according to claim 5 wherein the disease is urinary incontinence.

*xvi. '980 Patent, Claim 7*

40. Claim 7 of the '980 Patent claims: The method according to claim 6 wherein the mammal is a human.

*xvii. '980 Patent, Claim 8*

41. Claim 8 of the '980 Patent claims: A compound selected from the group consisting of: acetic acid 4-acetoxy-3-(3-diisopropylamino- 1-phenylpropyl)-benzyl ester, n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl )-4-isobutyryloxymethylphenyl ester, n-butyric acid 4-nbutyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

*xviii. '980 Patent, Claim 9*

42. Claim 9 of the '980 Patent claims: The compound of claim 8 where the compound is selected from the group consisting of: n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropy 1)-4-hydroxymethylphenyl ester, propionic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester, and acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

*xix. '980 Patent, Claim 10*

43. Claim 10 of the '980 Patent claims: A pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: acetic acid 4-acetoxy-3-(3-

diisopropylamino-1-phenylpropyl)-benzyl ester, n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl )-4-isobutyryloxymethylphenyl ester, n-butyric acid 4-nbutyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid, and a pharmaceutically acceptable carrier.

*xx. '980 Patent, Claim 11*

44. Claim 11 of the '980 Patent claims: The pharmaceutical composition of claim 10 where the compound is selected from the group consisting of: n-butyric acid 2-(3-diisopropylamino-1aphenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

*xxi. '980 Patent, Claim 12*

45. Claim 12 of the '980 Patent claims: A method of treating a disease or condition in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering to the mammal a pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of: acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, nbutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, n-butyric acid 4-nbutyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

*xxii. '980 Patent, Claim 13*

46. Claim 13 of the '980 Patent claims: The method of claim 12 where the compound is selected from the group consisting of: n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-

hydroxymethylphenyl ester, including racemic mixtures and individual enantiomers of said compounds, and salts of said compounds with a physiologically acceptable acid.

*xxiii. '980 Patent, Claim 14*

47. Claim 14 of the '980 Patent claims: The method of claim 12 or 13 where the disease or condition is a spasmogenic condition that is caused by a muscarinic mechanism.

*xxiv. '980 Patent, Claim 15*

48. Claim 15 of the '980 Patent claims: The method of claim 12 or 13 where the disease or condition is urinary incontinence.

*xxv. '980 Patent, Claim 16*

49. Claim 16 of the '980 Patent claims: The method of claim 15 where the mammal is a human.

*xxvi. '230 Patent, Claim 1*

50. Claim 1 of the '230 Patent claims: A method of treating urinary incontinence in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound selected from the group consisting of: n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including the racemic mixtures and individual enantiomers of said compounds, and a salt of said compounds with a physiologically acceptable acid.

*xxvii. '230 Patent, Claim 2*

51. Claim 2 of the '230 Patent claims: The method according to claim 1, wherein the compound is isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including the racemic mixture and individual enantiomers of said compound, and a salt of said compound with a physiologically acceptable acid.

*xxviii. '230 Patent, Claim 3*

52. Claim 3 of the '230 Patent claims: The method according to claim 1, wherein the compound is R-(+) isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

*xxix. '230 Patent, Claim 4*

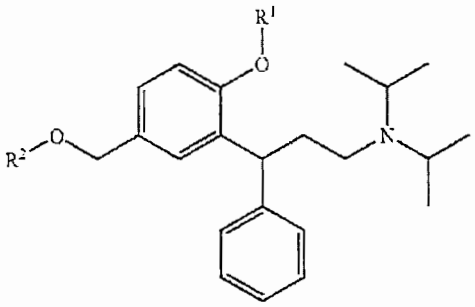
53. Claim 4 of the '230 Patent claims: The method according to claim 1, wherein the compound is a salt of R-(+) isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

*xxx. '230 Patent, Claim 5*

54. Claim 5 of the '230 Patent claims: The method according to any one of claims 1-4, wherein the compound is administered to the patient in the form of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

*xxxi. '772 Patent, Claim 1*

55. Claim 1 of the '772 Patent claims: 3,3-Diphenylpropylamines of the general formula:



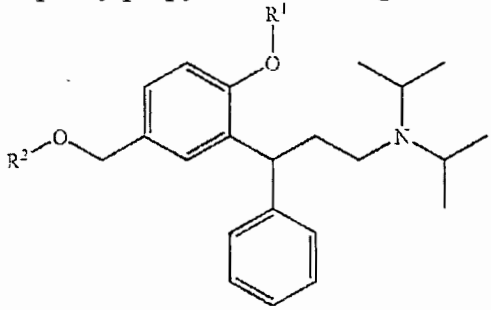
wherein R1 is hydrogen and R2 is C1-C6 alkylcarbonyl; or R1 is C1-C6 alkylcarbonyl and R2 is hydrogen; their salts with physiologically acceptable acids, their free bases and, when the 3,3-Diphenylpropylamines are in the form of optical isomers, the racemic mixture and the individual enantiomers.

