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 Nos. IPR2016-00510; IPR2016-00512; IPR2016-00514; IPR2016-00516; IPR2016-00517
Patent Nos. 6,858,650; 7,384,980; 7,855,230; 8,338,478; 7,985,772

DECLARATION OF WILLIAM R. ROUSH, PH.D.

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I. INTRODUCTION

1. I, William R. Roush, Ph.D., have been retained by White & Case LLP, counsel for Patent Owner UCB Pharma GmbH ("UCB"), as an expert witness in the above-captioned *inter partes* reviews of United States Patent Nos. 7,384,980 (the "'980 patent"), 7,855,230 (the "'230 patent"), 8,338,478 (the "'478 patent"), and 7,985,772 (the "'772 patent") (collectively, the "'980 patent family") and 6,858,650 (the "'650 patent"). I understand that Mylan Pharmaceuticals Inc. and Mylan Laboratories Limited (collectively with Mylan Pharmaceuticals Inc., "Petitioner") have petitioned for *inter partes* review of the '980 patent family and the '650 patent and request that the United States Patent and Trademark Office cancel as unpatentable certain claims of the '980 patent family and the '650 patent.

2. This declaration sets forth my analyses and opinions based on the materials I have considered thus far, as well as the bases for my opinions. I understand that this declaration will be used in each of the above mentioned *inter partes* reviews, as the subject matter is overlapping.

A. Background and Qualifications

3. I am a chemist with more than 35 years of professional experience in organic chemistry and medicinal chemistry. I am currently Professor of Chemistry and Executive Director of Medical Chemistry in the Drug Discovery Division of Scripps Translational Research Institute in Jupiter, Florida ("Scripps Florida"). I

previously served as the Associate Dean of the Graduate Program at Scripps Florida. A copy of my curriculum vitae is attached as Exhibit 2003. My educational background and my professional experience are summarized below.

4. I obtained a Bachelor of Science degree in Chemistry from the University of California, Los Angeles in 1974, graduating summa cum laude. I obtained my Ph.D. in Chemistry from Harvard University in 1977.

5. After a year of post-doctoral work at Harvard (1977-78), I joined the faculty at the Massachusetts Institute of Technology (MIT) as an Assistant Professor of Chemistry. I taught chemistry courses and performed research at MIT from 1978 to 1987. My research interests included the total synthesis of natural products and the development of new synthetic methods.

6. In 1987, I moved to Indiana University, where I ultimately became Distinguished Professor of Chemistry. At Indiana University, I initiated a research program on the design and synthesis of inhibitors of cysteine proteases. These inhibitors, designed to combat certain tropical parasitic diseases, are chemical compounds which prevent (i.e., inhibit) an enzyme, specifically a cysteine protease, from performing an essential chemical reaction in the parasite, resulting in the death of the microorganism.

7. In 1997, I was appointed the Warner-Lambert/Parke-Davis Professor of Chemistry at the University of Michigan. This is an endowed chair established by

a gift from Parke-Davis to the University of Michigan. I subsequently served as the Chairman of the Department of Chemistry at the University of Michigan from 2002-2004. While at the University of Michigan, I served as Co-Director of the Life Sciences Initiative Commission, which conceived the Life Sciences Institute (LSI), and laid out the blueprint for its creation and development to stimulate interdisciplinary research in the biomedical sciences. I also continued to develop my research program focusing on the synthesis of biologically active natural products, the development of new synthetic methodology, and the design and development of inhibitors of cysteine proteases.

8. In 2004, I was recruited to join the Scripps Research Institute at its new campus in Florida. I assumed my current positions – Professor of Chemistry and Executive Director of Medical Chemistry – in 2015. Scripps Florida is an expansion of the well-known Scripps Research Institute, which is headquartered in La Jolla, California. The Scripps Research Institute is one of the leading biomedical research institutes in the world and is internationally recognized for its commitment to, and its basic research in, the fields of immunology, biology, chemistry, neurosciences, virology, autoimmune and cardiovascular diseases, and synthetic vaccine development. Particularly significant is the Scripps Research Institute's study of the basic structure and design of biological molecules.

9. As Associate Dean of the Graduate Program at Scripps Florida (2005-2016), I developed and led the graduate program on the Jupiter campus.

10. I currently serve as Executive Director of Medicinal Chemistry in the Drug Discovery Division of Scripps' Translational Research Institute at Scripps Florida. In this position, I direct the research of twelve to sixteen (12-16) staff medicinal chemists who are charged with performing structure-activity relationship ("SAR") studies to optimize drug candidates for several drug discovery projects internal to Scripps. Projects at Scripps Florida that have been performed under my directorship, or are still active, include the development and optimization of enzyme inhibitors for cancer targets, central nervous system diseases (e.g., Parkinson's disease), and metabolic diseases, among others. In addition, I personally direct an academic research program with eleven (11) graduate students and postdoctoral associates that is funded primarily by the National Institutes of Health ("NIH"). This program includes medicinal chemistry research projects focusing on development of agonists and antagonists of nuclear receptors, development of inhibitors of enzyme targets (including kinases, cysteine proteases, metallomatrix proteinases, histone deacetylates, and cytochrome P51, among others) and development of inhibitors of transporters responsible for active transport of molecules into and out of cells.

11. An important aspect of my work is an understanding of the biochemistry of biological drug targets. I frequently work with biologists and pharmacologists on projects and I regularly review and assess the results of biological experiments and use those results to make decisions about how to further improve the compounds that are the subjects of these medicinal chemistry research projects.

12. From 2007 through 2014 I served as the Chairman of the Chemistry Coordination Committee of the Scripps Molecular Screening Center, which was one of four centers forming the Molecular Libraries Production Centers Network (MLPCN), an NIH-funded program which screened potential drug targets and performed SAR studies to optimize potential drug candidates.

13. I have served a five-year term on the National Institutes of Health (NIH) Medicinal Chemistry Study Section, including two (2) years as Chair. The Medicinal Chemistry Study Section reviewed research proposals in medicinal chemistry submitted to the NIH, and ranked these applications in terms of their scientific merit.

14. I have presented my research in more than two hundred (200) invited lectures at universities and pharmaceutical companies. In addition, I have been invited to deliver more than one hundred (100) named, keynote, or plenary lectures at universities and national and international symposia and conferences. All of the invited, named, keynote and plenary lectures that I have presented during my

career have been based on my research on compound synthesis and/or the biological evaluation of specific compounds that I have synthesized.

15. I have published extensively in the scientific literature and have authored or co-authored over three hundred forty (340) papers relating to organic synthesis and medicinal chemistry, including more than fifty (50) scientific articles dealing specifically with the synthesis and biochemical and/or biological evaluation of small molecule inhibitors of protein targets.

16. I have experience with the discovery and development of prodrugs due to my work as a medicinal chemist. By consulting in the pharmaceutical industry, I have gained first hand exposure to the selection and optimization of prodrug candidates. I have been involved in research in which prodrugs were used to evaluate the activity of inhibitors in appropriate biological assays. I have also been involved in the development of a commercial process for manufacture of a prodrug (Clindamycin Phosphate) that was marketed by Genzyme Corporation beginning in the late 1980s.

17. I am currently engaged in an NIH funded project to develop a novel class of prodrugs, specifically antibody-drug conjugates, in which the antibody targets specific cells, and the drug is cleaved by enzymes within the cell after the conjugate is internalized.

18. I am on the editorial board of Organic Letters and previously served on the editorial advisory board of Chemical Biology and Drug Design. I am also a member of the Boards of Directors of Organic Syntheses, Inc. and Organic Reactions, Inc., which publish the Organic Syntheses and Organic Reactions monographs. In addition, I previously served as an Associate Editor of the Journal of the American Chemical Society.

19. I regularly consult with pharmaceutical and biotechnology companies. These consultations focus, in general, on aspects of medicinal chemistry, synthetic chemistry, and process chemistry for companies engaged in drug discovery and development. I also participate, as a consultant, in strategic planning exercises. The companies I currently consult with are Eli Lilly and Company and IMF Therapeutics. In the past I have also consulted with Pfizer Inc., Genzyme Corporation, Lycera Corporation, ArQule Inc., NeXstar Pharmaceuticals Inc. and GMP-Immunotherapeutics, among others.

20. I have received a number of awards for my research, including the Arthur C. Cope Scholar Award (1994) from the American Chemical Society, the Paul G. Gassmann Distinguished Service Award from the American Chemical Society Division of Organic Chemistry, and the Ernest Guenther Award in the Chemistry of Natural Products from the American Chemical Society. In 2006, I

was elected a Fellow of the American Association for the Advancement of Science, and in 2009, I was elected a Fellow of the American Chemical Society.

B. Materials Considered

21. The opinions that I express in this declaration are based on the information and evidence currently available to me. The following table lists the materials that I considered in forming my opinions set forth in this declaration. I also relied on my general knowledge, experience, and my own scientific analysis.

Exhibit No.	Materials
1001	The United States Patent that is the subject of this proceeding (either U.S.P.N. 7,384,980; 7,855,230; 8,338,478; 7,985,772; or 6,858,650).
1002	The file history for Exhibit 1001.
1003	Declaration of Dr. Steven Patterson, Ph.D.
1004	C.V. for Dr. Steven Patterson, Ph.D.
1005	WO 94/11337 Filed 6 November 1992 – "Novel 3,3-Diphenylpropylamines, Their Use and Preparation" ("Johansson").
1006	BJU International (1999), 84, 923-947 – "The Pharmacological Treatment of Urinary Incontinence"; KE Andersson, R. Appell, L.D. Cardozo, C. Chapple, H.P. Drutz, A.E. Finkbeiner, F. Haab, and R. Vela Navarrete ("Andersson Review").
1007	N. Brynne et al., Pharmacokinetics and Pharmacodynamics of Tolterodine in Man: A New Drug for the Treatment of Urinary Bladder Overactivity, 35 INT'L J. CLIN. PHARMACOLOGY & THERAPEUTICS 287 (1997) ("Brynne 1997").
1008	British Heart Journal (1995), 74, 53-56 – "Concentration dependent cardiotoxicity of terodine in patients treated for urinary incontinence"; S. Thomas, P. Higham, K Hartigan-Go, F. Kamali, P. Wood, R. Campbell, and G. Ford ("Thomas").
1009	Detrol® Label.

