UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

MYLAN TECHNOLOGIES, INC.
Petitioner,

v.

NOVEN PHARMACEUTICALS, INC.
Patent Owner.

Patent No. 9,730,900

Title: TRANSDERMAL ESTROGEN DEVICE AND DELIVERY

---

*Inter Partes* Review No. IPR2018-00174

---

# DECLARATION OF DR. ADRIAN C. WILLIAMS

# TABLE OF CONTENTS

# LIST OF CITED EXHIBITS

## Patent Owner Exhibits

| Ex # | Description |
|---|---|
| 2002 | *Curriculum Vitae* of Dr. Adrian C. Williams |
| 2003 | Minivelle® Product Label |
| 2004 | J. Hadgraft and R. Guy, *Feasibility Assessment in Topical and Transdermal Delivery*, *in* TRANSDERMAL DRUG DELIVERY 3-4 (R. Guy & J. Hadgraft eds., 2d ed. 2003) |
| 2005 | J. Hadgraft, *Passive enhancement strategies in topical and transdermal drug delivery*, 184 INT'L J. PHARMACEUTICS 1-6 (1999) |
| 2006 | B. Barry, *Transdermal Drug Delivery*, *in* AULTON'S PHARMACEUTICS – THE DESIGN AND MANUFACTURE OF MEDICINES 565, 571-72, 577 (M. Aulton ed., 3d ed. 2007) |
| 2007 | A. Williams & B. Barry, *Urea analogues in propylene glycol as penetration enhancers in human skin*, 36 INT'L J. PHARMACEUTICS 43-50 (1989) |
| 2008 | K. Brain & R. Chilcott, *Physicochemical Factors Affecting Skin Absorption, in* PRINCIPLES AND PRACTICE OF SKIN TOXICOLOGY 83-92 (R. Chilcott and S. Price eds., 2008) |

| Ex # | Description |
|---|---|
| 2009 | Esclim® Product Label |
| 2010 | J. Mantelle, *et al.*, *Effect of Silicone/Acrylic PSA Blends on Skin Permeation*, 26 PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS 415-16 (Rev. July 1999) ("the Mantelle Article") |
| 2011 | A. Williams & B. Barry, *Chemical Permeation Enhancement*, *in* ENHANCEMENT IN DRUG DELIVERY 233, 248-50 (E. Touitou & B. Barry eds., 2007) |
| 2012 | A. Williams & B. Barry, *The enhancement index concept applied to terpene penetration enhancers for human skin and model lipophilic (oestradiol) and hydrophilic (5-fluorouracil) drugs*, 74 INT'L J. PHARMACEUTICS 157-168 (1991) |
| 2013 | K. Walters & K. Brain, *Dematological Formulation and Transdermal Systems, in* DEMATOLOGICAL AND TRANSDERMAL FORMULATIONS 338-43 (K. Walters, ed., 2002) |

| Ex # | Description |
|---|---|
| 2014 | Google Scholar search results obtained March 7, 2018 – citations of Kim *et al.*, *Penetration Enhancement of β2-Selective Agonist, Tulobuterol, Across Hairless Mouse Skin*, J. Pharm. Invest. 33: 79-84 (2003), available online at https://scholar.google.com/scholar?cites=7903453726087495818&as_sdt=2005&sciodt=0,5&hl=en |
| 2015 | A. Ghosh *et al.*, *Current Pharmaceutical Design on Adhesive Based Transdermal Drug Delivery Systems*, 21 CURR. PHARM. DESIGN 2771-2783 (2015) |
| 2016 | U.S. Patent No. 8,029,820 |
| 2017 | B. Godin & E. Touitou, *Transdermal skin delivery: Predictions for humans from in vivo, ex vivo and animal models*, 59(11) ADV. DRUG DELIV. REVIEWS 1152-1161 (2007) |
| 2018 | R. Hinz *et al.*, *In vitro percutaneous penetration: evaluation of the utility of hairless mouse skin*, 93(1) J. INVEST. DERMATOL. 87-91 (1989) |
| 2019 | J. Bond & B. Barry, *Hairless mouse skin is limited as a model for assessing the effects of penetration enhancers in human skin*, 90(6) J. INVEST. DERMATOL. 810-813 (1988) |