*xxxii. '772 Patent, Claim 3*

56. Claim 3 of the '772 Patent claims: The 3,3-Diphenylpropylamine of claim 1 wherein R1 is C1-C6 alkylcarbonyl and R2 is hydrogen.

*xxxiii. '772 Patent, Claim 4*

57. Claim 4 of the '772 Patent claims: A method of treating urinary incontinence in a patient in need thereof, the method comprising administering to the patient an effective amount of a 3,3-Diphenylpropylamine of the general formula:



wherein: R1 is hydrogen and R2 is C1-C6 alkylcarbonyl; or R1 is C1-C6 alkylcarbonyl and R2 is hydrogen; or its salt with a physiologically acceptable acid, its free base or, when the 3,3

Diphenylpropylamine is in the form of optical isomers, the racemic mixture and the individual enantiomers."

*xxxiv. '772 Patent, Claim 6*

58. Claim 6 of the '772 Patent claims: The method of claim 4 whereinR1 is C1-C6 alkylcarbonyl and R2 is hydrogen.

*xxxv. '772 Patent, Claim 7*

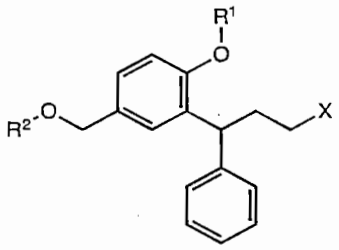
59. Claim 7 of the '772 Patent claims: The method according to any one of claims 4-6, wherein the 3,3-Diphenylpropylamine is administered to the patient in the form of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

*xxxvi. '772 Patent, Claim 8*

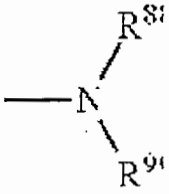
60. Claim 8 of the '772 Patent claims: A pharmaceutical composition comprising an effective amount of a 3,3-Diphenylpropylamine according to any one of claims 1-3 and a pharmaceutically acceptable carrier.

*xxxvii. '478 Patent, Claim 1*

61. Claim 1 of the '478 Patent claims: 3,3-Diphenylpropylamines of the formula




where: R1 is hydrogen and R2 is C1-C6 alkylcarbonyl; or R1 is C1-C6 alkylcarbonyl and R2 is hydrogen; and X is a tertiary amino group of formula



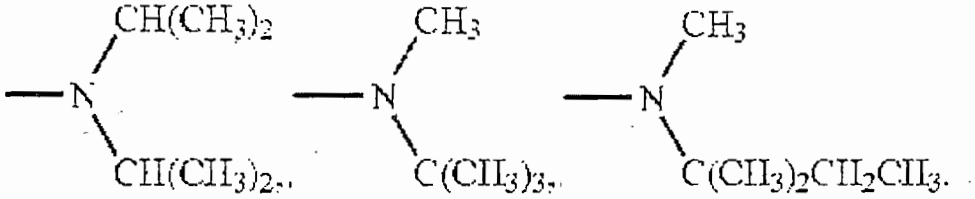

where R8 and R9 are each independently C1-C8 alkyl and together comprise at least three carbon atoms; their salts with physiologically acceptable acids, their free bases and, when the 3,3-Diphenylpropylamines are in the form of optical isomers, the racemic mixture and the individual enantiomers.

*xxxviii. '478 Patent, Claim 2*

62. Claim 2 of the '478 Patent claims: The 3,3-Diphenylpropylamines of claim 1, where R8 and R9 are each independently C1-C6 alkyl.

*xxxix. '478 Patent, Claim 3*

63. Claim 3 of the '478 Patent claims: The 3,3-Diphenylpropylamines of claim 1, where X is selected from the group consisting of:

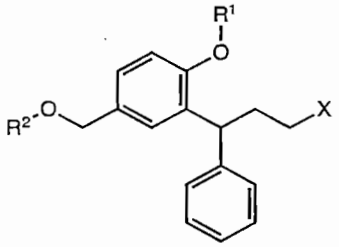


*xl. '478 Patent, Claim 5*

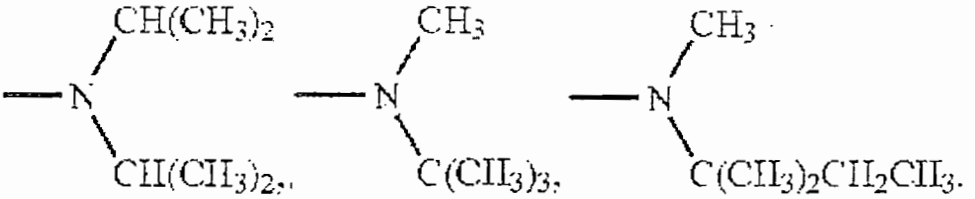
64. Claim 5 of the '478 Patent claims: The 3,3-Diphenylpropylamines of claim 1 wherein R1 is C1-C6 alkylcarbonyl and R2 is hydrogen.

