UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC. and MYLAN LABORATORIES LIMITED,
Petitioners,

v.

UCB PHARMA GMBH,
Patent Owner.

Case Nos. IPR2016-00510; IPR2016-00512; IPR2016-00514; IPR2016-00516; IPR2016-00517
Patent Nos. 6,858,650 B1; 7,384,980; 7,855,230; 8,338,478; 7,985,772

DECLARATION OF HANS MAAG, Sc.D.

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I. INTRODUCTION

1. I, Hans Maag, Sc.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 ("PTO") 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 medicinal chemist with thirty-five (35) years of professional experience in organic and medicinal chemistry in the pharmaceutical industry. I am currently Principal of Chemistry & Drug Discovery Consulting, LLC. A copy

of my *curriculum vitae* is attached hereto as Exhibit 2030. My educational background and my professional experience are summarized below.

4. I obtained a Diploma degree (equivalent to a Bachelor of Science degree) in Chemistry in 1969, and a Sc.D. in Organic Chemistry in 1973, from the Federal Institute of Technology (ETH) in Zürich, Switzerland. I then conducted two (2) years of post-doctoral work at California Institute of Technology (Cal Tech) (1973-1975), where my research interests included studies on the synthesis of the steroidal antibiotic fusidic acid. Synthesis is the process by which a molecule is constructed from commercially available precursors. Synthesis of drug substances frequently involves the design of a target compound structure, followed by synthesis and testing of the compound. Based on the testing results obtained, the next target structure is designed, synthesized, and tested.

5. I also have extensive industry experience in medicinal chemistry, which I obtained at Hoffmann-LaRoche Inc. ("Hoffmann-LaRoche"), Syntex Discovery Research ("Syntex"), Roche Bioscience and Roche Palo Alto LLC (collectively, "Roche"). From 1975 to 1985, I served as Senior Scientist, Assistant Research Group Chief, and Research Fellow at Hoffmann-LaRoche. Among other responsibilities, I was in charge of the synthesis of antibiotics, cardiovascular agents of the prostaglandin type, and compounds targeting central nervous system ("CNS") diseases.

6. In 1985, I moved to Syntex, where I served as Research Section Leader of the Institute of Bio-Organic Chemistry and Principal Scientist of the Institute of Organic Chemistry. In 1995, Syntex was acquired by Roche. I remained at Roche until the facility closed in 2010. During that time, I served as the Principal Scientist and Program Leader, Senior Research Scientist, Acting Director of Medicinal Chemistry, Director of Medicinal Chemistry, and Vice President of the Neurobiology Unit, eventually being named Vice President and Deputy Head of Chemistry for Roche Palo Alto. There, I led numerous project teams, from early drug discovery and lead identification stages to preclinical development and Investigational New Drug Application ("IND") stages.

7. At Syntex and Roche, a focus of my work in medicinal chemistry was the design of drug compounds to treat viral infections, incontinence, pain, depression, cognitive deficits, as well as modulators of the immune system. In particular, I led a medicinal chemistry group for the preclinical development of a prodrug of the antiviral agent ganciclovir. In addition, from 1996 to 2003, I headed a lead optimization program directed at an incontinence target and a preclinical overactive bladder ("OAB") drug development effort. In this role, I directed an OAB team that researched lead compounds for the development of novel anti-muscarinic compounds, two (2) of which made it to the clinical phase. As a part of

this project, I familiarized myself with the scientific literature on OAB and attended conferences on OAB drug development.

8. In 2010, I founded Chemistry & Drug Discovery Consulting, LLC, through which I have advised, and continue to advise, biotech and pharmaceutical companies in the United States and in Europe on all aspects of medicinal chemistry. I provide advice on wide-ranging aspects of medicinal chemistry and synthetic chemistry to companies engaged in preclinical drug discovery and development, with a particular focus on identifying successful lead compounds for drug development.

9. I have taught organic chemistry at Stanford University, serving as a Consulting Professor of Chemistry from 1995 to 1997. In addition, I have authored or co-authored over twenty (20) original papers pertaining to medicinal and synthetic chemistry, including prodrug chemistry. I also served as one (1) of the editors of the two (2)-volume book entitled PRODRUGS: CHALLENGES AND REWARDS (Valentino J. Stella et al. eds., 2007). More recently, I authored a paper on the role of prodrugs for oral drug delivery. Maag, H., *Overcoming Poor Permeability – The Role of Prodrugs for Oral Drug Delivery*, DRUG DISCOVERY TODAY: TECHS., 9, 121-30 (2012). I am also an inventor or co-inventor on over twenty (20) patents, including patents covering prodrugs and drugs targeting

muscarinic receptors. The patents and publications are fully listed in my *curriculum vitae* attached as Exhibit 2030.

B. Materials Considered

10. 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 education, training, and experience as a medicinal chemist and pharmaceutical scientist.

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").
2001	Memorandum Opinion, *Pfizer Inc. et al. v. Sandoz, Inc. et al*, 13-cv-01110 (D. Del.).

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.
2008	A. R. Wein et al., Pharmacologic Treatment of Voiding Dysfunction, *in* URODYNAMICS: PRINCIPLES, PRACTICE AND APPLICATION (A. R. Mundy et al. eds., 2d ed. 1994) ("Wein 1994").
2018	United States Patent No. 7,384,980.
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.").
2026	Transcript of the Deposition of Culley C. Carson III, M.D., dated August 25, 2016, C.A. No. 15-cv-0079 (D. Del.).
2028	Jiunn H. Lin & Anthony Y.H. Lu, *Role of Pharmacokinetics and Metabolism in Drug Discovery and Development*, 49 PHARMACOLOGICAL REVIEWS 407 (1997) ("Lin & Lu").
2029	N. Brynne et al., *Fluoxetine Inhibits the Metabolism of Tolterodine – Pharmacokinetic Implications and Proposed Clinical Relevance* 48 BR. J. CLIN. PHARMACOL. 553-63 ("Brynne 1999").
2030	C.V. of Hans Maag.
2031	Alan J. Wein, *Pharmacologic Options for the Overactive Bladder*, 51 UROLOGY (SUPP. 2A) 43 (1998) ("Wein 1998").
2032	Lisbeth Nilvebrant et al., *Tolterodine – A New Bladder-Selective Antimuscarinic Agent*, 327 EUR. J. PHARMACOL. 196 (1997) (hereinafter, "Nilvebrant 1997 III").
2033	J. Andrew Fantl et al., URINARY INCONTINENCE IN ADULTS: ACUTE AND CHRONIC MANAGEMENT, *in* CLINICAL PRACTICE GUIDELINE 1996 UPDATE (U.S. Dep't of Health & Human Servs., AHCPR Publication No. 96-0682, 1996) ("AHCPR").
2034	H. Madersbacher et al., *Trospium Chloride Versus Oxybutynin: A Randomized, Double-Blind, Multicentre Trial in the Treatment of Detrusor Hyper-Reflexia*, 75 BR. J. UROL. 452 (1995).

2035	G. Schladitz-Keil et al., *Determination of the Bioavailability of the Quaternary Ammonium Compound Trospium Chloride in Man from Urinary Excretion Data*, 36 ARZNEIMITTEL FORSCHUNG/DRUG RES. 984 (1986).
2036	Ditropan XL® Prescribing Information, Revised 07/2013.
2037	R.J. Baigre et al., *Oxybutynin: Is It Safe?*, 62 BRIT. J. UROL. 319 (1988).
2038	H. Madersbacher et al., *A Urodynamically Controlled Multicenter Study in Patients with Urge Incontinence: Tolerability and Efficacy of Propiverine Hydrochloride in Comparison to Oxybutynin*, in International Continence Society, 27th Annual Meeting, Yokohama, Abst. 187 (Sept. 1993).
2039	Hiroyuki Miyachi et al., *Novel Imidazole Derivatives with Subtype-Selective Antimuscarinic Activity (1)*, 8 BIOORG. MED. CHEM. LETT. 2163 (1998) ("Miyachi").
2040	Lisbeth Nilvebrant, *Clinical Experiences with Tolterodine*, 68 LIFE. SCI. 2549 (2001).
2041	Carolyn M. Smith & Rob M. Wallis, *Characterization of [^{3}H]-Darifenacin as a Novel Radioligand for the Study of Muscarinic M_3 Receptors*, 17 J. RECEPT. SIGNAL TR. R. 177 (1997).
2042	Karl-Erik Andersson, *The Overactive Bladder: Pharmacologic Basis of Drug Treatment*, 50 UROLOGY (SUPP. 6A) 44 (1997) ("Andersson 1997").
2043	Taniguchi et al., Agents for the Treatment of Overactive Detrusor. IX. Synthesis and Pharmacological Properties of Metabolites of N-tert-Butyl-4,4-diphenyl-2-cyclopentenylamine (FK584) in Human Urine, 44 CHEM. PHARM. BULL. 1188, (1996).
2044	Yasuo Sasaki et al., *Effect of NS-21, an Anticholinergic Drug with Calcium Antagonistic Activity, on Lower Urinary Tract Function in a Rat Model of Urinary Frequency*, 4 INT. J. UROL. 401 (1997) ("Sasaki (1997)").
2045	Hiroaki Kikukawa, *Pharmacologic Actions of Temiverine (p-INN) and its Active Metabolite, RCC-36, on Isolated Human Urinary Bladder Muscle*, 5 INT. J. UROL. 268 (1998).
2046	N. Mealy & J. Castañer, *YM-905*, 24 DRUGS FUTURE 871 (1999) ("Mealy & Castañer").