| Ex # | Description |
|---|---|
| 2020 | R. Subedi *et al.*, *Influence of formulation variable in transdermal drug delivery system containing zolmitriptan*, 419 INT'L J. PHARMACEUTICS 209-214 (2011) |
| 2021 | R. Subedi *et al.*, *Formulation and in vitro evaluation of transdermal drug delivery system for donezil*, 42 J. PHARMA. INVEST. 1-7 (2012) |
| 2022 | J. Mantelle, *DOT Matrix® Technology, in* MODIFIED RELEASE DRUG DELIVERY TECHNOLOGY 405-14 (Rathbone *et al.* eds., 2d ed. 2008) ("the Mantelle Chapter") |
| 2023 | J. van de Sandt *et al.*, *In vitro predictions of skin absorption of caffeine, testosterone, and benzoic acid: a multi-centre comparison study*, 39 REG. TOXICOL. PHARMACOL 271–281 (2004) |

**Petitioner Exhibits**

| Ex # | Description |
|---|---|
| 1001 | U.S. Patent No. 9,730,900 ("the '900 Patent") |
| 1002 | Declaration of Dr. Keith Brain |
| 1004 | File history of U.S. Patent No. 9,730,900 |

| Ex # | Description |
|---|---|
| 1005 | U.S. Patent Application Publication No. US 2003/0099695 ("Mueller") |
| 1006 | Vivelle-Dot® Transdermal System (Novartis) 05/03/2002 Supplemental Approval [Label Revisions] – FOI Document # 5236149B (2006) ("Vivelle-Dot® Label") |
| 1007 | U.S. Patent Application Publication No. US 2006/0078602 ("Kanios") |
| 1009 | U.S. Patent No. 5,145,682 ("Chien") |
| 1010 | Kim *et al.*, *Penetration Enhancement of β2-Selective Agonist, Tulobuterol, Across Hairless Mouse Skin*, 33 J. PHARM. INVEST. (2003) 79-84 ("Kim") |
| 1011 | U.S. Patent No. 5,656,286 to Miranda *et al.* |
| 1012 | PCT Application Publication WO 1996/003119 ("Fotinos") |
| 1013 | U.S. Patent No. 5,919,477 ("Bevan") |

| Ex # | Description |
|---|---|
| 1014 | Ghosh *et al.*, *Development of a Transdermal Patch of Methadone: In Vitro Evaluation Across Hairless Mouse and Human Cadaver Skin*, 1 PHARM. DEV. TECH. (1996) 285-91 ("Ghosh") |
| 1015 | Climara 0.025mg Transdermal System (Berlex Laboratories) 04/05/2001 Supplemental Approval Letter and Final Labeling – FOI Document # 5243107A ("Climara® Label") |
| 1016 | Alora 0.025mg, 0.05mg, 0.075mg, 0.1mg Transdermal System (Watson Laboratories) 04/05/2002 Approval Letter and Final Labeling – FOI Document # 5210490A ("Alora® Label") |
| 1018 | U.S. Patent No. 5,902,602 ("Müller") |
| 1019 | U.S. Patent No. 6,156,335 ("Rovati") |
| 1020 | U.S. Patent No. 6,521,250 ("Meconi") |
| 1023 | Dinger, E., *Noven Pharmaceuticals, Inc.* ENCYCLOPEDIA.COM (2006) http://www.encyclopedia.com/books/politics-andbusiness-magazines/noven-pharmaceuticals-inc (last accessed: June 29, 2017) ("Dinger") |

| Ex # | Description |
|---|---|
| 1024 | Butschli, J., *Tiny Patch 'Dots' Pharmaceutical Landscape*, PACKAGING WORLD (1999) https://www.packworld.com/article/machinery/inspection/checkweighers/tiny-patch-dots-pharmaceutical-landscape (last accessed: June 29, 2017) ("Butschli") |
| 1026 | Bronaugh R.L., Maibach H.I. (eds.), *In vitro percutaneous absorption: Principles, fundamentals and applications.* CRC Press, Boca Raton, Florida (1991) 85–114 ("Bronaugh") |
| 1027 | U.S. Patent No. 5,352,457 ("Jenkins") |
| 1028 | U.S. Patent No. 5,603,947 ("Wong") |
| 1029 | U.S. Patent Application Publication No. US 2006/0078601 ("Kanios '601") |
| 1030 | U.S. Patent No. 6,638,528 ("Kanios '528") |
| 1031 | U.S. Patent No. 4,624,665 ("Nuwayser") |
| 1032 | U.S. Patent Application Publication No. US 2009/0041831 ("Miller") |
| 1033 | U.S. Patent No. 6,024,976 to Miranda *et al.* |

# I. INTRODUCTION

1. I have been retained by Noven Pharmaceuticals, Inc. (Patent Owner) to serve as an expert in the field of transdermal drug delivery systems (TDSs) and transdermal drug delivery.