1010	Drug Metabolism and Disposition (1998), 26 (4), 289-293 – "Tolterodine, A New Muscarinic Receptor Antagonist, Is Metabolized by Cytochromes P450 2D6 and 3A in Human Liver Microsomes"; H. Postlind, A. Danielson, A. Lindgren, and S. Andersson ("Postlind").
1011	Niclas Brynne et al., Influence of CYP2D6 Polymorphism on the Pharmacokinetics and Pharmacodynamics of Tolterodine, 63 CLIN. PHARMACOLOGY & THERAPEUTICS 529 (1998) ("Brynne 1998").
1012	Hans Bundgaard, DESIGN OF PRODRUGS (Hans Bundgaard ed. 1985) ("Bundgaard").
1013	JOURNAL OF PHARMACEUTICAL SCIENCES (1977), 66 (1), 1-19 – "*Pharmaceutical Salts*"; S. Berge, L., Bighley, and D. Monkhouse ("Berge").
1014	Drug Metabolism and Disposition (1998), 26(6), 528-535 – "*Biotransformation of tolterodine, a new muscarinic receptor antagonist, in mice, rats, and dogs*"; S. Andersson, A. Lindgren, and H. Postlind ("Andersson 1998").
1015	Lisbeth Nilvebrant et al., *Antimuscarinic Potency and Bladder Selectivity of PNU-200577, a Major Metabolite of Tolterodine*, 81 PHARMACOLOGY & TOXICOLOGY 169 (1997) ("Nilvebrant 1997").
1016	P&T (2012), 37(6), 345-361 – "*Management of Urinary Incontinence*"; G. DeMaagd and T. Davenport ("DeMaagd").
1017	UROLOGY (1997), 50, 90-96 – "*Clinical efficacy and safety of tolterodine in the treatment of overactive balder: a pooled analysis*"; R. Appell ("Appell").
1018	Home Care Provider (1997), 2(3), 117-120 – "*Is My Antihistamine Safe?*"; L. Ashworth ("Ashworth").
1019	Christopher A. Lipinski et al., *Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings,* Advanced Drug Delivery Reviews 23 (1997) 3-25 ("Lipinski").
1020	WO 92/08459 Filed 11 November 1991 – "Topical Compositions for Transdermal Delivery of Prodrug Derivatives of Morphine" ("Bundgaard patent").

1021	American Urological Association Education and Research (2014) – "Diagnosis and Treatment of Overactive Bladder (Non-Neorogenic) in Adults: AUA/SUFU Guideline"; E. Gormley, et al. ("AUA Guideline").
1022	Aug. 2, 2012 "Study Shows Toviaz is Effective in Reducing Urge Urinary Incontinence in Patients with Overactive Bladder After Suboptimal Response to Detrol LA" – www.pfizer.com ("Pfizer 2012 Press Release").
1023	April 1, 2012 "Overactive Bladder Market: Managing the Future" – www. pm360online.com ("PM360").
1024	"Toviaz® Label" – Pfizer Labs
1025	"FDA Approval Letter" –NDA20-771
1026	Applications Covered by Section 505(b)(2) – October 1999 – FDA (CDER) ("FDA Guidance").
1027	INTERNATIONAL JOURNAL OF PHARMACEUTICS (1986), 3, 201-217 – "*Salt Section for Basic Drugs*"; P. Gould ("Gould").
1028	Discovery & Development of Selective M3 Antagonists for Clinical Use, 60 LIFE SCIENCE 1053 (1997) ("Alabaster").
1029	1,2,3,4-Tetrahydro-2-Isoquinolinecarboxylate Derivatives: A Novel Class of Selective Muscarinic Antagonists, III, in 213th ACS National Meeting, San Francisco, Abst. 046 (Apr. 13-17, 1997) ("Takeuchi").
1030	CLINICAL PHARMACOLOGY & THERAPEUTICS (1997) 61(1), 59-69 – "*DuP 532, an angiotensin II receptor antagonist: First Administration and comparison with losartan*"; M. Goldberg, M. Lo, D. Christ, R. Chiou, C. Furtek, O. Amit, A. Carides, J. Biollaz, V. Piguet, J. Nussberger, H. Brunner ("Goldberg").
1031	J. PHARM. PHARMACOL. (1996), 48, 136-146 – "*The Blood-brain Barrier: Principles for Targeting Peptides and Drugs to the Central Nervous System*"; D. Begley ("Begley").
1050	File History for U.S. Patent No. 5,686,464.
2001	Memorandum Opinion, *Pfizer Inc. et al. v. Sandoz, Inc. et al*, 13-cv-01110 (D. Del.).
2003	C.V. of William R. Roush.

2004	Lisbeth Nilvebrant et al., *Tolterodine – A New Bladder Selective Muscarinic Receptor Antagonist*: *Preclinical Pharmacological and Clinical Data*, 60 LIFE SCIENCES 1129 (1997) ("Nilvebrant 1997 II").
2006	Trial Transcript, July 13-16, 2015, *Pfizer Inc. et al. v. Sandoz, Inc. et al*, 13-cv-01110 (D. Del.).
2007	The file history of United States Patent No. 7,384,980.
2013	Jeffrey P. Krise et al., *Novel Prodrug Approach for Tertiary Amines: Synthesis and Preliminary Evaluation of N-Phosphonooxymethyl Prodrugs*, 42 J. MED. CHEM. 3094 (1999) ("Krise").
2014	A.A. Sinkula et al., *Rationale for Design of Biologically Reversible Drug Derivatives: Prodrugs*, 64 J. PHARM. SCI. 181 (1975) ("Sinkula").
2015	Hans Bundgaard, *Novel Chemical Approaches in Prodrug Design*, 16 DRUGS OF THE FUTURE 443 (1991) ("Bundgaard (1991)").
2016	Michael W. Jann et al., *Clinical Pharmacokinetics of the Depot Antipsychotics*, 10 CLINICAL PHARMACOKINETICS 315 (1985) ("Jann").
2017	R. Beresford et al., *Haloperidol Decanoate a Preliminary Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Use in Psychosis*, 22 DRUGS 31 (1987) ("Beresford").
2018	United States Patent No. 7,384,980.
2019	United States Patent No. 6,858,650.
2020	Transcript of the Deposition of Steven Patterson, Ph.D., dated October 4, 2016, Case IPR2016-00510, Case IPR2016-00512, Case IPR2016-00514, Case IPR2016-00516, Case IPR2016-00517 ("Patterson Tr.").
2047	L.P. Balant et al., *Prodrugs for the Improvement of Drug Absorption via Different Routes of Administration*, 15 EUROPEAN J. DRUG METABOLISM & PHARMACOKINETICS 143 (1990) ("Balant").
2048	Kevin Beaumont et al., *Design of Ester Prodrugs to Enhance Oral Absorption of Poorly Permeable Compounds: Challenges to the Discovery Scientist*, 4 CURR. DRUG. METAB. 461 (2003) ("Beaumont").
2049	Valentino J. Stella et al., *Prodrugs and Site-Specific Drug Delivery*, 23 J. MEDICINAL CHEMISTRY 1275 (1980) ("Stella").
2050	Peter Ettmayer et al., *Lessons Learned from Marketed and Investigational Prodrugs*, 47 J. MED. CHEM. 2393 (2004) ("Ettmayer").

2051	Bruce D. Roth et al., *Relationship Between Tissue Selectivity and Lipophilicity for Inhibitors of HMG-CoA Reductase*, 34 J. MED. CHEM. 463 (1991) ("Roth").
2052	J. Magyar et al., *Effects of Norfluoxetine on the Action Potential and Transmembrane Ion Currents in Canine Ventricular Cardiomyocytes*, 370 NAUNYN SCHMIEDEBERGS ARCH. PHARMACOL. 203 (2004) ("Magyar").
2053	U.S. Patent No. 5,382,600 (the "'600 patent").
2054	Prescribing Information for Accupril® retrieved on March 10, 2015.
2055	Milind M. Narurkar et al., *Synthesis, Physicochemical Properties, and Cytotoxicity of a Series of 5'-Ester Prodrugs of 5-Iodo-2'-Deoxyuridine*, 5 PHARM. RES. 734, 734 (1988) ("Narurkar").
2056	Thomas Hartung, *Food for Thought Look Back in Anger – What Clinical Studies Tell Us About Preclinical Work*, 30 ALTEX 275 (2013) ("Hartung").
2057	Chart of FDA Approvals of New Drug Applications for New Molecular Entities and New Active Ingredients from January 1994 – December 1998.
2058	Daniel S. Sitar, *Clinical Pharmacokinetics of Bambuterol*, 31 CLIN. PHARMACOKINET. 246 (1996) ("Sitar").
2059	J. Greg Slatter et al., *Bioactivation of the Anticancer Agent CPT- 11 to SN-38 by Human Hepatic Microsomal Carboxylesterases and the* in vitro *Assessment of Potential Drug Interactions,* 25 DRUG METABOLISM & DISPOSITION 1157 (1997) ("Slatter").
2060	Alan J. Wein, *Pharmacologic Options for the Overactive Bladder*, 51 UROLOGY (SUPP. 2A) 43 (1998).

II. SUMMARY OF OPINIONS

22. I have reviewed the Declaration of Steven E. Patterson, Ph.D. (the "Patterson Decl."), Petitioner's Petitions for *inter partes* review of U.S. Patent Nos. 7,384,980, 7,855,230, 8,338,478, 7,985,772, and 6,858,650, the specifications, claims, and file histories of the '980 patent family, as well as the

'650 patent and its associated file history. I disagree with a number of the opinions expressed in the Patterson Declaration and the positions taken in the Petitions regarding the obviousness of the challenged claims of the '980 patent family and the '650 patent. The Petition alleges that the challenged claims would have been obvious because fesoterodine and the fumarate salt form of fesoterodine would have been obvious. I disagree. It is my opinion that neither fesoterodine nor its fumarate salt form would have been obvious to a person of ordinary skill in the art.