*xli. '478 Patent, Claim 6*

65. Claim 6 of the '478 Patent claims: A method of treating urinary incontinence in a patient in need thereof, the method comprising administering to the patient an effective amount of a 3,3-Diphenylpropylamine of the formula



where: R1 is hydrogen and R2 is C1-C6 alkylcarbonyl; or R1 is C1-C6 alkylcarbonyl and R2 is hydrogen; and X is a tertiary amino group of formula



where R8 and R9 are each independently C1 -C8 alkyl and together comprise at least three carbon atoms; or its salt with a physiologically acceptable acid, its free base or, when the 3,3-

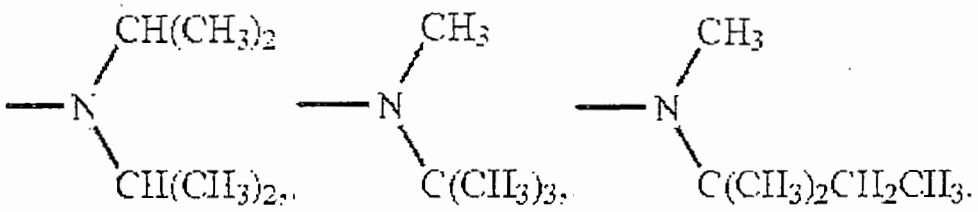
Diphenylpropylamine is in the form of optical isomers, the racemic mixture and the individual enantiomers.

*xlii. '478 Patent, Claim 7*

66. Claim 7 of the '478 Patent claims: 96. The method of claim 6 wherein R8 and R9 are each independently C1-C6 alkyl.

*xliii. '478 Patent, Claim 8*

67. Claim 8 of the '478 Patent claims: The method of claim 6 where X is selected from the group consisting of:



*xliv. '478 Patent, Claim 10*

68. Claim 10 of the '478 Patent claims: The method of claim 6 where R1 is C1-C6 alkylcarbonyl and R2 is hydrogen."

*xlv. '478 Patent, Claim 11*

69. Claim 11 of the '478 Patent claims: The method of claim 6, where the 3,3-Diphenylpropylamine is administered to the patient in the form of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

*xlvi. '478 Patent, Claim 12*

70. Claim 12 of the '478 Patent claims: A pharmaceutical composition comprising an effective amount of a 3,3-Diphenylpropylamine according to any one of claims 1-5 and a pharmaceutically acceptable carrier.

**(2) <u>The Accused Product</u>**

*i. ANDA No. 20-6701 Submitted by Mylan*

71. Mylan submitted Abbreviated New Drug Application No. 20-6701 ("Mylan's ANDA") to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to market a generic version of fesoterodine fumarate extended release tablets in 4 and 8 mg dosage strengths ("Mylan's Product").

72. Mylan's ANDA refers to and relies upon the Toviaz® NDA and contains data that, according to Mylan, demonstrates that Mylan's Product is bioequivalent to Toviaz®.

73. Mylan included certifications in its ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '650, '980, '230, '772, and '478 patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of Mylan's Product.

74. On December 11, 2014, Mylan sent Notice of its Paragraph IV certifications to Plaintiffs, providing its asserted factual and legal bases for its contentions that the '650, '980, '230, '772, and '478 patents are not infringed, invalid or unenforceable.

75. In response to Mylan's Notice, on January 23, 2015, Plaintiffs sued Mylan for infringement of the '650, '980, '230, '772, and '478 patents, pursuant to 35 U.S.C. § 271(e)(2)(A).

### D. Procedural History

76. On January 23, 2015, Plaintiffs sued Mylan for patent infringement related to ANDA No. 20-6701 under Civil Action No. 15-79.

77. The court held a bench trial on January 23, January 25, and January 26, 2017. Mylan argued that all asserted claims are invalid as obvious under 35 U.S.C. § 103. Mylan stipulated to infringement on all asserted claims of all asserted patents.

78. At the close of Plaintiffs' prima facie case for invalidity of the asserted patents, Mylan moved pursuant to Federal Rule of Civil Procedure 52(c) for judgment on partial findings on the issue of obviousness. (Tr. 408:1-5.) The court denied Pfizer's motion. (Tr. 408:6-8.)

## III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). Mylan challenges the validity of each of the asserted claims of the patents-in-suit as obvious in light of the prior art. After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that the defendant has failed to establish by clear and convincing evidence that the asserted claims of the asserted patents would have been obvious to a person of ordinary skill in the art. Pfizer's Rule 52(c) motion is granted and Mylan's Rule 52(c) motion is denied. The court's reasoning follows.