2068	Karl-Erik Andersson, Current Concepts in the Treatment of Disorders of Micturition, Drugs 35:477-494 (1988) ("Andersson 1988").
2093	"History of SPM 007" dated November 17, 2000.
2094	"Chemical Development Plan, Incontinence Project," dated February 20, 1998.
2095	"Timetable of the development of Fesoterodine."

II. SUMMARY OF OPINIONS

11. I have reviewed the Declaration of Steven E. Patterson, Ph.D. (the "Patterson Decl."), Petitioner's Petition 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, and the PTAB's Decisions on Institution. 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 Petitions alleges that the challenged claims would have been obvious because the fumarate salt form of fesoterodine would have been obvious. I disagree. It is my opinion that fesoterodine fumarate would not have been obvious to a person of ordinary skill in the art. In particular, it is my opinion that it would not have been obvious to develop a prodrug of 5-hydroxymethyltolterodine ("5-HMT"), tolterodine's active metabolite, for use as an improved OAB drug.

12. I disagree that a person of skill in the art likely would have selected 5-HMT as a lead compound over the many, other available options as of the relevant date; a skilled artisan would have been just as likely, if not more likely, to select one of the many other compounds known in the art as promising leads for a new OAB drug candidate.

13. Additionally, there is nothing in the prior art that would have suggested to a person of skill in the art that a prodrug of 5-HMT would provide any favorable or improved properties over tolterodine or any other OAB drug. If anything, highly relevant prior art suggested that a 5-HMT prodrug would be inferior to tolterodine, at least as to side effects, and particularly at doses escalated above the then-approved dosages of tolterodine. The reasons that Dr. Patterson offers for why a person of skill in the art would have pursued a prodrug of 5-HMT are factually inaccurate, unsupported by the prior art, and, in my view, hindsight-driven in order to mirror the same design approach taken by the Inventors of the '980 patent family and the '650 patent.

14. The true state of the art was that there was considerable and diverse research being undertaken in furtherance of developing new and improved OAB drugs as of 1998, including in my group at Roche, yet I am not aware of any other scientist or research team that considered a prodrug of 5-HMT, of any other tolterodine analog, or of any other non-specific antimuscarinic, which both

tolterodine and 5-HMT are. Instead, the state of the art was focused on identifying agents that had new or improved mechanisms of action, or identifying antimuscarinic agents that exhibited improved "tissue selectivity" for the bladder over other organs, with the ultimate goal of providing a more effective drug. Dr. Patterson has not identified, and I am not aware of, any reason why a person of skill in the art would have suspected that a prodrug of 5-HMT would have met either of those goals.

15. It is also my opinion that fesoterodine was a surprisingly and unexpectedly superior compound. In particular, fesoterodine was surprisingly and unexpectedly superior to novel structural analogs that were designed and synthesized by the Inventors. It was also surprisingly and unexpectedly superior relative to the prior art compounds tolterodine and the active metabolite of tolterodine, 5-HMT. These unexpected results of fesoterodine are demonstrated by numerous data, including the data reported in the '650 patent and the '980 patent families, and preclinical and clinical testing conducted in the development of fesoterodine by Schwarz Pharma AG ("Schwarz") and Pfizer.

16. Notably, it is my opinion that fesoterodine achieved an ideal balance of properties in terms of metabolic conversion, permeability, bioavailability, off-target effects, stability, and safety. This optimal balance of properties is extremely difficult to achieve; that any compound would achieve this balance of properties

could not have been predicted by a person skilled in the art at the time of fesoterodine's invention. Nor could a skilled person have predicted that fesoterodine, in particular, would achieve this balance, especially as compared to the numerous other structurally similar prodrug compounds the Inventors synthesized and tested.

III. LEGAL STANDARDS

17. 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.

18. 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.

19. 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.

20. 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.

21. 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.

22. 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.

23. 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

24. 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.

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

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

27. 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.

28. 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 (Exhibit 1010), the Bundgaard Publications (Exhibits 1012 and 1020), the Detrol® Label (Exhibit 1009), and Berge (Exhibit 1013); and

- Obviousness over the combination of Brynne (Exhibit 1011), the Bundgaard Publications (Exhibits 1012 and 1020), and Johansson (Exhibit 1005).

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.

29. 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 the '650 patent were not obvious. *See* Exs. 2001, 2006 at 13-15, 18. The Court determined that I am an expert in the fields of medicinal chemistry and drug design, including OAB drug design and prodrug design. *See* Ex. 2006 at 523:11-17 (July 15, 2015).

30. 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. and UCB Pharma GmbH v. Mylan Pharmaceuticals Inc.*, No. 1:15-cv-000079(GMS) (D. Del.), also related to the '980 patent family and the '650 patent.

31. 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 as well as about the compound fesoterodine and the fumarate salt form of that compound. I am also knowledgeable about OAB drug design at and around the time of the priority date since I was working in this very field at the relevant time.

V. PERSON HAVING ORDINARY SKILL IN THE ART

32. 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 patents 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.

33. I have reviewed Dr. Patterson's definition of a person of ordinary skill in the art. *See, e.g.,* '650 Pet. at 6 (citing 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.

34. 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. OAB DRUGS AND DRUG DEVELOPMENT AS OF 1998

A. Antimuscarinic and Mixed Action Drugs

35. Antimuscarinic compounds block the action of acetylcholine, preventing abnormal detrusor contractions from occurring and hopefully relieving the patient's symptoms. Because they block these contractions, antimuscarinic compounds have long been used to treat OAB. However, muscarinic receptors are present in a variety of tissues in addition to the bladder, such as the heart, brain, gut, and salivary glands. Administration of antimuscarinic compounds to patients can therefore have effects other than preventing bladder contractions; they can increase heart rate, produce central nervous system ("CNS") side effects like dizziness or confusion, cause constipation, or prevent secretion of saliva, resulting in dry mouth. *See, e.g.*, A. R. Wein et al., Pharmacologic Treatment of Voiding Dysfunction, *in* URODYNAMICS: PRINCIPLES, PRACTICE AND APPLICATION, at 53 (A.

R. Mundy et al. eds., 2d ed. 1994) ("Wein 1994") (Ex. 2008) ("A lack of selectivity is a major problem with all the antimuscarinic compounds . . ."). As of 1998, the incidence of these side effects varied somewhat between the known antimuscarinic drugs.

36. At least five "subtypes" of muscarinic receptors exist (M1, M2, M3, M4, and M5), and their distribution varies in the body amongst different tissues. *See e.g.*, Karl-Erik Andersson, *The Pharmacological Treatment of Urinary Incontinence*, BJU INTERNATIONAL (1999) 84:923-47 ("Andersson Review") (Ex. 1006) at 925. As of 1998, M3 receptors were believed to be most directly responsible for contractions of the bladder muscle that resulted in voiding. *E.g.*, V.A. Alabaster, *Discovery & Development of Selective M_3 Antagonists for Clinical Use*, 60 LIFE SCI. 1053, 1057-58 (1997) (hereinafter, "Alabaster") (Ex. 1028).

37. Atropine is a classical antimuscarinic compound against which other antimuscarinics are frequently compared. *E.g.*, Lisbeth Nilvebrant et al., *Tolterodine – A New Bladder-Selective Antimuscarinic Agent*, 327 EUR. J. PHARMACOL. 196 (1997) (hereinafter, "Nilvebrant 1997 III") (Ex. 2032) (atropine is a "classical non-selective muscarinic receptor antagonist"). As a non-specific, non-selective antimuscarinic, atropine is potent on the bladder, but also on other tissues, and it displays no selectivity for any particular receptor subtype. *Id.* at 196, 200, 202-03; *see also* Karl-Erik Andersson, *Current Concepts in the*

Treatment of Disorders of Micturition, DRUGS 35:477-494 (1988) ("Andersson 1988") (Ex. 2068) at 479. Consequently, for example, atropine antagonizes (M1) muscarinic receptors in the brain as it readily crosses the blood-brain-barrier ("BBB"). Ex. 2068 (Andersson 1988) at 480; J. ANDREW FANTL ET AL., URINARY INCONTINENCE IN ADULTS: ACUTE AND CHRONIC MANAGEMENT, *in* CLINICAL PRACTICE GUIDELINE 1996 UPDATE, at 45 (U.S. Dep't of Health & Human Servs., AHCPR Publication No. 96-0682, 1996) ("AHCPR") (Ex. 2033). Atropine's lack of selectivity caused it to be used infrequently to treat OAB.