III. LEGAL STANDARDS

23. I am not an attorney, and therefore, my understanding of patent law and the legal standards set forth in this report is based on explanations provided by counsel.

24. I understand that even if an alleged claimed invention is not identically disclosed or described in a single piece of prior art, the patent claim may still be unpatentable if the differences between the claimed invention and the prior art (alone or in combination) are such that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. I understand that the level of ordinary skill in the pertinent art is evaluated as of the time of the invention, here the effective filing date of the '980 patent family or the '650 patent.

25. I also understand that, in addressing obviousness, the following factors must be considered from the perspective of a hypothetical person of ordinary skill in the relevant art: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) any other indications ("objective indicia") of non-obviousness, such as commercial success, long-felt but unsolved needs, failure of others, industry acclaim, and unexpected results.

26. I understand that if an experiment leads to unexpected results or a compound exhibits unexpected properties, that result or compound likely would not have been obvious to a person of ordinary skill in the pertinent art. In that instance, such unexpected results or properties suggest that the compound would not have been obvious.

27. I understand that prior art references may be combined to render a claim obvious if a person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success. I also understand that the use of hindsight to select or combine prior art references is improper for purposes of an obviousness analysis.

28. I understand that in considering obviousness, it is relevant to consider whether the art includes references that "teach away" from the claimed invention. I have been informed that a reference teaches away from the claimed invention if a

person of ordinary skill, reading the reference, would be discouraged from following the path of the claimed invention or would be led in a divergent direction.

29. I also understand that for a chemical compound to be unpatentable as obvious, generally there is identified a lead compound (or compounds) in the prior art that would have reasonably been the subject of further development work by a person of skill in the art seeking to discover a new and improved drug. I also understand that for a chemical compound to be unpatentable as obvious there must be some reason why a person of ordinary skill in the art would have made the specific molecular modifications necessary to convert the lead compound(s) into the claimed compound. I also understand that for a chemical compound to be unpatentable as obvious a person of skill in the art would have a reasonable expectation that the compound would be successful, in that it would work for its intended purpose.

IV. THE CHALLENGED CLAIMS

30. I understand that Petitioner has petitioned for review and cancellation of the following claims (collectively, the "challenged claims"):

- Claims 1-16 of the '980 patent;
- Claims 1-5 of the '230 patent;
- Claims 1-3, 5-8, and 10-12 of the '478 patent;

- Claims 1, 3, 4, and 6-8 of the '772 patent; and
- Claims 1-5 and 21-24 of the '650 patent.

31. I understand that the challenged claims cover the chemical compound fesoterodine fumarate, which is the active ingredient in Toviaz®, other salt forms of fesoterodine, pharmaceutical compositions containing fesoterodine, or methods of treating overactive bladder ("OAB") with fesoterodine.

32. I understand that Petitioner alleges that the challenged claims are invalid because fesoterodine fumarate and the use of fesoterodine fumarate to treat OAB would have been obvious as of the priority date of the '980 patent family and/or the '650 patent.

33. I understand that the priority date of the '980 patent family is May 12, 1998. I understand that the priority date of the '650 patent is November 16, 1999. I note that Dr. Patterson assessed the prior art as of May 11, 1998 in his Declaration. (Patterson Decl. at ¶ 24.) I have conducted my analysis on the basis of May 12, 1998 for the '980 patent family and November 16, 1999 for the '650 patent, but I note that my opinion would not change if I assessed the prior art for all patents as of May 11, 1998.

34. I understand that between July 20-26, 2016, the PTAB instituted an *inter partes* review of the challenged claims on the following grounds:

- Obviousness over the combination of Postlind (Ex. 1010), the Bundgaard publications (Exs. 1012 and 1020), the Detrol® Label (Ex. 1009), and Berge (Ex. 1013); and
- Obviousness over the combination of Brynne 1998 (Ex. 1011), the Bundgaard publications (Exs. 1012 and 1020), and Johansson (Ex. 1005).

See Paper 12 (July 20, 2016) ("'980 Decision") at 29; Paper 12 (July 22, 2016) ("'230 Decision") at 29; Paper 12 (July 26, 2016) ("'478 Decision") at 30; Paper 12 (July 20, 2016) ("'772 Decision") at 29; Paper 12 (July 20, 2016) ("'650 Decision") at 29.

35. I provided expert testimony in the action, *Pfizer Inc. et al., v. Sandoz Inc.*, C.A. No. 13-1110-GMS (D. Del.), also related to the '980 patent family and the '650 patent. I was cited by the Court for a number of facts relevant to the Court's determination that the asserted claims of the '980 patent family and '650 patent were not obvious. *See e.g.*, Exs. 2001 at 15-18, 2006 at 590-637. The Court determined that I am an expert in the fields of medicinal chemistry and drug design, including design of prodrugs and synthetic chemistry.

36. I have also provided expert testimony in the form of reports and deposition testimony in the pending action between the parties to this proceeding,

Pfizer Inc. v. Mylan Pharmaceuticals Inc., No. 1:15-CV-00079-GMS, also related to the '980 patent family and the '650 patent.

37. In view of my work as an expert in the above cases and my review of materials in connection with this declaration, I am knowledgeable about the chemical and biological properties of tolterodine and its metabolite 5-HMT. I am also knowledgeable about the compound fesoterodine and the fumarate salt form of that compound.

V. PERSON HAVING ORDINARY SKILL IN THE ART

38. It is my view that a person having ordinary skill in the art to which the '980 patent family and the '650 patent pertain would have at least a Ph.D. or Sc.D. degree in Chemistry or Pharmacology, or would be a highly skilled scientist lacking a Ph.D. or Sc.D., but with several years of experience working with pharmaceutical compound synthesis or pharmacology. Such a person would be familiar with the synthesis, optimization, and testing of pharmaceutical compounds; with the desired and favorable characteristics of pharmaceutical compounds; and with the tests and data designed to discern those characteristics. Because the '980 patent family and '650 patent relate to the field of treatment of OAB with pharmaceuticals, the person of ordinary skill in the art would review the prior art regarding the physiology of the bladder, the causes and symptoms of OAB, and the pharmaceuticals used to treat OAB.

39. I have reviewed Dr. Patterson's definition of a person of ordinary skill in the art. (Patterson Decl. at ¶¶ 22-23.) I also understand that the PTAB has accepted Petitioner's definition for purposes of institution. *See, e.g.,* '650 Decision at 6.

40. I have applied my definition in forming my opinions. However, my opinions do not change if I apply Petitioner's definition of a person of ordinary skill in the art.

VI. PRODRUG DEVELOPMENT IS EXTREMELY COMPLEX AND UNPREDICTABLE

41. As a general proposition, drug design is complex, time-consuming, resource-intensive, and highly unpredictable. Beginning with a desired mechanism of action and biological target, a medicinal chemist selects a lead compound, decides to make any number of modifications to the lead compound, determines how to synthesize each variant of the compound, and tests each resulting compound for the desired properties. A successful compound must have potent activity at the intended biological target and lesser activity at other unintended targets. A compound must also exhibit favorable "ADMET" properties (absorption, distribution, metabolism, elimination, and toxicity), and suitable physicochemical properties (e.g., stability, solubility), to be worthy of consideration as a pharmaceutical. Any one of the numerous small modifications

made to the compound during development can cause significant differences in its properties that cannot be predicted in advance.

42. A prodrug is a compound that is inactive or partially inactive against the biological target, but is metabolically converted to a compound that will be active against the biological target (an "active metabolite"). One goal in developing an oral prodrug is to produce a modified compound that is stable enough to survive the gastrointestinal ("GI") tract intact, yet capable of being quickly and extensively metabolized into the active compound at the desired location after absorption. In some cases, the desired location is the bloodstream. The conversion from prodrug to active metabolite should be extensive, such that all or most of the prodrug is converted to the active metabolite. This is a very delicate balance to achieve. For example, for orally administered drugs there is a risk that the compound will be metabolized too early by a number of degradation enzymes in the GI tract. *See* L.P. Balant et al., *Prodrugs for the Improvement of Drug Absorption via Different Routes of Administration*, 15 EUROPEAN J. DRUG METABOLISM & PHARMACOKINETICS 143 (1990) ("Balant") (Ex. 2047) at 145, 149; Kevin Beaumont et al., *Design of Ester Prodrugs to Enhance Oral Absorption of Poorly Permeable Compounds: Challenges to the Discovery Scientist*, 4 CURR. DRUG. METAB. 461 (2003) ("Beaumont") (Ex. 2048) at 478. Conversely, a prodrug compound that is stable enough to survive the GI tract might be so stable that it is converted too slowly or

incompletely to its active metabolite after absorption. Ex. 2047 at 145, 149. Moreover, changes made to improve absorption tend to decrease with solubility, creating a rather delicate balance for the medicinal chemist to try to strike. *See* Ex. 2048 at 475.

43. 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. *See* Ex. 2047 at 149 ("In this context it must be remembered that the modification of one pharmacokinetic property, frequently alters other properties of the drug molecule and caution must thus be exercised when embarking on a program of this nature."); Valentino J. Stella et al., *Prodrugs and Site-Specific Drug Delivery*, 23 J. MEDICINAL CHEMISTRY 1275 (1980) ("Stella") (Ex. 2029) at 1281 ("Even though a prodrug may exhibit excellent physicochemical properties for the delivery of parent drug to a tissue, it may also exhibit improved transport to another tissue, thus increasing the incidence of side effects because of the selectivity for the other tissue."); Ex. 2048 at 480 (citing examples of prodrugs that have metabolites other than the observed active metabolite).