### A. The Legal Standard

35 U.S.C. § 103(a) provides that a patent may not be obtained "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 having ordinary skill in the art." Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"A patent shall be presumed valid." 35 U.S.C. § 282. A party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence[2] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit teaching, suggestion, or motivation in the prior art, the "TSM test," in order to find obviousness. *See id.* at 415. The *KSR* Court acknowledged, however, the importance of

[2] "Clear and convincing evidence is evidence that places in the fact finder an abiding conviction that the truth of [the] factual contentions are highly probable." *Alza Corp v. Andrx Pharms., LLC,* 607 F. Supp. 2d 614, 631 (D. Del. 2009) (internal quotations omitted) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

identifying "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." *Id.* at 418.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

**B. The Level of Ordinary Skill in the Art**

A person of ordinary skill in the art ("POSA") with respect to the patents-in-suit would have a Ph.D. in chemistry, medicinal chemistry, pharmacology, or a related field.[3] Additional experience in drug discovery, drug synthesis, and structure-activity work could substitute for the advanced degree. A POSA would further have knowledge of bladder physiology and overactive bladder. The court concludes that the parties' definitions of a person of ordinary skill in the art do not differ in a meaningful way.

[3] Plaintiffs' identification of a person of ordinary skill in the art is derived from Dr. Maag and Dr. Roush. (Tr. 415:18-24 (Maag); Tr. 531:4-15 (Roush).) Defendant's identification of a person of skill in the art is derived from Dr. Janero. (Tr. 259:10-260:2 (Janero).)

### C. The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

Mylan argues a POSA would have found it obvious to synthesize fesoterodine as an improved overactive bladder treatment. Mylan bases its theory on the prior art molecule tolterodine and its metabolite, 5-Hydroxymethyl Tolterodine ("5-HMT"). To determine whether the Defendant has established a prima facie case of obviousness, the court must determine (1) "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for future development efforts"; and (2) whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012).

#### (1) 5-HMT as a Lead Compound

Mylan argues a POSA would have selected 5-HMT as a lead compound for an improved overactive bladder treatment. (D.I. 80 at 8.) As of the May 12, 1998 priority date, overactive bladder treatments included negative limitations such as urinary retention, dry mouth, constipation, and central nervous system effects. (D.I. 81 at 5-6.) According to Mylan, a POSA seeking to create an improved overactive bladder drug would have focused on antimuscarinic compounds. Antimuscarninc compounds block the neurotransmitter acetylcholine from binding to one or more of the five types of muscarinic receptors found in the body. Both parties agree that antimuscarinics were a popular treatment for overactive bladder at that time. (D.I. 80 at 7; D.I. 81 at 5.) Oxybutynin and tolterodine were the primary antimuscarinic compounds approved to treat overactive bladder in the United States. (Tr. at 112:4-17, 116:4-7 (Carson).) Mylan contends that because the prior art detailed the efficacy and safety of 5-HMT as associated with tolterodine administration, a person of skill in the art would have been motivated to choose 5-HMT for further

development. (D.I. 80 at 8.) Lead compound analysis "requires the challenger to demonstrate . . . that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art." *Daiichi Sankyo Co. v. Matrix Labs., Ltd*, 619 F.3d 1346, 1354 (Fed. Cir. 2010).

Mylan's lead compound theory is flawed for several reasons. First, Mylan failed to justify its expert's narrow focus on tolterodine and 5-HMT. Pfizer's expert, Dr. Maag, testified that researchers eschewed nonselective antimuscarinic compounds and were actively pursuing a number of different strategies in search of improved overactive bladder treatments. (Tr. 417:9-421:5, 422:10-25 (Maag).) In contrast, Mylan's expert, Dr. Carson, posited that 5-HMT seemed to be "at the forefront" of overactive bladder compounds, which made it prime for further investigation. (Tr. 146:15-23 (Carson).) Dr. Carson's lead compound analysis strikes the court as somewhat constrained. For example, Dr. Maag testified that the state of the art design approaches were directed to (1) receptor subtype-selective antimuscarinics (PTX-510; PTX- 271; PTX-666) and (2) alternative mechanisms of action (PTX-666; PTX-104). (Tr. 417:9-412:5 (Maag).)[4] In addition, Dr. Carson acknowledged that nothing in the prior art suggested administering 5-HMT to patients, which contradicts focusing on 5-HMT as a lead compound. (Tr. 155:8-15 (Carson).) The court finds Dr. Maag's testimony more persuasive because it is consistent with the field of overactive bladder treatment as of the priority date. The court therefore concludes that a POSA would have considered tolterodine and 5-HMT in addition to several other lead compounds.