38. The antimuscarinic compound propantheline had been widely used to treat OAB and was the second-line therapy in the prior art. AHCPR at 44-45. Propantheline was known to approximate atropine's effect on the bladder, but was less likely to cause CNS side effects. *Id.* Propantheline is a quaternary ammonium compound, which means that it carries a positive charge. Ex. 2068 (Andersson 1988) at 480. This charge is likely partially responsible for its reduced propensity to enter the brain, but is also responsible for its poor absorption, compromising its utility as an oral OAB drug. *Id.*

39. Due to its poor absorption, propantheline has relatively low bioavailability, and its bioavailability varies significantly amongst patients, making dose titration necessary. Ex. 2068 (Andersson 1988) at 479. Propantheline was typically dosed 3-5x/day, at dosages of 7.5-30 mg, with doses occasionally

increasing to 60 mg. *Id.*; AHCPR at 44; Alan J. Wein, *Pharmacologic Options for the Overactive Bladder*, 51 UROLOGY (SUPP. 2A) 43 (1998) ("Wein 1998") (Ex. 2031). Propantheline was sold under the trade names Propantel® and Probanthine®.

40. Emepronium is another quaternary ammonium compound that has been used to treat OAB due to its antimuscarinic activity. Ex. 2068 (Andersson 1988) at 479. Like propantheline, emepronium has low and variable bioavailability, requiring individual titration and frequent dosing (200 mg 3-4x/day). *Id.* at 479-80. Emepronium was sold under the trade name Cetiprin®.

41. Trospium is also a quaternary ammonium compound that has been used to treat incontinence due to its antimuscarinic activity. *E.g.*, Ex. 1006 (Andersson Review) at 928. Trospium was developed in the early to mid- 1990s and marketed outside of the U.S. under the trade name Spasmex® before being approved and sold in the U.S. under the trade names Sanctura® (approved in 2004) and Sanctura XR® (approved in 2007). At least one study concluded that trospium was approximately as effective as oxybutynin (discussed *infra*) but displayed a favorable tolerability profile. *See* H. Madersbacher et al., *Trospium Chloride Versus Oxybutynin: A Randomized, Double-Blind, Multicentre Trial in the Treatment of Detrusor Hyper-Reflexia*, 75 BR. J. UROL. 452, 452-56 (1995) (Ex. 2034); *see also* Ex. 1006 (Andersson Review) at 928 Like propantheline and

emepronium, trospium has relatively low bioavailability. G. Schladitz-Keil et al., *Determination of the Bioavailability of the Quaternary Ammonium Compound Trospium Chloride in Man from Urinary Excretion Data*, 36 ARZNEIMITTEL FORSCHUNG/DRUG RES. 984, 984-87 (1986) (Ex. 2035) (reporting oral bioavailability of about 3%).

42. A number of prior art OAB drugs and drug candidates were characterized as having "mixed" actions, typically meaning that they exhibit antimuscarinic activity in addition to some other mechanism of action that have (or were suspected to have) some beneficial effect on the bladder. One such drug, oxybutynin (Ditropan®), was the first-line OAB treatment in the prior art. Ex. 2031 (Wein 1998) at 44; Ex. 2033 (AHCPR) at 44. Oxybutynin has anticholinergic activity, as well as direct smooth muscle relaxant properties resulting from blocking calcium channels. Ex. 2031 (Wein 1998) at 44; Ex. 2033 (AHCPR) at 44. Typical dosing was 2.5-5 mg 3-4x/day. Ex. 2031 (Wein 1998) at 44; Ex. 2033 (AHCPR) at 44. As of 1998, a once-daily, controlled release formulation of oxybutynin was being developed; it was approved in 2001 as Ditropan XL®. *See* Ditropan XL® Prescribing Information, Revised 07/2013 (Ex. 2036).

43. Oxybutynin exhibits little selectivity for the bladder and caused a high incidence of anticholinergic side effects. Ex. 2068 (Andersson 1988) at 481

(oxybutynin "is associated with a high incidence of side effects . . . [that] are typically anticholinergic in nature and often dose-limiting); Ex. 2031 (Wein 1998) at 44 (oxybutynin's side effects "cause a considerable number of patients to discontinue this medication."). In particular, oxybutynin was known to act preferentially on muscarinic receptors in the salivary glands, causing severe dry mouth, and was known to cross the BBB and produce CNS side effects. Ex. 2068 (Andersson 1988) at 481 ("However, 8 of 20 women receiving oxybutynin stopped medication because of side effects and of those completing therapy 80% suffered significant side effects, of dry mouth and dry skin."); R.J. Baigre et al., *Oxybutynin: Is It Safe?*, 62 BRIT. J. UROL. 319, 321 (1988) (Ex. 2037) (19 of 180 patients reported CNS side effects).

44. Like oxybutynin, dicyclomine has anticholinergic activity and direct smooth muscle relaxant properties. Ex. 2068 (Andersson 1988) at 481; Ex. 2033 (AHCPR) at 45; Ex. 1006 (Andersson Review) at 930. Although it was initially approved in 1950 for the treatment of irritable bowel syndrome ("IBS"), it was also known to be effective in treating OAB in dosages of 10-20 mg 3x/day, although the available clinical data were somewhat more limited than for other compounds. Ex. 2068 (Andersson 1988) at 481; Ex. 2033 (AHCPR) at 45; Ex. 1006 (Andersson Review) at 930.

45. Propiverine (Mictonorm®) has anticholinergic and anti-calcium effects. It was known to be effective in treating OAB; some studies showed that propiverine was as effective as oxybutynin but was more tolerable. H. Madersbacher et al., *A Urodynamically Controlled Multicenter Study in Patients with Urge Incontinence: Tolerability and Efficacy of Propiverine Hydrochloride in Comparison to Oxybutynin*, *in* International Continence Society, 27th Annual Meeting, Yokohama, Abst. 187 (Sept. 1993) (Ex. 2038); Ex. 1006 (Andersson Review) at 931. Propiverine was known to yield several metabolites that were believed to be active. Ex. 1006 (Andersson Review) at 931.

46. Terodiline, which also has anticholinergic and anti-calcium activity, was sold as an OAB drug under the trade name Mictrol®. Terodiline was known to be an effective and well-tolerated drug (*see* Ex. 2068 (Andersson 1988) at 482), but it was believed to be possibly responsible for serious cardiac side effects in some patients and was therefore withdrawn quickly from the market. Ex. 1006 (Andersson Review) at 929; Ex. 2031 (Wein 1998) at 44-45. I understand that the inventors of tolterodine (see *infra*) and other researchers at Kabi Pharmacia used terodiline as a lead compound in their OAB drug development efforts. Hiroyuki Miyachi et al., *Novel Imidazole Derivatives with Subtype-Selective Antimuscarinic Activity (1)*, 8 BIOORG. MED. CHEM. LETT. 2163, 2163-64 (1998) ("Miyachi") (Ex. 2039); *see also infra* ¶ 59 (discussing NK584).

47. In March 1998 the FDA approved tolterodine for use as an OAB drug under the trade name Detrol®. Ex. 1009 at 7. Tolterodine is a diphenylpropylamine with an anticholinergic mechanism of action that was shown to have similar efficacy to oxybutynin. However, preclinical testing indicated that tolterodine had a favorable tissue-selectivity profile, in that it preferentially bound to muscarinic receptors in the bladder over those in other tissues, such as the salivary glands. Lisbeth Nilvebrant et al., *Tolterodine: A New Bladder-Selective Muscarinic Receptor Antagonist: Preclinical Pharmacological and Clinical Data*, 60 LIFE SCI. 1129, 1130-32 (1997) (hereinafter, "Nilvebrant 1997 II") (Ex. 2004). Clinical testing evidenced this apparent selectivity, as tolterodine showed a somewhat favorable tolerability profile over oxybutynin. *Id.* at 1133, 1135; *see also* Rodney A. Appell, *Clinical Efficacy and Safety of Tolterodine in the Treatment of Overactive Bladder: A Pooled Analysis*, 50 UROLOGY (SUPP. 6A) 90 (1997) (Ex. 1017). Detrol® was initially approved in 1 and 2 mg doses for twice-daily administration. In 2001, a once-daily, controlled release ("CR") formulation of tolterodine was launched under the trade name Detrol® LA.