44. Dr. Patterson suggests that developing a prodrug would have been a predictable solution. Patterson Decl. at ¶¶ 80, 105-09. I disagree. Developing a prodrug is a complete drug development exercise of an entirely new chemical

entity, involving synthetic issues, preclinical evaluation, clinical studies, and safety assessments, all of which must produce favorable results for the prodrug to be viable for use in treating human patients. *See generally* Ex. 2047 at 149 (discussing a variety of practical considerations in prodrug development). Drug developers must also consider pharmaceutical issues, such as stability in storage and in solution, scalability of process, hygroscopicity, electrostatic properties, and physical properties, such as solubility, as with developing any other potential pharmaceutical compound. *See id.*

45. In fact, developing a prodrug is no easier than developing an entirely new molecule or developing a compound that will work on an entirely new target. There is never any guarantee of success under either pathway. Ex. 2029 at 1282 ("To be successful, prodrug design requires a multidisciplinary approach that draws upon the expertise of chemists, pharmacologists, toxicologists, synthetic organic and medicinal chemists, pharmaceutical chemists, as well as adequate feedback from clinicians.").

46. To the contrary, developing a prodrug in 1998, and still today, is more accurately thought of as an approach of last resort, taken only when there is a clear, specific problem that a prodrug can overcome and other avenues for solving that problem have been exhausted. *See* Ex. 2029 at 1276 (prodrugs are utilized "[w]hen the parent or active drug is not fully utilized because of some identifiable barrier or

problem"); Peter Ettmayer et al., *Lessons Learned from Marketed and Investigational Prodrugs*, 47 J. MED. CHEM. 2393, 2393 (2004) (Ex. 2050) ("In medicinal chemistry, a prodrug strategy is practically never considered in the early phases of drug design but only when classic analoguing programs fail to provide the required drug profile."); *see also id.* at 2401 ("A prodrug might be considered when the structure-activity relationship (SAR) of a compound class for the drug target and the pharmacokinetic properties appear chemically incompatible . . . ."); Ex. 2048 at 482-83 ("[T]he hurdles to oral delivery of an ester prodrug are not trivial. . . . Given the complexities outlined in this review, it is recommended that the prodrug strategy is only considered as a last resort to improve the oral bioavailability of important therapeutic agents.").

47. One potential pitfall in prodrug development is that once in the body, a new prodrug may not convert to its active moiety in a manner that provides the desired therapeutic activity. *See* Ex. 2047 at 149. Another potential pitfall of prodrug development is that metabolism of the prodrug to the active metabolite could result in unexpected and/or undesired byproducts, which may pose toxicity concerns and disqualify a prodrug candidate. *Id.* at 145, 149. Additionally, the newly designed prodrug may interact with unintended targets causing "off-target effects" (i.e., unwanted side effects, etc.). The risk of "off-target effects" is compounded with prodrugs because there are two compounds in circulation – the

prodrug and the active metabolite – each with the potential to cause undesirable activities. *See id.*

48. As in any drug development project, prodrug development involves many necessary choices for a medical chemist. The chemist can make numerous substitutions, at different locations on the compound, and in different combinations. The many possible variations often number in the millions, producing a process of trial and error that often results in failure, in one or more of many attributes (i.e., toxicity, inadequate absorption, stability in storage and in solution, bioavailability, tolerability, etc.). *See* Ex. 2047 at 149. Many steps must be taken successfully to arrive at a possible prodrug candidate. Failure at any one step could lead to rejection of the compound from further stages of development. It's impossible to know in advance whether the prodrug will pass all of the points of development until it has been synthesized and tested.

49. As discussed in more detail below, as of 1998, a person of ordinary skill in the art contemplating a prodrug approach would have been aware of, and considered, a variety of possible prodrug options, including esters, ethers, carbamates, carbonates, phosphate esters, Mannich bases, and macromolecular prodrugs. *See* Hans Bundgaard, *Design of Prodrugs: Bioreversible Derivatives for Various Functional Groups and Chemical Entities, in* DESIGN OF PRODRUGS

(Hans Bundgaard ed. 1985) ("Bundgaard") (Ex. 1012) at 3, Table 2; Ex. 2047 at 145-46, 149; *infra* Section X.A.

VII. 5-HMT WOULD NOT HAVE BEEN SELECTED AS A LEAD COMPOUND

50. The need that existed in the prior art was for an OAB treatment with an improved balance of efficacy and tolerability. *See* Alan J. Wein, *Pharmacologic Options for the Overactive Bladder*, 51 UROLOGY (SUPP. 2A) 43, 43-44, 46 (1998) (Ex. 2031). Nothing in the prior art suggests that a prodrug of 5-HMT (or a prodrug of any other compound) would have met this need.

51. Instead of focusing on the broader objective of discovering an OAB drug with an improved balance of efficacy and tolerability, Dr. Patterson focuses on a need to improve upon tolterodine's alleged shortcomings, as he perceives them. *See* Patterson Decl. at ¶¶ 95-103. To justify focusing on 5-HMT in support of his obviousness theory, Dr. Patterson misstates and manufactures problems with tolterodine. And while Dr. Patterson quickly dismisses many other prior art compounds as possible lead compounds based on various alleged shortcomings, (Patterson Decl. ¶¶ 85-91), he offers no explanation for why some of these same perceived problems in tolterodine would instead be viewed as areas for possible improvement. A person of ordinary skill would not have expected a prodrug of 5-HMT to satisfy any such perceived problem and would not have pursued one.

VIII. THERE IS NO EVIDENCE THAT 5-HMT WOULD NOT BE ORALLY ABSORBED

52. Dr. Patterson assumes that after pivoting from tolterodine to 5-HMT a person of ordinary skill in the art would have concluded that 5-HMT was not likely to be well absorbed when administered orally. Patterson Decl. at ¶¶ 112-15. Dr. Patterson's assumption is based on 5-HMT's lipophilicity relative to tolterodine. However, even if a person of ordinary skill 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 had a bioavailability or absorption problem because bioavailability and oral absorption are not determined solely by lipophilicity. *See, e.g.,* Bundgaard (Ex. 1012) at 183. Other factors such as pKa, solubility, and active transport may affect a compound's oral absorption properties. Due to the variety of factors that influence oral absorption, persons of ordinary skill in the art would not have assumed that 5-HMT had an oral absorption problem without testing it.

53. Dr. Patterson cites no prior art stating or otherwise suggesting that 5-HMT would not be well absorbed if administered orally. Neither the Petitioner nor Dr. Patterson point to any reference or any data that 5-HMT has ever been orally administered to humans or that its bioavailability properties had been determined. In fact, during his cross-examination, Dr. Patterson acknowledged that the oral absorption of 5-HMT had not been disclosed. Transcript of the Deposition of

Steven Patterson, Ph.D. dated October 4, 2016 ("Patterson Tr.") (Ex. 2020) at 209:18-23. Based on my own review, I am not aware of any such information. Thus, there could not have been any teaching in the prior art that 5-HMT is not well absorbed. Persons of ordinary skill in the art would not have made this assumption.

54. Lipophilicity, expressed as clogP values, shows that a person of ordinary skill in the art would have had no reason to be concerned with the oral absorption of 5-HMT. In fact, 5-HMT, with a clogP value of 3.70, was likely "bracketed" by well-absorbed drugs that were both more and less lipophilic than 5-HMT. This is because the lipophilicity of a compound is not determinative of its bioavailability. For example, antibiotics, including amoxicillin, ampicillin, ceclor, imipenem, and ciprofloxin are far less lipophilic than 5-HMT, most with negative clogP values, yet they are still orally bioavailable. In contrast, azithromycin is more lipophilic than these other antibiotics, yet it too is orally bioavailable.

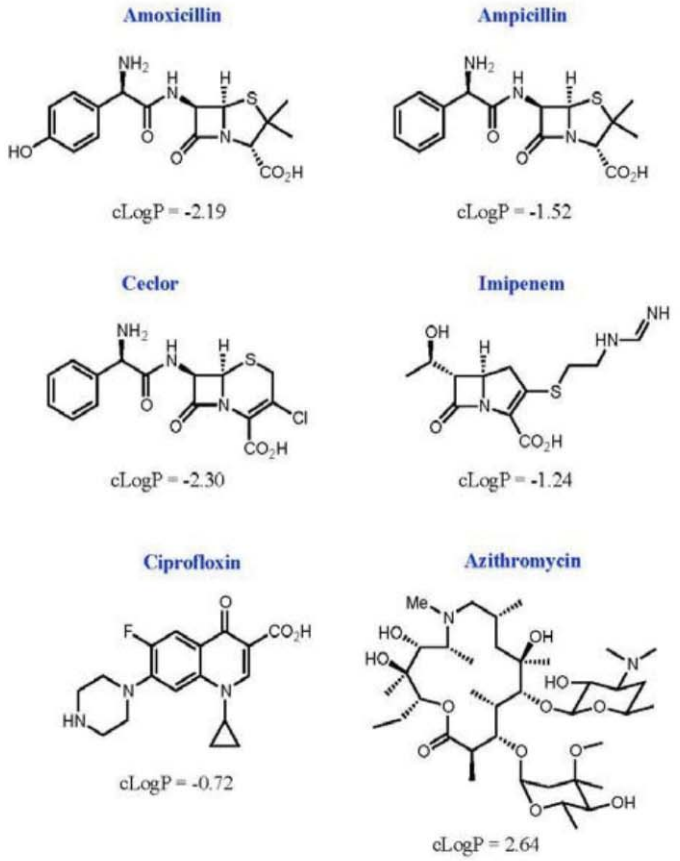

Figure 1. clogP values and chemical structures of antibiotics.

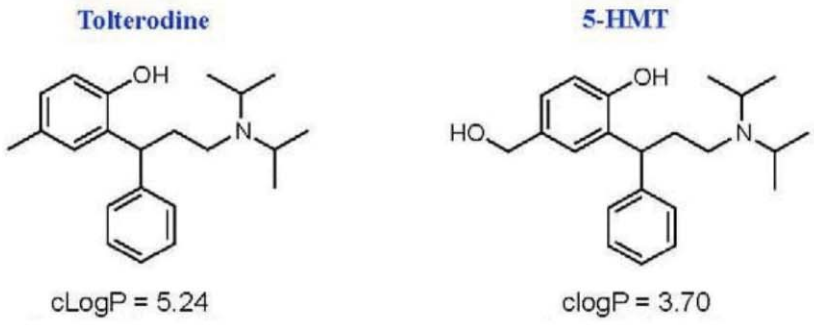

Figure 2. clogP values of tolterodine and 5HMT.