Second, even if a person of skill in the art would have focused on tolterodine and 5-HMT, tolterodine did not have problems that would have caused a POSA to develop 5-HMT. Mylan

[4] The court notes that Dr. Maag identified specific M3 receptor-selective compounds—darifenacin (PTX-271) and solifenacin (PTX-48). (D.I. 81 at 7.) He also delineated the alternative mechanisms of action as: (1) compounds having both antimuscarinic and calcium antagonistic activity; (2) potassium channel agonists; and (3) compounds acting on adrenoceptors. (Tr. 420:3-8 (Maag).)

contends that the metabolism of tolterodine to arrive at 5-HMT presented a concern. (D.I. 80 at 9.) Mylan relies on the Nilvebrant (DTX-50) and Postlind (DTX-35) prior art publications to support this assertion. Nilvebrant disclosed that the activity profile of 5-HMT was identical to tolterodine and reported 5-HMT was significantly more potent at inhibiting bladder contractions in an in vivo analysis. (Tr. 247:7-22 (Janero).) Postlind confirms that the most common metabolic pathway utilizes CYP2D6 to convert tolterodine to 5-HMT. (Tr. 250:15-251:4 (Janero).) Dr. Janero explained that patients known as extensive metabolizers utilize this metabolic pathway. (Tr. 251:5-8 (Janero).) Further, the evidence showed that tolterodine is also metabolized via an alternative metabolic pathway that is mediated by a CYP3A4. (DTX-35) Patients that are poor metabolizers utilize this second pathway. (Tr. 251:23-252:17 (Janero).) According to Dr. Janero, because tolterodine is metabolized via the CYP2D6 pathway and CYP2D6 polymorphism can adversely affect the metabolism of a given drug, a POSA would have sought to dose "a potent muscarinic antagonist without the involvement of CYP2D6." (Tr. 252:18-253:18 (Janero).)

In response, Pfizer argues that a POSA would not have ignored the prior art references that taught polymorphism was *not* a problem for tolterodine because poor and extensive metabolizers experienced nearly identical effects from the drug. (Tr. 423:13-17 (Maag); Tr. 589:3-14 (MacDiarmid).) Particularly, Pfizer points to the teachings of the Detrol Label (DTX-34), Brynne reference (DTX-39), and Nilvebrant reference (DTX-50). The Detrol Label taught that "the net activity of DETROL Tablets is expected to be similar in extensive and poor metabolizers." (DTX-34 at 2.) The Brynne reference (DTX-39) disclosed that "[d]espite the influence of CYP2D6 polymorphism on the pharmacokinetics of tolterodine, this does not appear to be of great pharmacodynamics importance." (DTX-39 at 10.) The Nilvebrant reference concluded that "the pharmacological *in vitro* and *in vivo* profiles of [5-HMT] are almost identical to those of

tolterodine, the parent compound." (DTX-50 at 4.) Mylan's expert, Dr. Janero, supported the conclusion that there is no evidence that any POSA would have disregarded these conclusions, undermining the weight of Mylan's assertions. (Tr. 361:6-12 (Janero).) The court believes that a POSA would not have disregarded these conclusions. Thus, the court concludes that polymorphism would not have motivated a POSA to shift focus from tolterodine to its metabolite, 5-HMT.

Third, Mylan argues that a POSA would have focused on 5-HMT instead of tolterodine because tolterodine was associated with certain side effects not attributable to 5-HMT. (D.I. 80 at 10.) In support of this contention, Mylan relied on the Brynne reference. (DTX-39.) According to this reference, tolterodine likely caused heart rate issues; visual accommodation; and was ten times more lipophilic than 5-HMT. (D.I. 80 at 11.) Mylan contends that a POSA would have recognized that the lipophilic profile would have likely permitted tolterodine to cross the blood-brain barrier leading to adverse side effects, such as headache, paresthesia, dizziness, and nervousness, which are identified as treatment related side effects in clinical reports and the FDA label for tolterodine. (*Id.*; Tr. 130:3-18 (Carson).)

The court is not persuaded. Dr. Carson's testimony undermines the credibility of Mylan's assertions. Dr. Carson admitted that the clinical data considered tolterodine and 5-HMT together and, as a clinician, he knew of no differences between the two compounds. (Tr. 132:24-133:6 (Carson).) Moreover, Dr. Maag testified that a POSA would have expected the benefits and limitations associated with tolterodine to also be associated with 5-HMT. (Tr. 449:10-14 (Maag).) At minimum, given the state of the art, a POSA could not have drawn inferences about whether tolterodine or 5-HMT was driving any one of the side effects. (Tr. 358:19-359:8 (Janero).)