48. Testing of tolterodine's and oxybutynin's comparative affinities for the various muscarinic receptor subtypes did not explain tolterodine's improved tissue selectivity (i.e., its preference for receptors in the bladder over receptors in the salivary glands). Ex. 2032 (Nilvebrant 1997 III) at 204; Ex. 2004 (Nilvebrant 1997

II) at 1130-32. Oxybutynin appeared to be specific for M3 receptors while tolterodine was non-specific. Ex. 2032 (Nilvebrant 1997 III) at 204; Ex. 2004 (Nilvebrant 1997 II) at 1130-32. This could have explained oxybutynin's apparent preference for the salivary glands, where M3 receptors predominate. Ex. 2032 (Nilvebrant 1997 III) at 204; Ex. 2004 (Nilvebrant 1997 II) at 1130-32. By that logic, a person of skill also would have expected oxybutynin to be more potent than tolterodine at inhibiting bladder contractions, which had been assumed in 1998 to be mediated by M3 receptors. Ex. 2032 (Nilvebrant 1997 III) at 204; Ex. 2004 (Nilvebrant 1997 II) at 1130-32. However, tolterodine's potency on the bladder appeared roughly equivalent to oxybutynin. Ex. 2032 (Nilvebrant 1997 III) at 204; Ex. 2004 (Nilvebrant 1997 II) at 1130-32. Although tolterodine was reported to have a selective effect on the bladder muscle over the salivary glands, a lack of selectivity for the bladder in OAB drugs remained a problem even after its launch, with researchers targeting drugs that were selective for muscarinic receptor subtypes in hopes that they would yield a better therapeutic index. *See* Ex. 1006 (Andersson Review) ("Antimuscarinic agents are still the most widely used treatment for urge and urge incontinence. However, currently used drugs lack selectivity for the bladder and effects on other organ systems may result in side-effects which may limit their usefulness. Theoretically, drugs with selectivity for the bladder may be obtained, if the receptor subtype(s) mediating bladder

contraction, and those producing the main side-effects of antimuscarinic drugs, were different.").

49. Tolterodine is metabolized in the liver by cytochrome p450 2D6 ("CYP2D6") enzymes into 5-HMT, which differs from tolterodine by virtue of an additional hydroxy function on a methyl group on one of the compound's phenyl rings. Ex. 1009; N. Brynne et al., *Pharmacokinetics and Pharmacodynamics of Tolterodine in Man: A New Drug for the Treatment of Urinary Bladder Overactivity*, 35 INT. J. CLIN. PHARM. TH., 287, 293 (1997) ("Brynne 1997") (Ex. 1007); Niclas Brynne et al., *Influence of CYP2D6 Polymorphism on the Pharmacokinetics and Pharmacodynamics of Tolterodine*, 63 CLIN. PHARMACOL. THER. 529, 529-39 (1998) ("Brynne 1998") (Ex. 1011). Preclinical studies showed that 5-HMT has similar pharmacological activity to tolterodine, and, while both are active moieties, it was therefore assumed that 5-HMT is responsible for much of tolterodine's effects in most patients. Ex. 2004 (Nilvebrant 1997 II) at 1130-33; *see also generally* Lisbeth Nilvebrant et al., *Antimuscarinic Potency and Bladder Selectivity of PNU-200577, a Major Metabolite of Tolterodine*, 81 PHARMACOL. TOXICOL. 169, 169-72 (1997) (Ex. 1015).

50. Some individuals ("poor metabolizers") are deficient in the CYP2D6 enzyme that converts tolterodine into 5-HMT. In those patients, it is tolterodine, not 5-HMT, that causes a pharmacological response. *See* Ex. 1009; Ex. 1011 at

538 ("[E]ither high concentrations of the parent compound are mainly responsible for the effect among poor metabolizers or substantial concentrations of the active metabolites 5-HM [sic] are responsible for the effect among extensive metabolizers."); Lisbeth Nilvebrant, *Clinical Experiences with Tolterodine*, 68 LIFE. SCI. 2549, 2550 (2001) (Ex. 2040). This polymorphism in metabolism was reported repeatedly in the prior art by March 1998 to have no clinical consequence; according to Brynne et al., for example, "[i]n contrast to the pharmacokinetics, the pharmacodynamics of tolterodine were not generally influenced by metabolic phenotype." Ex. 1011 at 537; *see also id.* at 529 ("[T]he CYP2D6 polymorphism does not appear to be of great importance in the antimuscarinic effect, probably because of the additive action of parent drug and active metabolite."). As separately stated in the prior art FDA-approved prescribing information for Detrol®:

> Because of differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the sum of unbound serum concentrations of tolterodine and the 5-hydroxymethyl metabolite is similar in extensive and poor metabolizers at steady state. Since tolterodine and the 5-hydroxymethyl metabolite have similar antimuscarinic effects, the net activity of DETROL tablets is expected to be similar in extensive and poor metabolizers.

Ex. 1009 at "Variability in Metabolism"; *see also id.* at "Drug-Drug Interactions" ("Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be extensive metabolizers of tolterodine to resemble the pharmacokinetic profile in

poor metabolizers. . . . No dose adjustment is required when DETROL and fluoxetine are coadministered.").

B. Non-Antimuscarinic Drugs

51. In addition to antimuscarinic, several other mechanisms of action were known in the prior art as potentially effective for OAB treatment.

52. The compound flavoxate demonstrates an inhibitory effect on smooth muscle contractions in vitro and had been widely used as an incontinence treatment. Ex. 2068 (Andersson 1988) at 480; Ex. 2033 (AHCPR) at 46. Although the main mechanism of the effect of flavoxate on the smooth muscle has not been established, flavoxate does not present any anticholinergic effect. Ex. 1006 (Andersson Review) at 931. Flavoxate is well-tolerated, but reports of its clinical benefits were inconclusive. Ex. 2068 (Andersson 1988) at 480; Ex. 2033 (AHCPR) at 44.

53. Oxybutynin and dicyclomine's effects were thought to have been partly attributable to direct inhibitory activity. *See supra* ¶¶ 42-44 (discussing oxybutynin and dicyclomine); *see also* Ex. 2008 (Wein 1994). However, as I explained above, oxybutynin is known to cause a high incidence of anticholinergic side effects, particularly by acting preferentially on muscarinic receptors in the salivary glands, causing severe dry mouth. *See supra* ¶ 43; *see also* Ex. 1006 (Andersson Review) at 930. With respect to dicyclomine, published reports

indicate that the effect of this compound on uninhibited bladder contractions was favorable. Ex. 2068 (Andersson 1988) at 482; Ex. 2008 (Wein 1994) at 44. However, there are limited clinical trials studying the efficacy and side-effects of dicyclomine. *Id.*

54. Because the influx of extracellular calcium was known to be important for contraction of the bladder muscle, researchers had experimented with calcium antagonists as potential OAB treatments; blocking the influx could prevent contractions, thus alleviating symptoms. Ex. 2068 (Andersson 1988) at 480; Ex. 2031 (Wein 1998) at 44-45. Terodiline had already suggested that calcium antagonism could be useful in treating OAB, when combined with anticholinergic activity. Ex. 2031 (Wein 1998) at 44. As of 1998, reports indicated that "[a]n agent that combines calcium antagonistic activity with anticholinergic activity may therefore offer improved clinical efficacy." Ex. 2031 (Wein 1998) at 44; *see also* Ex. 1006 (Andersson Review) at 924 (indicating that, as of 1999, calcium antagonists were "[u]nder investigation" as potential OAB treatments).

55. Researchers also had investigated α-adrenoreceptor agonists and β-adrenoreceptor antagonists as potential OAB treatments. Both categories of compounds showed the potential to inhibit contractions of the bladder muscle, but their clinical effect had not been confirmed, as some studies showed efficacy while others did not. Ex. 2068 (Andersson 1988) at 483.

56. Several tricyclic antidepressants ("TCAs") had also been evaluated for their ability to treat OAB, including imipramine, desipramine, nortriptyline, and doxepin. Ex. 2031 (Wein 1998) at 45; Ex. 2033 (AHCPR) at 46-47; Ex. 2008 (Wein 1994) (describing TCAs, particularly imipramine, as "especially useful agents"). TCAs have anticholinergic and sedative effects, and they block reuptake of norepinephrine and serotonin, but the mechanism by which they acted on the bladder was uncertain. Ex. 2031 (Wein 1998) at 45. TCAs showed efficacy, but with notable side effects. *Id.*; *see also* Ex. 2033 (AHCPR) at 46-47.

C. New Drugs Under Investigation

57. Several pharmaceutical companies had active OAB drug discovery programs in the mid-1990's. For example, Pfizer was researching the compound darifenacin, which is selective for M3 muscarinic receptors. Carolyn M. Smith & Rob M. Wallis, *Characterization of [^{3}H]-Darifenacin as a Novel Radioligand for the Study of Muscarinic M_3 Receptors*, 17 J. RECEPT. SIGNAL TR. R. 177, 177-84 (1997) (Ex. 2041); Ex. 1028 (Alabaster). Because the M3 receptor subtype was thought to be critical for contraction of the bladder muscle, researchers hoped that M3-selective antagonists could provide a better separation between effects on the bladder and effects on other tissues. Ex. 1028 (Alabaster) at 1054, 1057; Karl-Erik Andersson, *The Overactive Bladder: Pharmacologic Basis of Drug Treatment*, 50 UROLOGY (SUPP. 6A) 44, 77 (1997) ("Andersson 1997") (Ex. 2042). Preclinical

tests appeared to confirm that darifenacin had significantly higher affinity for M3 receptors in the bladder and gut over receptors in the salivary glands. Ex. 1028 (Alabaster) at 1057-59. Clinical studies were ongoing in 1997. *Id.* at 1059. The FDA approved darifenacin for treatment of OAB in 2004 under the trade name Enablex®.