2. I have been asked by Noven Pharmaceuticals, Inc. (Patent Owner) to provide my opinions and analysis of issues raised in the Petition for *Inter Partes* Review of U.S. Patent No. 9,730,900 filed by Mylan Technologies, Inc. (IPR2018-00174) (the "Petition"). My opinions and analysis are set forth below, and are based on my review of U.S. Patent No. 9,730,900 ("the '900 Patent") and its prosecution history, the state of scientific and technical knowledge regarding the claimed subject matter on or before the priority date of the '900 Patent, the purported prior art cited by Petitioner, and the opinions of Dr. Keith Brain stated in the Declaration of Keith Brain, Ph.D. (the "Brain Declaration") (EX1002). Evidence underlying my opinions and analysis includes certain documents cited in the Petition and Brain Declaration and additional evidence listed in the List of Cited Exhibits above.

3. I am being compensated for my time at my customary rate of £350 per hour. My compensation does not depend in any way on the outcome of this proceeding.

## II. QUALIFICATIONS

4. I have over 30 years' research experience in transdermal and topical drug delivery as well as in other areas of drug delivery science including pharmaceutical materials characterization and novel drug delivery systems using polymers. My work has covered understanding of the fundamental skin barrier, strategies to increase topical and transdermal drug delivery and the development of novel drug delivery formulations.

5. During my academic career I have taught most aspects of pharmaceutical formulation to undergraduate pharmacy students, from basic principles of physical chemistry relevant to drug delivery through to more specialized courses on topical formulations and the treatment of common skin conditions. In addition, I have also taught Masters students on topics related to skin and formulation development and have provided expert teaching on external courses for Qualified Person qualifications at the University of Brighton and for RSSL, a company in Reading.

6. I am currently Professor of Pharmaceutics in the School of Pharmacy at the University of Reading (UK) and am also the University of Reading Research Dean for Health. I obtained a B.Sc. (Hons) in 1987 and then began a Ph.D. program under the supervision of Professor Brian Barry at the University of Bradford (UK), entitled "Terpenes and Urea Analogues as Penetration Enhancers

for Human Skin". I was then appointed as lecturer in pharmaceutical technology in the Bradford School of Pharmacy where I stayed, progressing from lecturer to Professor of Biophysical Pharmaceutics. I was appointed as Professor of Pharmaceutics at the University of Reading in 2004, and held this position whilst progressing to be appointed Head of Pharmacy in 2008, then Head of the School of Chemistry, Food and Pharmacy in 2011, and then Research Dean for Health in 2015.

7. During my academic career, I have authored or co-authored 100 original peer-reviewed research articles in addition to nine review articles and 30 chapters in books. I have studied estradiol delivery through human skin since I began my Ph.D. research and have published papers on this topic including: *The enhancement index concept applied to terpene penetration enhancers for human skin and model lipophilic (oestradiol) and hydrophilic (5-fluorouracil) drugs*, INT. J. PHARM., 1991, 74, 157-168.; *Oestradiol permeation through human skin and silastic membrane: effects of propylene glycol and supersaturation*, J. CONTROL. RELEASE, 1995, 36, 277-294.; *Oestradiol permeation across human skin, silastic and snake skin membranes: the effects of ethanol/water co-solvent systems*, INT. J. PHARM., 1995, 116, 101-112.; *FT-Raman microscopic study of drug distribution in a transdermal drug delivery device*, VIBRATIONAL SPECTROSCOPY, 1996, 11, 105-113.; *Skin delivery of oestradiol from deformable and traditional liposomes:*

*mechanistic studies*, J. PHARM. PHARMACOL., 1999, 51, 1123-1134.; *Skin hydration and possible shunt route penetration in controlled estradiol delivery from deformable and standard liposomes*, J. PHARM. PHARMACOL., 2001, 53, 1311-1322.