Finally, Mylan suggests that tolterodine's metabolism via the CYP3A4 pathway in poor metabolizers was a potential problem to solve. (D.I. 80 at 12.) Mylan relies on the Detrol® label, which discloses that "[p]atients receiving cytochrome P450 3A4 inhibitors should not receive doses of DETROL greater than 1 mg twice daily." (DTX-34 at 5.) Mylan's expert, Dr. Carson, points out that the Appell reference (DTX-238) teaches that 1 mg twice daily is statistically less effective than the higher dosage of tolterodine. (Tr. 125:21-126:6 (Carson).) In light of this prior art, Mylan asserts that a POSA would have been motivated to eliminate dosing a compound such as tolterodine from the metabolic pathway responsible for delivering 5-HMT to the body. (D.I. 80 at 12.) The evidence adduced at trial established that if a patient takes multiple CYP3A4 drugs, including tolterodine, there may be a reduction in the metabolism of tolterodine. (D.I. 81 at 11.) This reduced metabolism of tolterodine may lead to an accumulation of tolterodine in the system, in addition to other drugs a patient is taking, resulting in adverse effects. (*Id.*) Mylan's own experts concede, however, that if CYP3A4 metabolism had been a real concern, a POSA would have also rejected 5-HMT since 5-HMT is also metabolized via the CYP3A4 pathway. (Tr. 165:14-25 (Carson); Tr. 359:16-23 (Janero).) Put simply, if 3A4 metabolism was a concern for tolterodine, it also would have been for 5-HMT. Mylan's argument is to the contrary is unconvincing. Thus, the court rejects Mylan's arguments as to the selection of a lead compound, and concludes that Mylan has failed to meet its burden in this regard.

**(2) Modification of 5-HMT**

Even accepting Mylan's selection of 5-HMT as lead compound, the court finds that Mylan has not established by clear and convincing evidence that modifying the lead to yield fesoterodine would have been obvious to a POSA. *See Daiichi*, 619 F.3d 1346 at1352 ("Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of

ordinary skill would have been motivated to select and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old.").

Mylan argues that a POSA would have sought to develop a new prodrug[5] of 5-HMT that would have similar absorption to tolterodine, but that had less CNS penetration, and did not exhibit variable bioavailability. (Tr. 284:12-285:12 (Janero).) Prodrug strategies were known options for modifying the lipophilicity, hydrophilicity, and solubility of drug compounds. (Tr. 288:1-12 (Janero).) Mylan therefore argues that a POSA would have expected that creating a new prodrug of 5-HMT would yield a compound with similar, but improved properties over tolterodine and 5-HMT.

In contrast, Pfizer offered evidence that 5-HMT's oral absorption properties were, and still are, unknown. (Tr. 421:18-422:1, (Maag); Tr. 536:10-20 (Roush); Tr. 155:8-15, 162:10-12 (Carson).) Nonetheless, Pfizer contends that, based on 5-HMT's properties, a POSA would have expected 5-HMT to be well absorbed. (D.I. 81 at 12.) The evidence adduced at trial established that 5-HMT is "bracketed" by many other compounds that are significantly more and significantly less lipophilic, but which are well absorbed orally. (Tr. 510:7-511:22 (Roush).) Dr. Roush testified that a POSA would have observed 5-HMT amongst the previously noted compounds that are sufficiently bioavailable and would have identified no reason to assume poor oral absorption associated with 5-HMT. (Tr. 511:19-22 (Roush).) Dr. Roush also testified that the Lipinski Rule of Five[6] shows 5-HMT is safely within each of the Rule's four criteria, indicating that nothing

[5] "Prodrug design comprises an area of drug research that is concerned with the optimization of drug delivery. A prodrug is a pharmaceutically inactive derivative of a parent 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." (DTX-41 at 5.)

[6] The Lipinski Rule of Five, designed and published in 1997 to identify candidate compounds with the potential for poor absorption, is derived from a seminal paper in the field of medicinal chemistry. (D.I. 81 at 12.)

about its structure suggests that 5-HMT would have oral absorption problems. (Tr. 513:9-515:8 (Roush).) Given that 5-HMT was "bracketed" by other well-absorbed compounds, satisfied the Rule of Five, and in the absence of data to the contrary, a POSA would have expected 5-HMT to be well-absorbed orally and would not have seen a reason to modify the compound to alter its absorption properties.