58. In 1997, scientists from Yamanouchi Pharmaceutical Co. presented their research into bladder-selective M3 receptor antagonists for use as urinary incontinence drugs. 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") (Ex. 1029). They synthesized a series of 1,2,3,4-tetrahydro-2-isoquinoline derivatives and tested their receptor affinities and effect on bladder contractions and salivary secretions. They concluded that one of the compounds, designated YM-53705, had high affinity for M3 receptors and was selective for inhibiting bladder contractions over salivary secretions. That compound, also known as solifenacin, was eventually FDA approved in 2004 for treatment of OAB and marketed under the trade name Vesicare®.

59. Researchers at Fujisawa Pharmaceutical Co. published a series of papers describing their efforts to identify improved OAB drugs based on the lead compounds oxybutynin and terodiline. At least one of the compounds they

synthesized, N-*tert*-Butyl-4,4-diphenyl-2-cyclopentylamine ("NK584"), was believed to have favorable anticholinergic activity over terodiline and was advanced into clinical trials. *See, e.g.,* Taniguchi et al., Agents for the Treatment of Overactive Detrusor. IX. Synthesis and Pharmacological Properties of Metabolites of N-tert-Butyl-4,4-diphenyl-2-cyclopentenylamine (FK584) in Human Urine, 44 CHEM. PHARM. BULL. 1188, 1188-95 (1996) (Ex. 2043).

60. In 1997, scientists working for Nippon Shinyaku Co. reported that they had discovered NS-21, "a novel compound intended for the treatment of urinary frequency and urinary incontinence." Yasuo Sasaki et al., *Effect of NS-21, an Anticholinergic Drug with Calcium Antagonistic Activity, on Lower Urinary Tract Function in a Rat Model of Urinary Frequency*, 4 INT. J. UROL. 401, 401 (1997) ("Sasaki (1997)") (Ex. 2044). NS-21, also known as temiverine, is a structural analog of oxybutynin. Hiroaki Kikukawa, *Pharmacologic Actions of Temiverine (p-INN) and its Active Metabolite, RCC-36, on Isolated Human Urinary Bladder Muscle*, 5 INT. J. UROL. 268, 268-75 (1998) (Ex. 2045). The authors of Sasaki explained that they had designed NS-21 to have anticholinergic and anti-calcium effects, like terodiline, propiverine, and oxybutynin. Ex. 2044 (Sasaki (1997)); *see also* Ex. 2068 (Andersson 1988) at 489 ("[I]t appears that drugs with 'mixed' actions, for example oxybutynin and terodiline, have the best documented effect."). The Nippon Shinyaku scientists compared NS-21 to terodiline, propiverine,

oxybutynin, flavoxate, verapamil (a calcium antagonist), and atropine, using an "animal frequency model that reflect[s] the clinical symptoms of impaired bladder function." Ex. 2044 (Sasaki (1997)) at 401. They concluded that "NS-21 may be a more effective therapeutic drug than propiverine, oxybutynin, or flavoxate." *Id.*

61. A February 1998 article identified three specific mechanisms that would likely be prominent in OAB drug research: (1) drugs that affect peripheral excitatory mechanisms (including more specific receptor antagonists); (2) drugs that inhibit afferent (sensory) mechanisms; and (3) drugs that affect more central actions at either the ganglionic, spinal cord, or supraspinal level. Ex. 2031 (Wein 1998) at 45-46; *see also* Ex. 2008 (Wein 1994) at 54 ("[A]n anticholinergic with a significant ganglionic blocking action as well . . . might be more effective in suppressing bladder contractility."), 60 (describing desensitization of afferent neurons as "an interesting concept that holds promise of future avenues of drug treatment"). The article indicated that the second category (afferent mechanisms) was most prominent at the 1997 meeting of the American Urological Association. Ex. 2031 (Wein 1998) at 46. Nine abstracts from that meeting concerned capsaicin, an irritant and allogenic compound that was believed to be able to desensitize afferent neurons. *Id.*; Ex. 2008 (Wein 1994) at 60-61. One abstract concerned a new potassium channel opener (YM-934), and another concerned a phosphodiesterase inhibitor (vinpocetine). *Id.*; *see also* Ex. 2008 (Wein 1994) at

57 ("Further experimental and clinical trials with potassium channel openers are awaited."); Ex. 1006 (Andersson Review) at 924 (indicating that, as of 1999, potassium channel openers were still "[u]nder investigation" as potential OAB treatments). Two abstracts described work on tolterodine.

62. By the late 1990's, a wide variety of drugs, with diverse structures and mechanisms of action, were the subject of clinical trials for urinary incontinence, many of which were known in the prior art. N. Mealy & J. Castañer, *YM-905*, 24 DRUGS FUTURE 871 (1999) ("Mealy & Castañer") (Ex. 2046). In addition to temiverine, darifenacin, and YM-53705 (solifenacin), discussed *supra*, the following drugs were the subject of clinical studies by 1999:

- Inaperisone (muscle relaxant)
- Duloxetine oxalate (serotonin and norepinephrine reuptake inhibitor)
- (S)-oxybutynin
- KRP-197 (M1 and M3 antagonist)
- NC-1800 (centrally acting agent)
- NS-49 (α_{1a}-adrenoreceptor agonist)
- ZD-6169 (potassium channel activator)
- Resiniferatoxin (vanilloid compound)
- Saredutant (tachykinin NK2 antagonist)
- HCT-1026 (nitric oxide donor)

Ex. 2046 (Mealy & Castañer) at 873.

63. In the mid to late-1990's, I was leading a drug discovery team at Roche that was seeking an improved OAB drug. The focus of our work was trying to identify a compound with an improved muscarinic receptor selectivity profile, such that the compound would have increased potency at the bladder and decreased potency on other tissues. This would yield a drug with an improved tolerability profile, or, alternatively, a drug that could be given in higher doses, maintaining an acceptable tolerability profile while increasing the effects on the bladder. We used secoverine, a well-known, prior art antimuscarinic, as the lead compound in our efforts, which resulted in two compounds being tested in clinical trials.

VII. A PERSON OF ORDINARY SKILL IN THE ART WOULD NOT HAVE FOCUSED ON TOLTERODINE

64. If a person of skill in the art were seeking to develop an improved OAB drug, there is no reason that a skilled artisan would have honed in on tolterodine, rather than any of the many other available options, particularly where many such options were more reflective of the state of the art in the OAB treatment field than tolterodine was by 1998. There were many compounds in the prior art that were known to be either effective incontinence treatments or promising compounds in that regard (e.g., propantheline, emepronium, trospium, oxybutynin, dicyclomine, propiverine, terodiline, tolterodine, flavoxate, imipramine, darifenacin, solifenacin, NK584, temiverine, capsacin, etc.) *See supra* Section VI. Dr. Patterson

summarily dismisses them as being less effective or lacking clinically proven efficacy. Patterson Decl., ¶¶ 85-91.

65. However, I have reviewed the transcript from the cross-examination of Dr. Patterson, and during his cross-examination, Dr. Patterson agreed with my opinion that a person of ordinary skill in 1998 or 1999 would have had a number of available options to pursue in developing a new OAB drug and that at least some of these mechanisms had been reported to have clinical efficacy and pre-clinical evaluation. Transcript of the Deposition of Steven Patterson, Ph.D., dated October 4, 2016 ("Patterson Tr.") (Ex. 2020) 27:14-20, 66:16-67:13. Specifically, when asked about trospium during his cross-examination, Dr. Patterson backtracked and opined that a person of ordinary skill might use trospium as a starting point and that it could be a promising compound to modify to improve bioavailability. Patterson Tr. (Ex. 2020) 56:14-21, 58:10-15. He further acknowledged that that the prior art taught that trospium had fewer side effects compared to oxybutynin. Patterson Tr. (Ex. 2020) 58:21-59:2, discussing Ex. 1006.

66. In his Declaration, Dr. Patterson does not fully consider mechanisms of action other than antimuscarinic activity. In fact, the state of the art at the time of fesoterodine's invention was that several other mechanisms were being explored, such as calcium antagonism, afferent mechanisms, ganglionic/spinal/supraspinal mechanisms, potassium channel activation, adrenoreceptor inhibition/activation,

and direct action on the detrusor muscle. *See supra* ¶¶ 51-63. The prior art taught that the combination of calcium antagonism and antimuscarinic activity was particularly promising, with at least one pharmaceutical research group pursuing that specific combination of effects. *See supra* ¶¶ 45-46, 54, 60.