55. Additionally, the clogP values of statins vary widely, and yet they are also orally bioavailable. For example, the clogP value of pravastatin and rosuvastatin (Crestor), are 1.03 and 1.90, respectively. Meanwhile, the clogP values of lovastatin, simvastatin, and atorvastatin (Lipitor), are 3.28, 3.64, and 4.94, respectively.

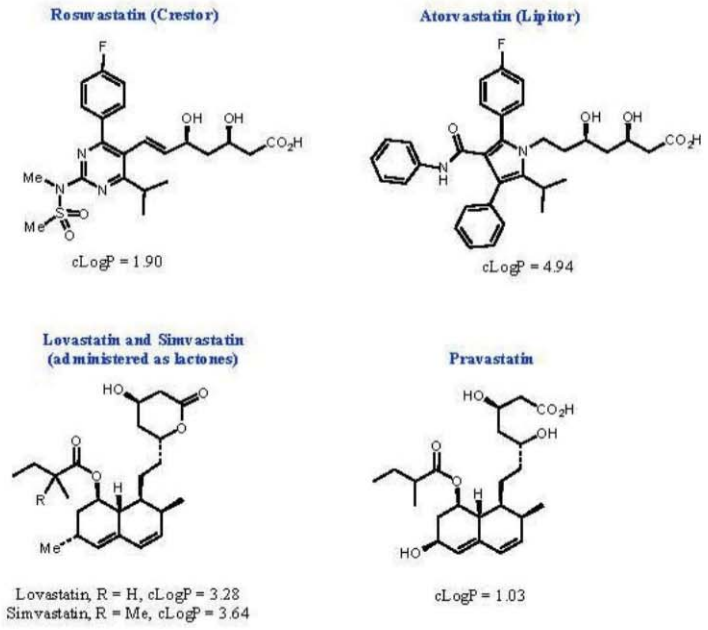

Figure 3. clogP values and chemical structures of statins.

See also Bruce D. Roth et al., *Relationship Between Tissue Selectivity and Lipophilicity for Inhibitors of HMG-CoA Reductase*, 34 J. MED. CHEM. 463 (1991) ("Roth") at 463 (reporting a "broad range of calculated lipophilicities" for fifteen different HMG-CoA reductase inhibitors).

56. Dr. Patterson cites a publication that provides guiding principles for gauging whether a compound will have poor absorption, a 1997 publication by Christopher Lipinski that describes the so-called "Rule of 5." (Ex. 1019). According to Lipinski, if a compound meets two of the following four factors, poor absorption is a possibility: (1) the compound has more than 5 H-bond donors, (2) its molecular weight is over 500, (3) its LogP is over 5 (or MlogP is over 4.15), or (4) it has more than 10 H-bond acceptors. *Id.* at 9. All of these properties are inherent to a compound and would have been readily discernible to a person of ordinary skill in the art in the 1998-1999 period, including for 5-HMT. I note as well that the Lipinski "rules" are not absolute and serve only as guidelines of properties above which absorption is potentially problematic.

57. Figure 4 depicts the structure of 5-HMT.

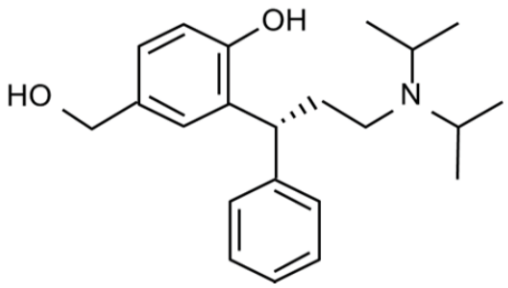

Figure 4. 5-HMT.

As can be seen in the table below, 5-HMT does not "violate" any of the four factors addressed by Lipinski:

Lipinski Factors that Disfavor Oral Absorption	Properties of 5-HMT	Is Absorption of 5-HMT Disfavored Based on Lipinski?
More than 5 H-bond donors (expressed as the sum of OH's and NH's)	2	NO
Molecular weight is over 500	341.487	NO
LogP is over 5 (or MlogP is over 4.15)	3.7	NO
More than 10 H-bond acceptors (expressed as the sum of N's and O's)	3	NO

58. The conclusion a person of ordinary skill would have drawn from Lipinski is that there would have been no reason to suspect that 5-HMT would possess poor oral absorption. If a person of ordinary skill focused on 5-HMT's lipophilicity, he would not have seen any "red flag" regarding absorption. Since a person of ordinary skill would not have suspected 5-HMT to have poor oral absorption, he would not have undertaken prodrug development.

59. As Dr. Patterson acknowledged during his cross-examination, if 5-HMT was thought to have sufficient oral absorption (and there was no reason to suspect it didn't), direct administration of the metabolite, 5-HMT, would have been much simpler. Patterson Tr. (Ex. 2020) at 132:11-17. In fact, the prior art teaches that approach. As Dr. Patterson acknowledges in his declaration, fexofenadine (Allegra®) is the active metabolite of terfenadine (Seldane®). Patterson Decl. ¶

109, citing Laurel Ashworth, *Is My Antihistamine Safe?* 2(3) HOME CARE PROVIDER, 117-120 ("Ashworth") (Ex. 1018). Like tolterodine, terfenadine, is metabolized by cytochrome P450, and, also like tolterodine, both terfenadine and its active metabolite have activity. Ex. 1018 at 118-119. Terfenadine's active metabolite is responsible for its antihistaminic effect, but the activity of terfenadine itself, if not metabolized, causes adverse cardiac effects (Torsades de Pointes). *Id.* This risk of adverse cardiac effects led to terfenadine (Seldane®) being withdrawn from the market. *Id.* at 117. The prior art taught, however, that direct administration of terfenadine's active metabolite, fexofenadine, avoided terfenadine's adverse cardiac effects. *Id.* The prior art did not teach modification of that active metabolite, fexofenadine, into a prodrug.

IX. A PRODRUG APPROACH WOULD NOT HAVE BEEN CONSIDERED SUITABLE FOR 5-HMT

60. Even if a person of ordinary skill did conclude that 5-HMT was not likely to be well absorbed – and the prior art did not suggest that was the case – developing a prodrug would not have been the first solution that a person of ordinary skill in the art would consider.

61. Dr. Patterson suggests that developing a prodrug of 5-HMT would have been a predictable solution because 5-HMT was a "known compound." *See* Patterson Decl. at ¶¶ 80, 105-109. However, there is no guarantee that an active metabolite of a known drug will be suitable for use as a pharmaceutical. For

example, fluoxetine's active metabolite norfluoxetine was investigated for use as an antidepressant but development was halted due to toxicity issues. *See* J. Magyar et al., *Effects of Norfluoxetine on the Action Potential and Transmembrane Ion Currents in Canine Ventricular Cardiomyocytes*, 370 NAUNYN SCHMIEDEBERGS ARCH PHARMACOL. 203 (2004) (Ex. 2052). A person of skill in the art would have been particularly unlikely to develop a prodrug of a metabolite where the prior art did not suggest that the metabolite would provide any therapeutic improvement. Therefore, instead of designing a drug discovery program to tackle an alleged absorption problem of an untested metabolite, a person of ordinary skill would have selected a different lead compound altogether. *See* Ex. 2047 at 149.

62. If a person of ordinary skill has selected 5-HMT for further development, in view of the teachings of the prior art, several approaches other than a prodrug design would have been preferable to address the alleged problem confronting a person of ordinary skill with 5-HMT – lack of bioavailability. For example, assuming a person of ordinary skill in the art had determined that 5-HMT was not orally absorbed, she would have considered a formulation approach, a larger dose, or addressing solid-state issues through, for example, crystalline polymorphs, amorphous forms, or micronization. *See* Paterson Tr. (Ex. 2020) at 129:6-16 (acknowledging that a person of ordinary skill in the art would consider a

formulation approach). Each of these solutions was well-known in the art in 1998 and would have been a more straightforward design choice.

63. For example, as of 1998, a person of ordinary skill would have known that micronizing particle size and increasing surface area could significantly impact a compound's rate of dissolution in water, and that increasing the rate of dissolution could mirror the effects of increased water solubility, which would improve bioavailability. In addition, formulation alternatives such as using water-miscible co-solvents, surfactants, and solid-dispersion techniques were generally accepted ways of improving aqueous solubility.

64. If a person of ordinary skill were focused on improving bioavailability of a known, effective agent for the treatment of OAB, other compounds, such as quaternary amines (e.g., trospium, emepronium, and propantheline) would have been excellent choices. The main drawback of those compounds was inefficient absorption, but they had been shown to treat OAB. In contrast, by selecting an untested metabolite of a known compound, a person of ordinary skill would be left with many unknown variables to consider (e.g., toxicity and safety due to unknown off-target pharmacology, pharmacokinetics, tissue distribution, modes of metabolism, and elimination). These unknowns would have disincentivized a person of ordinary skill from selecting an active metabolite that had never been orally administered.

65. Further, Dr. Patterson does not address that no one practicing in the field of designing antimuscarinic drugs or drugs for the treatment of overactive bladder ("OAB"), other than the inventors, had published research on developing prodrugs for antimuscarinics or to treat OAB. Dr. Patterson did not identify any teachings in the prior art regarding prodrugs of diphenylpropylamines, the only possibly structurally similar prodrugs that a person of skill in the art could have considered in making a prodrug of 5-HMT. Additionally, without more, 5-HMT's existence as an active metabolite of tolterodine provides no reason for a person of ordinary skill to focus on it for further development.