Pfizer also adduced evidence that POSAs viewed prodrug design as a complex "last resort" approach to drug development because of: (1) stability concerns in drug manufacture, in formulation, and in the body, (Tr. 431:6-13 (Maag)); (2) higher potential for negative side effects due to multiple chemical entities/moieties, (Tr. 432:8-17 (Maag)); and (3) risk of premature metabolism, (Tr. 431:17-25 (Maag). Drs. Roush and Maag testified that POSAs would have considered developing a prodrug only after satisfaction of the following conditions: (1) a clearly defined and understood problem requiring use of a prodrug, (Tr. 441:14-22 (Maag); Tr. 508:7-14 (Roush); PTX-623 at 14); (2) well-understood pharmacokinetics of the active compound, (Tr. 439:21-440:3 (Maag); Tr. 508:7-14 (Roush); PTX-616 at 7); and (3) a meaningful clinical advantage presented by the prodrug, (Tr. 440:9-13 (Maag); PTX-616 at 7). Pfizer argues that the prior art depicted 5-HMT as an unattractive prodrug candidate, as it failed to meet any of the requirements outlined by Drs. Maag and Roush. (Tr. 430:6-15 (Maag) (no known issue with 5-HMT); Tr. 439:21-440:3 (Maag) (pharmacokinetics not well understood); (Tr. 423:2-10 (Maag) (no meaningful clinical advantage because most patients already exposed to 5-HMT).)

Lastly, Pfizer contends that a POSA would have first pursued non-prodrug development approaches, such as performing structural modifications to create an analog of tolterodine, or experimenting with the formulation of 5-HMT. (Tr. 503:17-504:14 (Roush) (describing structural

(PTX-252). Specifically, the Lipinski Rule of Five entails analyzing four different physical properties of a compound to evaluate its potential to be orally available. (Tr. 512:7-513:3 (Roush).)

analogs as the "bread and butter of the activities of medicinal chemist everywhere"); Tr. 506:7-507:23 (Roush) (describing formulation approaches)). The court agrees with Pfizer. The dearth of information about 5-HMT's properties, the inherent risk associated with prodrug development, and the existence of more straightforward optimization techniques all suggest that a prodrug approach would not have been obvious.

**(3) Chemical Structure of Fesoterodine**

Even accepting Mylan's proposal that it would have been obvious to create a new 5-HMT prodrug, the court does not find it would have been obvious to obtain the final chemical structure of fesoterodine. To prevail, Mylan must prove that a person of ordinary skill would have known to (1) use an ester prodrug, (2) add the substituent to *only* the phenolic hydroxyl, and (3) use an isobutyryl substituent, *and* (4) that a person of ordinary skill would have had a reasonable expectation of success regarding the resulting compound's properties. (D.I. 80 at 14-21.)

Mylan argues that a POSA would have chosen to develop an alkyl ester prodrug because esters were among the most commonly used prodrug moieties. (D.I. 80 at 15.) Dr. Janero testified that a POSA would have recognized two possible options for developing an ester prodrug of 5-HMT: the hydroxyl group at either the 2 position or on the methyl group of the 5-HMT phenyl ring (at the 5 position), which could be esterified by standard medicinal chemistry. (Tr. 295:8-296:10 (Janero).) Dr. Janero also noted that other types of prodrug groups would have been more likely to carry different biological properties, biological activities, or chemical reactivities than the desired activity of 5-HMT. (Tr. 293:16-294:15 (Janero).) Mylan therefore argues that a POSA, using routine experimentation, would have focused on small hydrocarbon esters that would not be prone to other reactivities and would be readily eliminated from the body to make 5-HMT

available. (Tr. 293:16-294:15 (Janero).) Thus, Mylan submits that a POSA would have had a reasonable expectation of obtaining fesoterodine.

Mylan's analysis is unavailing for several reasons. First, Mylan improperly narrows the field to ester prodrugs. A POSA would have considered a variety of prodrug types in the prior art, including carboxylic esters, phosphate esters, carbamate esters, carbonate esters, ethers, and others, in search of the right set of aggregate properties. (Tr. 515:16-516:11, 516:19-25, 517:7-518:24 (Roush); PTX-95 at Table 2). Mylan's expert, Dr. Janero, relied on one prior art reference (Bundgaard, DTX-41) to support his argument that carboxylic ester prodrugs would have been obvious. The doctor's focus seems unduly narrow. The Bundgaard reference discussed other types of prodrug design that appear to have been overlooked in Dr. Janero's analysis. (Tr. 362:5-8 (Janero).) In addition, he conceded that a POSA would have considered other classes of prodrugs. (Tr. 293:18-25 (Janero).)[7] The court therefore believes a POSA would have not engaged in a limited review of the prodrug field.

Second, while Mylan contends that a POSA would have to modify only one of the hydroxyl groups, Pfizer points out that 5-HMT contains four possible substitutions: (1) single substitution at the benzylic (or 5-position) hydroxyl, (2) a single substitution at the phenolic (or 2-position) hydroxyl, (3) identical substitutions at both hydroxyls ("di-esters"), or (4) different substituents at each hydroxyl ("mixed di-esters"). (Tr. 521:12-21 (Roush).) The court is persuaded by Dr. Roush's testimony that pursuing one position to the exclusion of the others would be "like putting on a straightjacket or tying a hand behind your back." (Tr. 521:22-522:8 (Roush).) Indeed, the prior art would have taught a POSA to try monoesters and di-esters, (Tr. 363:5-20 (Janero)), and