67. If a person of skill were to pursue an improved antimuscarinic compound, the prior art showed a preference for M3-selective compounds, as it was believed that those compounds could be more selective for the bladder over other tissues. *See supra* ¶¶ 36, 57. During Dr. Patterson's cross-examination, he agreed that the Andersson Review did indicate that pursuing M3-selective compounds was a "very reasonable way to proceed." Patterson Tr. (Ex. 2020) 16:7-19, discussing Ex. 1006. And indeed, several research groups were in fact targeting M3-specific compounds as improved OAB drugs. *See supra* ¶¶ 57-58 (darifenacin, solifenacin). Tolterodine and 5-HMT, however, are relatively pure antimuscarinics. *See e.g.,* Ex. 2031 (Wein 1998) at 46; Ex. 1015 (Nilvebrant 1997) at 172. Had a person of skill been interested in pursuing an antimuscarinic, it is likely he would have instead shown a preference for a selective antimuscarinic.

68. Dr. Patterson also acknowledged in his cross-examination that a person of ordinary skill would have looked at terodiline and attempted to determine which enantiomer of terodiline resulted in the QT effect. Patterson Tr. (Ex. 2020) 52:17-53:3. The prior art shows that several research groups did select terodiline, in

addition to oxybutynin, as a lead compound for investigations into improved OAB drugs. *See supra* ¶¶ 46, 59-60. NK584 was based on terodiline, while temiverine was based on oxybutynin. *Id.*; *see also* Ex. 2039 (Miyachi) at 2163 (considering propiverine, terodiline, and oxybutynin as leads, and selecting terodiline). There is no evidence that any researchers had selected tolterodine or 5-HMT as a lead compound as of May 1998.

69. In May 1998, Detrol® had been FDA-approved for less than two months, meaning that clinical experience with the drug was limited. Compounds like oxybutynin, propantheline, emepronium, dicyclomine, terodiline, and imipramine had been known and used to treat OAB for over a decade at that time. *E.g.*, Ex. 2068 (Andersson 1988) at 479. In selecting a lead compound, a person of skill would have preferred compounds that were more well-known and long-used to a drug that, like tolterodine, was only just approved by the FDA. While terodiline had been withdrawn from the market due to cardiac safety concerns, this clearly did not deter researchers from using it as a lead compound in their own development efforts. *See supra* ¶¶ 46, 59, 68 (tolterodine, NK584, Miyachi). If a person of ordinary skill in the art did consider compounds like 5-HMT that had not been administered orally, had not had its safety or efficacy studied, and had not been FDA approved, they would have had many other options available to them, such as darifenacin, solifenacin, temiverine, capsacin, NK584, among others.

70. Dr. Patterson also does not consider that nearly all the prior art OAB drugs were dosed three or more times daily; Detrol®, which was dosed just twice daily, was the exception. Clinical trials of controlled release versions of oxybutynin, which would have addressed this problem by enabling once-daily dosing, were ongoing as of 1998. *See supra* ¶ 42. Accordingly, a person of skill would likely have been motivated to seek a solution to the convenience and compliance problem of multiple daily doses.

71. When the full scope of the prior art is considered, including the research that was actually ongoing at the time, there is no teaching in the prior art that would have singled out tolterodine or 5-HMT as preferred lead compounds for further development. Indeed, even after tolterodine was launched in the US, publications indicate that researchers were still actively pursuing improved compounds, with better selectivity and an improved balance of efficacy and tolerability. *See supra* ¶ 48.

72. I am personally familiar with the active fields of research into OAB drugs as of the mid to late 1990s, as I was directing a research group at Roche at that time that was tasked with identifying new and promising compounds for the treatment of OAB. We pursued a hypothesis of a particular muscarinic subtype selectivity, prototypically exemplified by the agent secoverine. Our goal was to produce a new compound with an improved balance of efficacy and tolerability,

which was the need existing in the art of OAB treatment at this time. As described supra, numerous other research groups were pursuing the same goal at this time, by antimuscarinic mechanisms and otherwise, using a variety of chemical structures, most of which are quite dissimilar from tolterodine and 5-HMT. There was nothing in the prior art to suggest that selecting tolterodine or 5-HMT as a lead and then taking a prodrug approach would meet the need that existed in the art. Nor is there any indication that any of the numerous research groups working on development at the time, other than that Inventors at Schwarz, considered developing a prodrug of 5-HMT.

VIII. CYP2D6 POLYMORPHISM WOULD NOT HAVE MOTIVATED A PERSON OF ORDINARY SKILL TO PIVOT FROM TOLTERODINE TO 5-HMT

73. After focusing in on tolterodine, Dr. Patterson takes the unsupported position that a person of ordinary skill would view CYP2D6 polymorphism as a problem. Patterson Decl., ¶¶ 95 – 102. Dr. Patterson opines in his Declaration that a person of skill in the art would have wanted to develop 5-HMT to improve upon tolterodine and "to avoid the potential for 2D6 drug-drug interactions or the propensity of 2D6 poor metabolizers to develop adverse side effects when using drugs subject to this pathway." *See, e.g.,* '650 Decision at 16; see also Patterson Decl., ¶¶ 95-96, 99, 101-102. In support of this theory, Petitioner cites Postlind (Ex. 1010), which expresses a general caution about drugs subject to CYP2D6

polymorphism, based on a 1986 publication concerning experiences with drugs other than tolterodine, written years before tolterodine was even discovered. Postlind (Ex. 1010) at 292 citing Smith (1986). Postlind would not have suggested to a person of skill to pivot from tolterodine to 5-HMT as lead compound.

74. Additionally, the prior art did not suggest that tolterodine's CYP2D6 polymorphism was the cause of any of Detrol®'s adverse events. In reporting adverse events, the Detrol® Label does not parse between poor and extensive metabolizers. *See* Ex. 1009 at 6. Brynne 1998, meanwhile, did parse between poor and extensive metabolizers in reporting adverse events, and in doing so demonstrated that adverse events were not limited to poor metabolizers. Ex. 1011 at 536. A person of ordinary skill would have had no reason to believe that bypassing the CYP2D6 metabolism of tolterodine would avoid adverse events associated with Detrol®.

75. Although Dr. Patterson opines that tolterodine's CYP2D6-dependent metabolism leads to "patient variability" and dosing issues, Patterson Decl., ¶¶ 99, 101, there is no evidence that polymorphism in the metabolism of tolterodine has any clinical relevance. The very references on which Dr. Patterson relies teach that poor and extensive metabolizers experience similar clinical effects, in terms of efficacy and tolerability, from administration of tolterodine. Ex. 1011 at 537-538; Ex. 1009 at column 2. During his cross-examination, he could cite no sources to

suggest otherwise. Patterson Tr. (Ex. 2020) 112:24-113:7. In fact, Dr. Culley C. Carson, III, M.D., Petitioner's expert urologist in the pending, related litigation *Pfizer Inc. and UCB Pharma GmbH v. Mylan Pharmaceuticals Inc.*, No. 1:15-cv-000079 (GMS) (D. Del.), agreed that tolterodine acts in extensive and poor metabolizers to give the same net activity. Transcript of the Deposition of Culley C. Carson, III, M.D., dated August 25, 2016, *Pfizer Inc. and UCB Pharma GmbH v. Mylan Pharmaceuticals Inc.*, No. 1:15-cv-000079 (GMS) ("Carson Tr.") (Ex. 2026) at 76:23-77:4.

76. First, I disagree with Dr. Patterson's opinion that a person of ordinary skill would view CYP2D6 polymorphism as a problem. Patterson Decl., ¶¶ 95 – 102. CYP2D6 polymorphism was the "most studied genetic polymorphism in drug metabolism." Jiunn H. Lin & Anthony Y.H. Lu, *Role of Pharmacokinetics and Metabolism in Drug Discovery and Development*, 49 PHARMACOLOGICAL REVIEWS 407 (1997) ("Lin & Lu") (Ex. 2028) at 436. The prior art taught that its effects depend largely on whether the parent compound, the metabolite, or both, are active. *Id.* at 437. For example, encanide and propafenone were two prior art drugs that, like tolterodine, are mediated by CYP2D6 and have two active moieties. *Id.* And, like tolterodine, they each produce similar therapeutic responses between extensive and poor metabolizers. *Id.* This is why the "clinical relevance of genetic polymorphism must be assessed carefully" for the compound

at issue before drawing any conclusions. *Id.* at 438. In my opinion, a person of ordinary skill in the art would not have been motivated to isolate 5-HMT from tolterodine simply due to the fact that tolterodine was mediated by CYP2D6, especially given the prior art specific to tolterodine suggesting that CYP2D6 was not a problem for tolterodine.