8. I wrote a textbook in 2003 that was published by the Pharmaceutical Press (London) entitled TRANSDERMAL AND TOPICAL DRUG DELIVERY; FROM THEORY TO CLINICAL PRACTICE. In 2013, I was asked to write the chapter *Topical and Transdermal Drug Delivery* for the well-known standard pharmaceutics textbook used by many UK Pharmacy students AULTON'S PHARMACEUTICS, and have subsequently updated this in future editions of the book.

9. To date, my publications have been cited over 11,200 times by other researchers.

10. I have supervised 50 Ph.D. students and seven post-doctoral researchers who have worked on projects variously funded by competitively won research grant awards, by commercial sponsorship or from overseas funding. Projects have spanned various aspects of pharmaceutics and drug delivery, including "Oestradiol permeation through human skin, silastic and snake membranes; effects of supersaturation and binary co-solvent systems" and "Promotion of oestradiol permeation through human skin".

11. I have also been invited to give presentations and to chair sessions at national and international conferences. Examples of such presentations include: "Maximising the bioavailability of topical drugs", Introductory Course on the Biology of the Skin, Fitzwilliam College, Cambridge, 1998.; "Patchy responses to transdermal delivery", British Pharmaceutical Conference, Manchester, September 2008.; "Controlled release transdermal therapeutic systems – current trends and future directions", Controlled Release Society, Istanbul, Turkey, May 2005.; "Do corneocytes leak?" Session chair & debate leader, Gordon Research Conference on the Barrier Function of Mammalian Skin, Newport, Rhode Island, Aug 2007.; "Formulation issues of dermal products", CiToxLAB Dermal Minisymposium, Paris, France, October 2012.

12. I currently act as a reviewer for grant awarding bodies including the Commonwealth Scholarship Commission, the UK Medical Research Council, the UK Engineering and Physical Sciences Research Council and the UK Biotechnology and Biological Sciences Research Council. I also regularly review articles submitted to international scientific journals and I am a member of the editorial board for the Journal of Pharmacy and Pharmacology and a member of the editorial advisory board for the Journal of Pharmaceutical Sciences.

13. Throughout my research career I have worked with numerous pharmaceutical companies, either by providing expect lectures, working on joint

research projects or through consultancy. For example, I provided a lecture on "Strategies for improving transdermal drug delivery", to Unilever Research, Port Sunlight (UK) in 1996, and in 2016 I was a consultant for Pfizer, Jersey City, NJ, on their Topical Pain Advisory Board.

14. My research and standing in the field has been recognized by my election as a Fellow of the Royal Society of Chemistry in 1992, being awarded a Fellow of the UK Higher Education Academy in 2007, and my election as a Fellow of the UK Academy of Pharmaceutical Sciences in 2013.

15. A copy of my *curriculum vitae*, which includes my education background, work and research history, and a list of selected publications and presentations, is attached to this declaration as Exhibit 2002.

16. The analysis set forth in this declaration is based on my education, knowledge and experience in the area of transdermal drug delivery systems over the past 30 plus years.

## III. PATENT LAW STANDARDS

17. I have been informed by counsel that the claims of a patent are interpreted as a person of skill in the art would have understood them in the relevant time period, which I understand is the earliest filing date accorded to the patent. I understand that the '900 Patent benefits from a filing date of July 10, 2008. Accordingly, my comments, opinions, and analysis herein refer to the

knowledge and understanding in the field of transdermal drug delivery systems and transdermal drug delivery as of July 10, 2008.

18. I have been informed by counsel that a claim is anticipated (*i.e.*, deemed not novel) only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. I understand that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. Rather, the feature at issue must necessarily be present in the thing described.

19. I have been informed by counsel that a claim is obvious if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art to which the claimed invention pertains (a "POSA") as of the earliest filing date of the patent. I understand that a person of ordinary skill in the art is a hypothetical person or persons deemed to have knowledge of all relevant prior art at the time of the earliest filing date of the patent (here, July 10, 2008). I also understand that a POSA is considered to possess ordinary creativity. My discussion herein of a POSA refers to such a person as of July 10, 2008.