66. In fact, the only prior art prodrug compound identified in the Petitions or Dr. Patterson's declarations is a prodrug of morphine. *See* WO 92/08459 ("the Bundgaard patent") (Ex.1020). The Bundgaard patent would not have been a relevant teaching to a person of ordinary skill attempting to deliver orally a prodrug of 5-HMT because the Bundgaard patent discloses transdermal administration of prodrugs of morphine.

67. A person of ordinary skill in the art would not look to a disclosure about transdermal administration if they sought to make a prodrug for oral administration. The properties of the skin and the gut wall relevant to prodrug design are entirely different, and an effective prodrug for one route of administration would not necessarily be effective for the other. For example, for

transdermal delivery, a person of ordinary skill in the art could seek a prodrug that would rapidly convert to the parent drug in the skin or once it had passed through the transdermal layer and had entered systemic circulation. For oral delivery, the person of ordinary skill would target a prodrug that would remain stable in the gut and did not hydrolyze until after it passes through the gut wall. The chemical properties (including susceptibility to enzymatic conversion) of the prodrug would be very different for these two different applications.

68. In addition, a person of ordinary skill in the art would not look to a disclosure of an analgesic, like morphine, if they sought to make a prodrug of an OAB treatment, like 5-HMT. Analgesics need to be delivered to the central nervous system and OAB treatments need to be delivered to the bladder. As an analgesic, morphine must pass through the blood-brain barrier ("BBB"), whereas in designing a drug for treating OAB, a person of ordinary skill would seek to avoid compounds that cross the BBB in order to avoid and minimize cognitive and other CNS side effects.

69. A person of ordinary skill in the art would additionally not have viewed morphine as relevant to 5-HMT due to their very different lipophilicities and pKa values. Morphine is a very polar molecule, as indicated by the clogP (-1.53) and logD (0.57) values presented below. These data indicate that morphine is highly

soluble in water, even at pH 7.4. In contrast, the clogP (3.70) and logD (3.01) values that I calculated demonstrate that 5-HMT is a more lipophilic molecule.

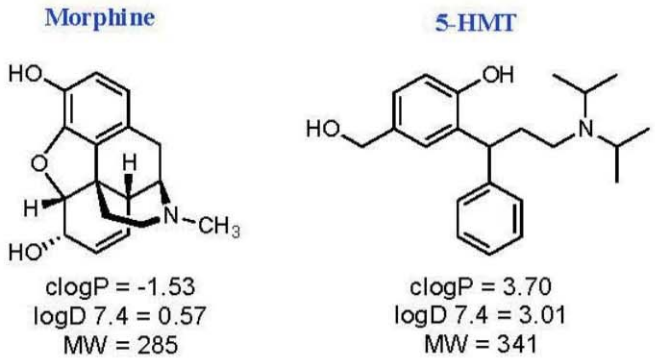

Figure 5. Structures, clogP and logD values, and molecular weights of morphine and 5-HMT.

70. Further, morphine has an extremely rigid structure, by virtue of its polycyclic nature. In contrast, 5-HMT is likely to have several different 3-dimensional conformations. As a result, the functional groups of morphine will likely be oriented in space very differently from those of 5-HMT. It stands to reason that this is the case, as morphine and 5-HMT preferentially bind to entirely different receptors and have very different affinities for enzymes, such as esterases. A person of ordinary skill would therefore not consider morphine as relevant to designing a new OAB drug based on 5-HMT.

71. The decision to generate lipophilic prodrugs of morphine to transport the very hydrophilic molecule (morphine) across a dermal layer provides no

motivation for a person of skill in the art to make lipophilic prodrugs of an already lipophilic molecule, 5-HMT. A person of ordinary skill in the art would consider these facts when selecting relevant prior art and would not have considered the Bundgaard patent.

72. Even if a person of ordinary skill did want to avoid metabolism by CYP2D6, as Petitioner suggests, (*see* Patterson Decl. ¶¶ 95-102), they would not have looked first to a prodrug approach. The administration of tolterodine already involved monitoring two active moieties (tolterodine and 5-HMT). If anything, a person of ordinary skill who wanted to avoid CYP2D6 metabolism would have sought to reduce this complexity, not maintain it in a prodrug. Instead, they would have modified tolterodine's structure or 5-HMT's structure in a way that would lead to a different metabolic pathway. For example, Table 1 of U.S. Patent No. 5,382,600 (the "'600 patent") (Ex. 2053) provides several compounds with structures related to tolterodine, including compounds that do not have a methyl group in the same position as 5-HMT, and therefore might not be subject to hydroxylation in that position by CYP2D6. A person of skill could have experimented with one or more of those compounds in an effort to avoid the CYP2D6 pathway.

73. The prodrug approach was also unsuitable for 5-HMT because of the potential it presented for off-target effects via modification of the ortho position,

which was known to be a key for selectivity of anticholinergic activity over other activities. *See* '600 patent (Ex. 2053), col.1 l.63 – col.2 l.31, Table 1.

74. Prodrug development is extremely difficult and, in 1998, was a disfavored approach that was typically the last resort of drug developers. *See supra* Section VI. I disagree with Dr. Patterson's suggestion that because use of prodrugs was known in the art, development of a prodrug of 5-HMT would have been predictable. 5-HMT prodrug development, specifically synthesis resulting in optimal performance, would not have been routine in 1998, nor would it be today. Prodrug development requires an extensive process of trial and error, and success is not guaranteed.

75. In this case, nothing in the prior art suggested that developing 5-HMT into a prodrug would yield any real benefit. Historically, prodrugs were developed only when a compound had been extensively studied, administered to humans, and proven safe and effective, but had a specific, well-documented deficit that a prodrug approach could potentially remedy. *See, e.g.,* Ex. 2047 at 149. Here, 5-HMT had never been administered to humans in any dose and, comparatively, had not been studied in particular detail for its clinical effects. Nor was there any specific deficit for 5-HMT identified in the prior art, as explained *supra*. *See also* Hans Bundgaard, Novel Chemical Approaches in Prodrug Design, 16 DRUGS OF THE FUTURE 443 (1991) ("Bundgaard (1991)") (Ex. 2015) at 456 (before

embarking on a prodrug approach the underlying causes leading to the use of a prodrug should be "defined and clearly understood," including by first identifying the drug delivery problem, identifying the properties required for optimal delivery, and selecting a prodrug derivative that would provide those properties and would be cleaved in the desired biological compartment). Given the relative lack of information on 5-HMT, both concerning its benefits and potential drawbacks, a person of ordinary skill in the art would not have taken a prodrug approach.

X. IN DECIDING TO PURSUE A PRODRUG OF 5-HMT, A PERSON OF ORDINARY SKILL WOULD HAVE FACED MANY OPTIONS WITH NO EXPECTATION OF SUCCESS

76. Dr. Patterson presents a series of steps that he believes would have been obvious for to person of ordinary skill in the art to take in the development of fesoterodine. Below, I address each of those in turn.

A. A Person of Ordinary Skill Would Have Had To Select the Type of Prodrug

77. On the assumption that 5-HMT's lipophilicity would need to be increased, Dr. Patterson opines that "a person of ordinary skill in the art in 1998 would have immediately recognized that esterifying hydroxyl groups on the 5-HMT would likely increase lipophilicity." Patterson Decl. at ¶ 119. I disagree. There are many different types of prodrugs from which a drug developer could select and no one choice would have been readily identifiable as more likely to succeed than any other.

78. Even assuming a person of ordinary skill would focus on prodrugs, Dr. Patterson presents a far too simple view of the possible prodrug approaches available at the time of the invention because there were many different types of prodrugs from which a drug developer could select. Instead of simply selecting an ester, a person of ordinary skill 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. She would have sought to identify the best possible option with the right aggregate set of properties for the compound under investigation, and would not have looked at ester prodrugs in isolation to do so.

79. As of 1998, a person of ordinary skill in the art would have recognized and 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)*;* Balant (Ex. 2047) at 145-46, 149; Patterson Tr. (Ex. 2020) at 173:24-174:10; 174:25-175:5 (acknowledging carbamates and carbonates would have been available as "alternatives" to esters, that they were "easy to synthesize, commercially available," and capable of increasing lipophilicity of 5-HMT); *id.* at 162:14-16 (acknowledging that a person of ordinary skill could have attempted to make a prodrug of 5-HMT using Mannich bases).

80. Dr. Patterson suggests that 5-HMT's two hydroxyl groups would have led a person of skill in the art to automatically choose an ester. Patterson Decl. at ¶ 112-13. However, there was no evidence in the prior art that a person of ordinary skill in the art would have used this factor to narrow the choices available.

81. But 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. Table 2 of Bundgaard (Ex. 1012) describes these many different types of such esters, all of which could have been used as substituents. The Bundgaard patent (Ex. 1020) further demonstrates the variety of ester prodrugs available. Its specification and claims are not limited to small chain monoesters and, instead, describe and claim a genus of compounds that involves hundreds of possible substitutions, including esters having up to 20 carbon atoms. *See* Exhibit 1020 at 2-5 and 15.

82. A carbamate (also known as a "carbamic acid ester") would have been a particularly good choice. For example, bambuterol is a clinically useful bis(dimethylcarbamic acid) diester prodrug of terbutaline. *See generally* Daniel S. Sitar, *Clinical Pharmacokinetics of Bambuterol,* 31 CLIN. PHARMACOKINET. 246 (1996) ("Sitar") (Ex. 2058). Another drug that utilizes a carbamic acid ester of a

phenol is the anticancer agent irinotecan (also known as CPT- 11). *See* J. Greg Slatter et al., *Bioactivation of the Anticancer Agent CPT-11 to SN-38 by Human Hepatic Microsomal Carboxylesterases and the in vitro Assessment of Potential Drug Interactions,* 25 DRUG METABOLISM & DISPOSITION 1157(1997) ("Slatter") (Ex. 2059).