77. In his Declaration, Dr. Patterson acknowledges Brynne 1998's conclusion that "[d]espite the influence of CYP2D6 polymorphism on the pharmacokinetics of tolterodine, this does not appear to be of great pharmacodynamics importance." *See* Patterson Decl., ¶ 54 (citing Ex. 1011 at 538). Yet Dr. Patterson, without providing any support, dismisses Brynne's conclusion as "equivocal" and "of no moment to the skilled person's use of Brynne as teaching important, reproducible facts about tolterodine's metabolism and other drug properties such as bioavailability." *Id.* However, during his cross-examination, Dr. Patterson agreed that Brynne 1998 would have suggested to a person of ordinary skill that CYP2D6 polymorphism *did not impact* the effect of tolterodine on patients. Patterson Tr. (Ex. 2020) 94:24-95:6.

78. If anything, the prior art suggested that administering 5-HMT, per se, would have been worse than tolterodine with respect to certain antimuscarinic side effects, including dry mouth, which was a main detractor with the existing OAB drugs at the time. Specifically, Brynne 1998 reports "a weak correlation between

tolterodine concentration and an effect on salivation," whereas a "stronger correlation was seen with [5-HMT] and effect." Ex. 1011 at 538; *see also id.* ("Tolterodine caused a similar decrease in salivation in [extensive and poor 2D6 metabolizer] panels."). In my opinion, a person of ordinary skill would read Brynne 1998 to suggest that if anything, the effect on salivation is worse with respect to 5-HMT as compared with tolterodine.

79. The Detrol® Label, also cited by Dr. Patterson, unequivocally teaches physicians that poor metabolizers and extensive metabolizers should receive the same dosages and experience the same effects from the drug: "[T]he net activity of Detrol Tablets is expected to be similar in extensive and poor metabolizers." Ex. 1009 at 2. During his cross-examination, Dr. Patterson agreed that the Detrol® Label taught that poor and extensive metabolizers experience similar antimuscarinic effects and similar net activity from administration of Detrol® regardless of metabolizer type. Patterson Tr. (Ex. 2020) 111:2-14; 112:4-13. If it was believed that there were no clinical differences between poor metabolizers and extensive metabolizers, then there would be no reasonable motivation to develop a prodrug of the metabolite.

80. There was no evidence that the approximately 7% of the population that are poor metabolizers of tolterodine did not benefit from the drug just as much as extensive metabolizers. Further, during his cross-examination, Dr. Patterson was

unable to identify a single prior art teaching that CYP2D6 polymorphism presented any issues for patients taking tolterodine. Patterson Tr. (Ex. 2020) 112:24-113:7. However, even assuming that there were some negligible clinical differences between poor metabolizers and extensive metabolizers – and I have seen no evidence of that – a person of skill would have had no motivation to develop a new drug to simply serve 7% of the population.

81. Dr. Patterson also opines that because "5-HMT is not metabolized by both CYPD6 and CYP3A, but only by CP3A4, the risk of drug-drug interactions is decreased compared to tolterodine." Patterson Decl., ¶¶ 96, 111. I disagree. First, tolterodine is converted to 5-HMT and 5-HMT is converted mainly by CYP3A4 to the N-des-isopropyl metabolite. The de-alkylation metabolism also happens in poor metabolizers in that tolterodine is converted to its N-des-isopropyl metabolite. The de-alkylated metabolites of either tolterodine or 5-HMT were and remain considered to be pharmacologically inactive. The critical importance of the de-alkylation metabolism mediated by CYP3A4 is highlighted in the Detrol® Label in that dose adjustments are recommended for patients to whom CYP3A4 inhibitors are co-administered. No dose adjustments are necessary in case a CYP2D6 inhibitor, such as fluoxetine, is co-administered. Ex. 1009 at 3; *see also* N. Brynne et al., *Fluoxetine Inhibits the Metabolism of Tolterodine – Pharmacokinetic Implications and Proposed Clinical Relevance* 48 BR. J. CLIN. PHARMACOL. 553-

63 ("Brynne 1999") (Ex. 2029) at 562 (concluding that dosage adjustment was not needed for patients treated with another drug known to inhibit CYP2D6). In fact, Petitioner's expert urologist in the pending litigation, Dr. Carson, agreed that no dose adjustment was necessary because the net activity for extensive metabolizers and poor metabolizers of tolterodine were judged to be the same. Carson Tr. (Ex. 2026) 75:23-76:6. Thus, from a pharmacological standpoint (as well as from a clinical standpoint), there are no differences between the major metabolic pathways of tolterodine and of 5-HMT, which result in pharmacologically inactive metabolites, and are excreted. Therefore, a person of ordinary skill would not have been motivated to isolate 5-HMT from tolterodine because there were no meaningful pharmacological differences in the metabolisms of tolterodine and 5-HMT.

IX. PRODRUG DESIGN WAS AND REMAINS PARTICULARLY UNPREDICTABLE AS EVIDENCED BY THE INVENTORS' WORK DEVELOPING FESOTERODINE

A. Prodrug Design

82. A prodrug is a compound that is inactive or partially inactive against the biological target, but is metabolically converted to its active metabolite inside the body. Prodrug design faces even greater uncertainties than ordinary drug design. For example, although every drug must be reasonably stable, a prodrug cannot be so stable that it does not convert to its active metabolite once in the body.

Furthermore, the prodrug's conversion must be extensive, such that all or most of the inactive prodrug is converted to its active metabolite. A prodrug intended for systemic distribution must be stable through the gastrointestinal tract, but must be able to penetrate through the gastrointestinal tract's cell membranes into the bloodstream. However, once in the bloodstream the prodrug must be efficiently metabolized to the active metabolite. If metabolism results in undesired byproducts and/or reactive cleaved products, it will lead to toxicity concerns, likely disqualifying the prodrug candidate.

83. A prodrug approach also complicates bioavailability, receptor affinity, and toxicity measurements, given that each of these properties must be considered with respect to the parent compound and its active metabolite. For example, with a prodrug, the bioavailability of the active moiety is critical for clinical efficacy, and thus the extent and rate of metabolic conversion of the prodrug also affects the bioavailability measurements. However, the prodrug compound itself may have toxic effects or bind to key off-target receptors, and thus often its properties must be measured as well.

84. Due in large part to the inherent unpredictability not faced by other forms of drug development, a prodrug approach was usually taken as an approach of last resort in 1998, at the time of inventions claimed in the '980 patent family

and the '650 patent. For instance, fesoterodine was the first prodrug designed as an antimuscarinic to treat urinary incontinence.

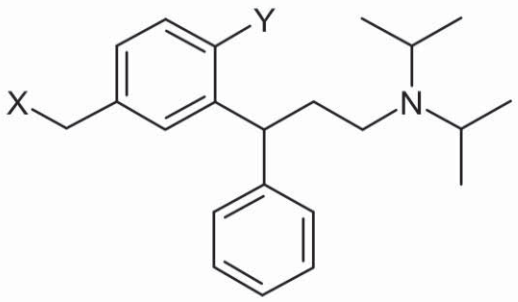
85. When prodrug approaches are taken, as with all drug design, none of the properties, including prodrug-specific properties, such as off-target effects, are predictable and can only be ascertained through synthesis of the compounds and subsequent experimental testing. This explanation of prodrug design is provided to give context to the testing undertaken by Schwarz and resulting data relied upon in providing the following bases for my opinion that fesoterodine exhibited unexpected results relative to tolterodine and 5-HMT.

B. The Inventors' Work and Fesoterodine

86. Even if a person of ordinary skill in the art had decided to make a prodrug of 5-HMT, such work would have been highly unpredictable, which is evidenced by the Inventors' work. In the search for a prodrug of 5-HMT, the active metabolite of tolterodine, Schwarz synthesized and tested a number of potential prodrugs of 5-HMT to determine whether it could develop a prodrug that would meet a range of criteria, including metabolic conversion and permeability through relevant membranes, in addition to other criteria, including bioavailability, lack of off-target effects, stability, and safety. This data presented in the '980 patent and study reports from early in fesoterodine's development (1997-1999) list

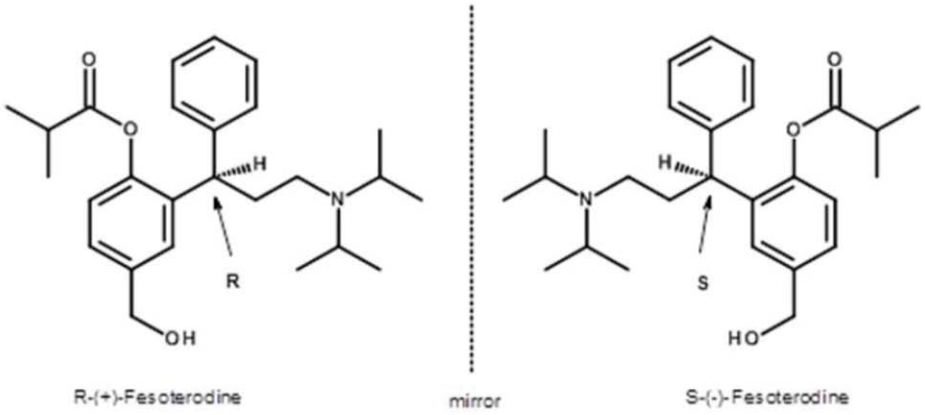
examples of these compounds. *E.g.*, '980 patent (Ex. 2018) 53:51-56:26; Ney Declaration, Ex. B (Ex. 2007) at 2167-2178.