[7] Notably, Dr. Janero failed to identify a known ester prodrug created using his allegedly obvious approach. The evidence adduced at trial revealed that codeine is an ether, not an ester, (Tr. 366:9-18 (Janero)), and the approach that would have rendered fesoterodine obvious failed with ampicillin, (Tr. 369:10-17 (Janero).)

nothing taught that monoesters are preferred to diesters (Tr. 365:16-22 (Janero)). Further, nothing in the prior art directed a POSA to only use a conservative small hydrocarbon ester (as Mylan suggests) and, if ease of conversion were the issue (as Mylan suggests), other types of esters would also provide for a one-step conversion process. (Tr. 364:12-17; 370:8-14; 371:11-18 (Janero).)

Third, Mylan provided no evidence specifically teaching towards a phenolic isobutyryl ester of 5-HMT. Instead, Mylan argues that a POSA would have only made conservative ester modifications of no more than four carbons so as not to markedly increase the molecular weight of the compound. (Tr. 307:11-308:5, 310:7-312:8, 364:18-24 (Janero).) Pfizer observes, however, that even limiting potential options to those presented by Mylan—esters with two to six carbons—a POSA would have had over 7,000 options for modifying the 5-HMT molecule. (Tr. 523:3-11 (Roush).) The sheer number of possible combinations seriously undermines Mylan's assertion that the obvious pathway to solve the problem would have been ester-based prodrug design. The prior art does not provide any suggestion or teaching that the isobutyrl prodrug group would be compatible with 5-HMT, (Tr. 519:2-7 (Roush); Tr. 377:8-12 (Janero)), and Mylan identified no reference that disclosed an isobutyryl derivative. (Tr. 371:24-372:6 (Janero).)

Finally, the process engaged by the inventors' demonstrates the highly unpredictable nature of the prodrug development approach. The inventors prepared 20 prodrug candidates and evaluated their conversion rates and absorption rates. Pfizer submitted evidence that their experiments yielded unpredictable results. (Tr. 435:10-18, 436:18-19, 437:1-12 (Maag).) The inventors' results, and Dr. Janero's ultimate admission that prodrugs are complicated, are powerful evidence of the unpredictability inherent in prodrug design, a factor that weighs strongly against an obviousness finding. *Procter & Gamble Co. v. Teva Pharm USA, Inc.*, 566 F.3d 989, 996 (Fed. Cir. 2009) (highlighting unpredictability seen with a class of compounds in finding

nonobviousness). This unpredictability militates against a finding that there was a reasonable expectation of success in discovering fesoterodine. Accordingly, the court concludes that the Composition Patents are not invalid for obviousness.

**(4) Salt Forms of Fesoterodine**

Mylan argues it would have been obvious to make salt forms of fesoterodine as claimed in the '650 patent. As fesoterodine is not prior art to the '650 patent, Mylan must prove fesoterodine would have been obvious to invalidate its claims. Mylan has failed to do so. Preparation of salt forms of a compound, like prodrugs, is a highly unpredictable exercise. (Tr. 372:7-373:8 (Janero); Tr. 561:18-562:2, 571:1-7 (Chyall).) The inventor's (Dr. Meese) testimony illuminates this unpredictability. Dr. Meese prepared more than 70 salts. All but the hydrogen fumarate salt of fesoterodine initially resulted in oils, rather than the desired crystalline solids. (Tr. 182:11-183:6 (Meese).) Dr. Meese fortuitously discovered the hydrochloride hydrate of festoerodine, which formed after the initial non-hydrate form was exposed to ambient moisture for some time. (Tr. 161:9-24, 182:4-10 (Meese).) The court finds that the asserted claims of the '650 patent are not obvious.

*****

In sum, Mylan has failed to present a prima facie case that the asserted claims of the patents-in-suit are invalid as obvious.[8]

## IV. CONCLUSION

For the reasons stated above, the court concludes that none of the asserted claims of the patents-in-suit are invalid due to obviousness.

[8] Because Mylan has failed to establish a prima facie case of obviousness, the court does not address Pfizer's secondary considerations. *See Graham*, 383 U.S. at 17-18.

Dated: August 9, 2017

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

| | | |
|---|---|---|
| PFIZER INC. and UCB PHARMA GMBH,<br><br>Plaintiffs,<br><br>v.<br><br>MYLAN PHARMACEUTICALS INC.,<br><br>Defendant. | ) | C.A. No. 15-79-GMS |

**ORDER**

At Wilmington, this 9th day of August, 2017, IT IS HEREBY ORDERED THAT:

1. The asserted claims of the patents-in-suit are not invalid due to obviousness;

2. The Clerk of Court is directed to enter final judgment in favor of the Plaintiffs.

UNITED STATES DISTRICT JUDGE