83. Further, not one of the drugs listed in Petitioner's prodrug reference, the Bundgaard patent, is an OAB drug and none of them are diphenylpropylamines like 5-HMT. Additionally, the biological target for the compounds disclosed in the Bundgaard patent is not a muscarinic receptor. The types and placement of functional groups in a drug candidate must be optimized to fit the specific binding pocket of the drug target, and the types and placement of functional groups that may be optimal for one target are not relevant to the types and placement of functional groups useful for binding to a different biological target. Because the compounds disclosed in the Bundgaard patent are different from 5-HMT in a variety of ways, including structure, pharmacology, and physicochemical properties, a person of ordinary skill in the art who was considering a 5-HMT prodrug never would have relied on them.

84. In order to quickly dismiss all other possible prodrug classes, Dr. Patterson erroneously argues that one of ordinary skill in the art would have

focused on ester prodrugs based on the Lipinski Rule of 5 and on the desire for a one-step conversion. For the reasons discussed below, I disagree.

85. Dr. Patterson suggests that a monoester would be preferred in order to release the active compound in a single-step conversion. Patterson Decl. at ¶ 124. However, Dr. Patterson fails to recognize that there are numerous types of prodrugs that require only a one-step metabolic reaction to yield the active compound. *See generally* Bundgaard (Ex. 1012) at 3 Table 2; Sitar (Ex. 2058); Slatter (Ex. 2059).

86. Dr. Patterson also suggests that esterification of a hydroxyl group would be "routine" and "predictable." Patterson Decl. at ¶119. I disagree. As discussed above, any modification, even the smallest of modifications, can cause significant differences in the properties of a compound. *Supra* Section VI.

87. Dr. Patterson's suggestion that a person of ordinary skill in the art would have limited his options and avoided diesters based on Lipinski is without merit. Patterson Decl. at ¶ 121-122. In fact, Lipinski would teach that molecular weight would not be a concern for a prodrug of 5-HMT. As one of *four* rules to be met, Lipinski teaches that compounds with molecular weights over 500 may have absorption problems (if at least one of the other three rules are also met). The molecular weight of 5-HMT is only 341.487 and therefore substantial modification of 5-HMT could be made before any concern about molecular weight would arise, if a person of ordinary skill even considered molecular weight to be relevant. That

is, given that the molecular weight of 5-HMT is 341, a person of ordinary skill would be unencumbered in adding up to an additional ca. 160 atomic units in the prodrug moiety (or moieties).

88. Instead of simply selecting an ester, a person of ordinary skill would consider a variety of factors, such as rate of conversion, level of uptake, and stability, and ease of storage, before deciding which type of prodrug to pursue. They would have sought to identify the best possible option with the right aggregate set of properties for the compound under investigation, and would not have looked at ester prodrugs in isolation to do so. Ease of synthesis is a consideration only when deciding between two otherwise identically useful prodrug candidates (as determined after initial synthesis and testing). In practice, a person of ordinary skill seeking to develop a prodrug would not have focused exclusively on one category but would have pursued different structural types in parallel. The prodrug with the most promising properties and results from biological testing would have been the one that was ultimately pursued, with the understanding that the chosen candidate compound must clear multiple obstacles to be deemed suitable to move into clinical trials, without any guarantees of clinical success. In real-world drug development, there are no straightforward or simple paths to a successful compound.

B. A Person of Ordinary Skill Would Have Needed to Select Where to Add the Prodrug Substituent

89. Assuming that a person of ordinary skill in the art elected to develop a 5-HMT prodrug, there are many potential locations on 5-HMT to which a person of ordinary skill could have added the prodrug substituent, and the target would not necessarily be an OH group, as Dr. Patterson suggests. *See* Figure 1. For example, a person of ordinary skill in the art could have added the prodrug substituent to the nitrogen of 5-HMT. *See* Jeffrey P. Krise et al., *Novel Prodrug Approach for Tertiary Amines: Synthesis and Preliminary Evaluation of N-Phosphonooxymethyl Prodrugs*, 42 J. MED. CHEM. 3094 (1999) (Ex. 2013).

90. Assuming the target was an OH group, a person of ordinary skill could have chosen the 2-position (i.e., phenolic/aromatic OH), the 5-position (i.e., benzylic/aliphatic OH), or both, as many prior art prodrugs are di- or tri-substituted. *See* A.A. Sinkula et al., *Rationale for Design of Biologically Reversible Drug Derivatives: Prodrugs*, 64 J. PHARM. SCI. 181 (1975) ("Sinkula") (Ex. 2014); Bundgaard 1991 (Ex. 2015); Patterson Tr. (Ex. 2020) at 187:18-21 (acknowledging that Bundgaard (Ex. 1012) discloses successful diesters).

91. Dr. Patterson suggests that a person of ordinary skill in the art would have focused on the phenolic OH ("2-position") over the benzylic OH ("5-position") in an attempt to utilize steric bulk to avoid transesterification. Patterson Decl. at ¶¶ 123-27. This suggestion overlooks the fact that, as Dr. Patterson agreed

during cross-examination, modification of both moieties into a homogeneous double ester or diester would eliminate the transesterification concern altogether. Patterson Tr. (Ex. 2020) at 190:18-24. Further, Dr. Patterson could identify no prior art to suggest that transesterification would be a concern informing the placement of a prodrug substituent. Patterson Tr. (Ex. 2020) at 193:16-20.

92. Dr. Patterson relies on Lipinski (Ex. 1019) to attempt to argue that diesters of 5-HMT would be too lipophilic (Patterson Decl. at ¶ 123), and yet he made no attempt to apply Lipinski's Rule of 5 to 5-HMT or to any diester of 5-HMT. As shown above, *supra* Section VIII, the properties of 5-HMT do not approach the factors set out in Lipinski's Rule of 5 and the addition of two esters to form a diester would not necessarily cause a problem. In addition, Dr. Patterson's one prodrug example, the Bundgaard patent (Ex. 1020), actually teaches the preparation of three diesters, out of ten total prepared, and that the diesters were successful prodrugs. Ex. 1020 at 7-8, 10 ("3,6-dihexanoyl and other 3,6-dipropionly morphine esters readily penetrated human skin."). If a person of ordinary skill in the art were to consider the Bundgaard patent it would have taught, if anything, the unpredictability of ester substitutions. Ex. 1020 at 7-11.

93. Separately from Dr. Patterson, Petitioner posits that a person of ordinary skill in the art would avoid the 5-position because the moiety at that position in tolterodine was affected by the CYP2D6 enzyme pathway. *See, e.g.*, '980 Petition

at 28. Susceptibility to the CYP2D6 enzyme pathway cannot be predicted by a compound's structure. Instead, the compound would need to be synthesized and tested before any determination could be made.

94. Because the 5-methyl group of tolterodine had already been metabolized in its conversion to 5-HMT, a person of ordinary skill would not be concerned about the possibility of further metabolism at that site—since 5-HMT was not known to undergo additional metabolism at that site. *See, e.g.,* Postlind (Ex. 1010) at 289. If anything, a person of ordinary skill would anticipate that by attaching a prodrug moiety to the 5-position, the prodrug moiety position would be more sterically crowded than the analogous site of tolterodine and 5-HMT. The result is that further metabolism at that position would be less likely or less problematic (as compared to 5-HMT) for steric reasons.

95. Further, deciding whether to add the prodrug group to the 2-position or the 5-position (or both) was not as simple as Dr. Patterson suggests. In fact, one of the inventors initially thought to add the prodrug group to the 5-position, rather than the 2-position. *See* Ex. 2006 at 49:12-50:6. Schwarz attempted to make 5-HMT prodrugs with substitutions at both positions, but discovered that 5-substituted prodrugs were exceedingly unstable, with 2-substituted and di-substituted prodrugs being preferable. *Id.; see also* Ex. 2001 at 17. In any event, Dr. Patterson is also conceptually incorrect; it is impossible to say in advance how

stable the prodrug molecule will or should be, or how the specific substituent would influence the rate of metabolic conversion.

96. The prior art also taught that "no generally applicable and optimal derivatives are as yet available" for use with the phenolic group in drugs that are susceptible to undergo extensive first-pass metabolism.[1] Bundgaard 1991 (Ex. 2015) at 456. While Petitioner argues that it would have been obvious to target the phenolic OH group at the 2-position of 5-HMT for esterification, and that "optimization" would have led to the mono-isobutyryl substitution, *see, e.g.,* '650 Petition at 28-29, Bundgaard 1991 – the one prior art reference that specifically addresses phenolic prodrug substitution – states that "no generally applicable and optimal derivatives are as yet available." Ex. 2015 at 456. As such, the prior art that addressed phenolic substitutions, such as the 2-position of 5-HMT, would have suggested to a person of ordinary skill to substitute elsewhere. It is my opinion that a person of ordinary skill would have considered Bundgaard 1991 to teach away from substitutions at the 2-position of 5-HMT.

97. In fact, many prodrugs were made with substituents at aliphatic positions, like the 5-position on 5-HMT. For instance, quinapril, a prodrug known before the patents' priority dates, is an aliphatic prodrug – an ethyl ester of an

[1] 5-HMT was known to undergo first pass metabolism. *See* Ex. 1024 at 10 (5-HMT is metabolized in the liver); Patterson Tr. (Ex. 2020) at 181:19-183:9 (admitting that 5-HMT undergoes first-pass metabolism).

aliphatic carboxylic acid. *See* Prescribing Information for Accupril® retrieved on March 10, 2015 (Ex. 2054), at 1. Similarly, prodrugs of IDU are also aliphatic ester prodrugs. Milind M. Narurkar et al., *Synthesis, Physicochemical Properties, and Cytotoxicity of a Series of 5'-Ester Prodrugs of 5-Iodo-2'- Deoxyuridine*, 5 PHARM. RES. 734, 734 (1988) ("Narurkar") (Ex. 2055) at 734. Other general references that Dr. Patterson cites include examples of aliphatic ester prodrugs. *E.g.*, Ex. 1012 at Tables 1 and 2.