87. The prodrug compounds the Inventors prepared are all derivatives of 5-HMT that vary according to the following structure, in which the varied substituents are represented by "X" and "Y":



88. In this declaration, I have described the Inventors' compounds by using the abbreviation convention from the '980 patent and the Inventors' test data. Specifically, compounds are described by referencing the substitutions at the "X" and "Y" positions of the above-depicted structure. For example, racemic fesoterodine is abbreviated in the '980 patent as "HO-/-OiBut," meaning that the "X" substitution is a hydroxyl group ("HO") and the "Y" substitution is a phenolic isobutyryl ester ("OiBut").

89. Fesoterodine (i.e., Toviaz®) is the R (+)-enantiomer of the phenolic isobutyryl ester of the above-depicted compound. Below the R (+)- and S (-)-enantiomers of fesoterodine are shown.



When both enantiomers are present in equal proportion, the mixture is called "racemic."

90. In this declaration, I have taken into consideration whether the Inventors' testing was on the racemate or the R (+)-enantiomer of fesoterodine in interpreting the results. For clarity, I will use "fesoterodine" to refer to the R (+)-enantiomer of the isobutyryl ester compound, and will specifically note where the compound tested was a racemic mixture of fesoterodine.

91. I have reviewed meeting notes and chemical development plans that the Inventors authored during their work to develop a prodrug of 5-HMT. Notably, the Inventors initially thought that substitutions at the "X" position ("benzylic" substitutions) were preferable because substitutions at the "Y" position ("phenolic" substitutions) would hinder muscarinic receptor binding, and thus therapeutic efficacy. "Timetable of the development of Fesoterodine" (Ex. 2095); "History of SPM 007" dated November 17, 2000 (Ex. 2093). The Inventors nevertheless synthesized benzylic monoesters, phenolic monoesters, identical diesters, and

mixed diesters (i.e., different ester groups in the "X" and "Y" positions, respectively), as well as ether-, carbamate-, and carbonate-substituted compounds. *E.g.*, Ney Declaration, Ex. B (Ex. 2007) at 2167-78. That fesoterodine, a compound substituted at the phenolic ortho position, was superior to the other compounds tested, including those substituted only at the benzylic position, was surprising and could not have been predicted. These data from Schwarz's early compound synthesis, as well as data from later preclinical and clinical studies conducted by Schwarz and later Pfizer on fesoterodine, show that fesoterodine was surprisingly superior to other candidate compounds based on an assessment of a collection of properties.

C. Fesoterodine Is Rapidly and Efficiently Converted to 5-HMT

92. One important criterion for a prodrug candidate is the rate and extent of conversion into the target metabolite. Metabolic conversion testing measures the turnover from the candidate prodrug compound to its active metabolite. Prodrugs are generally inactive; they must be metabolized into active compounds after they enter the body. For this reason, the Inventors sought a prodrug compound that could be rapidly and extensively converted to 5-HMT after absorption, so that 5-HMT could exert its antimuscarinic effects in vivo. However, the prodrug cannot convert too rapidly, namely prior to transport through the gut wall and entrance into the bloodstream. Thus, conversion must occur at the right point in the

absorption/distribution process so that it converts in the right location, at the right time, and then targets the correct tissue.

93. I have reviewed the metabolic conversion data in the '980 patent (Ex. 2018), 52:53-54:52 & Fig. 1, Exs. A and B to the Ney Declaration (Ex. 2007) at 2167-78, 2350-51 and a Report underlying the '980 patent data entitled "Chemical Development Plan, Incontinence Project," dated February 20, 1998 (Ex. 2094 at 5-35). Exhibit A to the Ney Declaration graphically presents the same data depicted in the '980 patent, but also includes data for twelve (12) additional candidate prodrugs of racemic 5-HMT tested in the study. Ex. 2007 at 2167-73; 2350-51.

94. Of the twenty (20) compounds reported in Exhibit A of the Ney Declaration, racemic fesoterodine displayed the third highest formation of racemic 5-HMT at approximately seventy-eight percent (78%) conversion. Ex. 2007 at 2167-73; 2350-51. These data, which result from widely used and scientifically sound tests, demonstrate that racemic fesoterodine exhibits superior metabolic conversion characteristics.

95. Deficiencies seen with the other candidates demonstrate that, in drug design, very small changes to a compound – as small as a single substitution – can yield significant, unpredictable results. For example AcO-/-OAc is much better than HO-/-OAc in terms of metabolic conversion; but HO-/-OiBut is notably better than iButO-/-OiBut. *Id*. Similarly HO-/-OBut is much better than HO-/-OProp,

despite differing in just one (1) carbon atom. *Id.* And while mono-substitutions on the phenolic side of the benzyl ring of AcO, ButO, iButO, and PivO yielded stable and relatively successful prodrug compounds (in terms of metabolic conversion), the same mono-substitutions on the benzylic side of the ring resulted in compounds too unstable to function as prodrugs. *Id.* One could not predict that these small changes in the substitutions on a much larger compound would cause such drastic changes in the compound's properties.

D. Fesoterodine's Permeability Across Biological Membranes Was Unexpected

96. Before an orally administered drug can enter systemic circulation and travel to its site of action in the body, it must permeate through the barrier presented by the gut wall. Therefore, sufficient gastrointestinal permeability is a prerequisite for any orally administered drug. Caco-2 studies are in vitro tests used to evaluate gastrointestinal permeability.

97. In 1998, the Inventors conducted a Caco-2 study on racemic 5-HMT, racemic tolterodine, and seven (7) candidate prodrugs of racemic 5-HMT, including racemic fesoterodine (the "1998 Caco-2 Study"). "Chemical Development Plan, Incontinence Project," dated February 20, 1998 (Ex. 2094) at 43-45. The inventors measured permeation of both the candidate prodrug and its metabolite. Caco-2 testing is widely used and scientifically sound. I have

reviewed Caco-2 monolayer data on fesoterodine's permeability resulting from the 1998 Caco-2 Study. *Id.*

98. The 1998 Caco-2 Study demonstrates that fesoterodine (as the racemate and R (+)-enantiomer) exhibits an unexpected permeability profile relative to other candidate prodrugs tested. *Id.* Approximately forty-five percent (45%) of racemic fesoterodine permeated as racemic fesoterodine and racemic 5-HMT over twenty-four (24) hours. *Id.* Of the candidate prodrugs tested, only HO-/-OAc demonstrated a permeation rate similar to racemic fesoterodine, with forty-five percent (45%) of the parent compound and racemic 5-HMT having been transported across the Caco-2 monolayer. *Id.* However, the metabolic conversion studies showed HO-/-OAc to have far less metabolic conversion than racemic fesoterodine – in fact the lowest for any of the compounds displayed in Figure 1 of the '980 patent – so it was likely an unsuitable candidate. *See* '980 patent (Ex. 2018) at Fig. 1.

99. In addition to poor permeation, the 1998 Caco-2 Study results show additional issues with the other candidate prodrug compounds tested, including instability, poor solubility, permeation as the parent rather than metabolizing into racemic 5-HMT. Ex. 2094 at 43-45. Racemic fesoterodine did not exhibit any of these issues. *Id.*

E. Fesoterodine's Superior Properties Could Not Have Been Predicted

100. As evidenced above by the Inventors' own work above, fesoterodine unpredictably achieved a unique balance of important properties including metabolic conversion and permeability, in addition to other properties such as bioavailability, off-target effects, stability, and safety.

101. When designing a new compound, in this case a prodrug compound to treat overactive bladder, a medicinal chemist would need to find a compound that is superior across a spectrum of relevant properties. Without the aid of hindsight, it would be impossible to know which candidate prodrug of 5-HMT, if any, would be superior and sit at the "sweet spot" in terms of all relevant characteristics. The only way to find such a compound is by running tests on a variety of compounds and determining if any of them indeed achieve that delicate balance. This is particularly true where some of the properties are inversely related to each other, and the right balance among all properties must be struck. The research on 5-HMT prodrugs conducted at Schwarz shows very clearly how unpredictable such an undertaking is. It is impossible to predict beforehand the properties of potential prodrugs, their stability, solubility and enzymatic lability, to make them clinically useful prodrugs. That fesoterodine exhibited the unique and superior balance of properties in comparison to a large number of structural analogs could only be determined after the structural analogs had been synthesized, tested in a variety of

ways, and discarded for certain deficiencies. Additionally, prior to making and testing the candidate prodrugs, there was no way to predict whether any of them would possess the desired balance of properties that fesoterodine possesses.

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.

October 24, 2016

Hans Maag