98. Dr. Patterson's suggestion that a person of ordinary skill in the art would have honed in on a particular substitution at that particular location initially is at odds with how drug discovery and development occurs. The process typically requires attempts at dozens, hundreds, or even thousands of possibilities, with no expectation that any one of the possibilities will be successful. In fact, many drug development programs fail to yield a single appropriate candidate and require multiple iterations and returns to the drawing board for different approaches. Out of all the compounds developed, only a very minor percentage leads to a drug that makes it into clinical trials. Of those that make it into clinical trials, a much smaller fraction reaches regulatory approval. *See, e.g.,* Thomas Hartung, *Food for Thought Look Back in Anger – What Clinical Studies Tell Us About Preclinical Work*, 30 ALTEX 275 (2013) ("Hartung") (Ex. 2056) at 275 ("A devastating attrition rate of more than 90% for substances entering clinical trials has received increasing

attention."). The odds are stacked against drug developers because drug development is such a complex and unpredictable field. Dr. Patterson's argument that prodrug approach would have been a matter of "optimization" or routine medicinal chemistry at the time of the invention is simply irreconcilable with the difficulty and unpredictability of drug development at the time of the invention, and today.

C. Even Having Selected an Ester Group, a Person of Ordinary Skill Would Have Had Thousands of Compounds to Consider

99. Dr. Patterson opines that it would have been obvious to a person of ordinary skill to try a group of esters having two to six carbons. Patterson Decl. at ¶ 129. But Bundgaard (Ex. 1012), Lipinski (Ex. 1019), and the Bundgaard patent (Ex. 1020) do not contain any such teaching to the extent they teach anything relevant at all. *See* Patterson Tr. (Ex. 2020) at 159:24-160:5; 161:3-12 (acknowledging that Bundgaard teaches numerous classes of esters and esters with more than 6 carbons); 179:24-180:6 (acknowledging that esters other than simple alkyl esters could be used to make a 5-HMT prodrug and not violate the Lipinski Rule of 5).

100. In fact, Dr. Patterson testified during his cross-examination that Bundgaard (Ex. 1012) does not teach the selection of any specific ester, much less the isobutyryl ester, and acknowledged that without making and testing various prodrug substituents, a person of ordinary skill would not have been able to predict

which selection would yield the desired characteristics to serve as a suitable pharmaceutical compound. Patterson Tr. (Ex. 2020) at 172:25-173:13; 176:2-20; 177:14-21.

101. In fact, if a person of ordinary skill did look to ester groups that had been used with approved prodrugs, they would have found little, if any, motivation to choose the isobutyryl group, and they certainly would not have chosen isobutyryl without investigating all the other possible choices. In fact, from 1994 through 1998, the years leading up to the priority date of the '980 patent, the FDA approved the New Drug Applications of 193 new molecular entities or new active ingredients, of which only 16 were prodrugs. And of those prodrugs, none had an isobutyryl ester group. *See* Chart of FDA Approvals of New Drug Applications for New Molecular Entities and New Active Ingredients from January 1994 – December 1998 (Ex. 2057).

102. Even if they did, and a person of ordinary skill focused only on this artificially limited group of substitutions for 5-HMT, she would have still been confronted with a wide array of options. First, this limitation yields at least 86 possible substitutions at just a single location (including C2-C6 acyl groups with unsaturation, rings, cis-trans isomers, and enantiomers). Second, even limited to OH groups as locations for ester substitutions, a person of ordinary skill in the art would have considered both the 2- position and the 5- positions alone and in

combination. Moreover, a person of ordinary skill in the art substituting at both locations could employ one substitution at the 2- position, and another substitution at the 5- position. Doing so would have yielded more than 7,500 permutations if a person of skill considered only substitutions, alone or together, at the 2-position, the 5-position, and substitutions at both positions. *See Figure 6.*

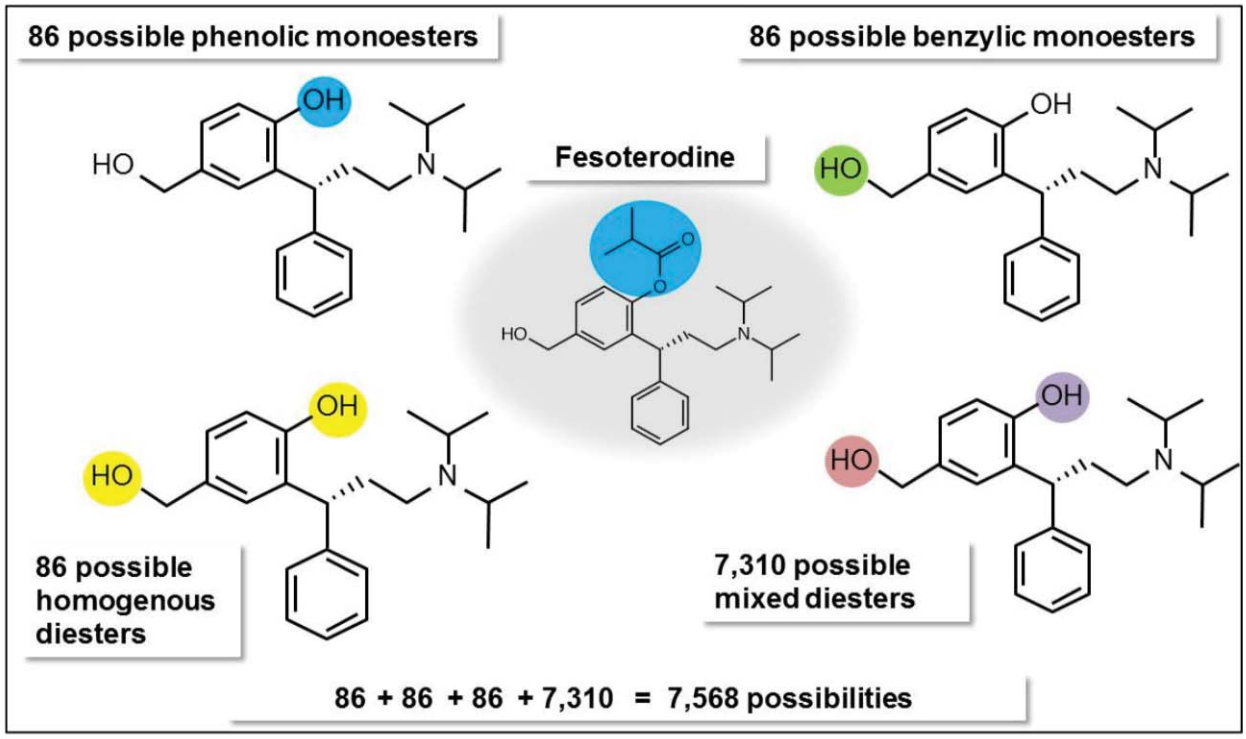

Figure 6. Possible 5-HMT Small-Chain Monoester Substitutions.

103. Additionally, 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. *See e.g.,* Michael W. Jann et al., *Clinical Pharmacokinetics of the Depot Antipsychotics*, 10 CLINICAL PHARMACOKINETICS 315 (1985) (Ex. 2016); R. Beresford et al., *Haloperidol*

Decanoate a Preliminary Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Use in Psychosis, 22 DRUGS 31 (1987) (Ex. 2017). The Bundgaard patent (Ex. 1020) and Bundgaard (Ex. 1012) cited by Dr. Patterson similarly describe esters of longer than six carbons. *See, e.g.,* Exhibit 1020 at 2-5, 7-8, 10, and 15; Exhibit 1012 at Table 2. Even expanding the universe to only carbon ester chains of eight carbons would have dramatically expanded the number of options available into the millions.

104. Dr. Patterson opines that a person of ordinary skill would have arrived at the claimed compound because there would have been only "a very small number of possible contenders," and it would have been only a "matter of routine testing and optimization" to identify one that was both stable and had the requisite lipophilicity. Patterson Decl. at ¶ 129. This greatly undervalues the number of possible compounds, the degree of unpredictability, and the vagaries of testing that are attendant to any drug development program. In fact, there is no way to predict in advance which substituent(s), if any, would have the appropriate balance of properties, including absorption, solubility, stability, and lability (i.e., correct rate of conversion to 5-HMT). 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.

XI. THE (R) ENANTIOMER OF FESOTERODINE WOULD NOT HAVE BEEN OBVIOUS TO A PERSON OF ORDINARY SKILL IN THE ART

105. Petitioner cites to WO 94/11337 ("Johansson") (Ex. 1005) to argue that the (R) enantiomer of fesoterodine would have been obvious. *See, e.g.,* '980 Petition at 49. However, Johansson only suggests that enantiomers of 3,3-diphenylpropylamines were possible. It is not uncommon for one enantiomer to be active while the other is inactive. Therefore, the fact that enantiomers are possible has no bearing on which enantiomer may be preferred or effective. Further, Johansson only discloses IV administration of 5-HMT and other diphenylpropylamines, and it is unclear which enantiomer of 5-HMT is reported as tested in this disclosure, or whether the testing was of the racemate. *See* Ex. 1005 at col.10 ll.1-3; col.10 l.56 – col.12 l.52. In order to conclude that the R enantiomer of 5-HMT was more active than the S enantiomer, a person of ordinary skill in the art would have had to make and test both.

106. Petitioner also relies on Postlind (Ex. 1010) to suggest that the (R) enantiomer of fesoterodine would have been preferred. *See, e.g.,* '980 Petition at 36-37 (*citing* Postlind). Contrary to Petitioner's argument, Postlind (Ex. 1010) – a reference that teaches the (R) enantiomer of tolterodine – teaches nothing about the preferred enantiomer of a separate compound, fesoterodine. For one, Postlind does not discuss the (S) enantiomer of tolterodine at all, thus telling the person of

ordinary skill nothing about the activity of that enantiomer. Second, the preferred enantiomer of one compound does not influence what the preferred enantiomer of a different compound may be, if there even is a preferred enantiomer.

I hereby declare that statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I reserve the right to revise or supplement my opinions as additional information becomes available. I declare under penalty of perjury that the foregoing Declaration is true and correct.

William R. Roush

October 22, 2016

William R. Roush