20. I also understand that patentability is not negated by the manner in which the invention was made.

21. I have been informed by counsel that when assessing obviousness one must determine: (1) the scope and content of the prior art; (2) the differences between the claimed invention of the patent and the prior art; (3) the level of ordinary skill in the art at the time the invention was made; and (4) any secondary considerations of non-obviousness. I understand that such secondary or objective evidence of nonobviousness can include evidence that an invention achieved a surprising or unexpected result and evidence of commercial success of the invention. I understand that such evidence must have a nexus, or causal relationship, to the claimed invention in order to be relevant to the nonobviousness of the claim.

22. I also have been informed and understand that when analyzing the question of obviousness, it is improper to use hindsight to reconstruct the invention, and that one cannot use the patent as a road map for selecting and combining items of prior art. I have been informed and understand that the relevant question is what a POSA would have understood without the benefit of the disclosure of the patent. I have been informed and understand that an obviousness inquiry can be based on a combination of multiple prior art references; however, the references must either be from the same field of endeavor as the claimed invention or reasonably pertinent to the problem faced by the inventor, in that it would logically commend itself to the inventor's attention in considering his or her

problem. I further understand that the obviousness inquiry considers whether a POSA would have had a reason to attempt to select, combine and modify the references in the manner asserted for obviousness, and a reasonable expectation of success in doing so.

23. I am further informed and understand that a claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was independently known in the prior art. There must have been an apparent reason to select and combine the known elements in the fashion claimed, a reasonable expectation of success in doing so, and the results must have been predictable to one of ordinary skill in the art.

24. Further, I have been informed and understand that claims can be found invalid under an "obvious to try" theory only if, at the time of the invention, there was a recognized problem or need in the art, a finite number of identified, predictable potential solutions to the recognized need or problem, and a POSA could have pursued the known potential solutions with a reasonable expectation of success. I also have been informed and understand that even then, secondary/objective evidence of nonobviousness must be considered.

25. Further, I understand that when the validity of a patent is challenged in a USPTO *inter partes* review proceeding, the burden falls on the Petitioner to

show invalidity by a preponderance of the evidence, *e.g.*, by evidence showing that invalidity is more likely than not.

## IV. LEVEL OF SKILL IN THE ART

26. Petitioner alleges that the person of ordinary skill in the art ("POSA") would have "an advanced degree, for example a Ph.D., in pharmaceutical chemistry, physical chemistry, bioengineering, or a drug delivery related disciple" or, alternatively, "a bachelor's degree plus two to five years' experience in the transdermal delivery industry." Petitioner also asserts that a POSA "would likely have familiarity with formulation of drugs for transdermal administration and would have been able to understand and interpret the references discussed in the field." Petition, 15; EX1002, ¶¶77-78.

27. I have adopted Petitioner's opinion for the purpose of this analysis with the clarification that a POSA who does not have an advanced degree in the listed fields would have a bachelor's degree in a field related to drug delivery.

28. As reflected in my *curriculum vitae* (EX2002), I have the scientific background and technical expertise to provide opinions and analysis from the perspective of a person of ordinary skill in the art as of the July 10, 2008 priority date of the '900 Patent. Moreover, as of that date, I met or exceeded the above qualifications of a hypothetical person of ordinary skill in the art.

# V. THE '900 PATENT

## A. Brief Overview of the Claimed Invention

29. I have read and understand the specification and claims of the '900 Patent. The claims of the '900 Patent are generally directed to methods for administering estradiol using transdermal drug delivery systems (*e.g.*, transdermal "patches," referred to herein as "TDSs") and methods of making such TDSs. As described in the '900 Patent, the TDSs of the '900 Patent have a smaller active surface area than the prior art Vivelle-Dot® product line, but achieve daily dosages that are about equal to or greater than the Vivelle-Dot® products, meaning that they achieve daily dosages that are about equal to a Vivelle-Dot® product in a smaller sized system. EX1001, 4:3-23. Indeed, the Minivelle® products for which the '900 Patent is an Orange Book-listed patent are only about 60% the size of the Vivelle-Dot® products but deliver the same daily doses of estradiol. EX2003, 16; EX1006, 12.

30. As discussed in the '900 Patent, "the ability to provide a smaller system without sacrificing daily dosage represents a significant advance," and was made possible by the surprising discovery that "increasing the coat weight of the drug-containing adhesive layer resulted in an increased flux per unit area, and thus permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages." EX1001, 2:58-3:2. As explained in the '900

Patent and as I discuss in more detail below, this result was surprising "because coat weight is typically selected to control the duration of delivery, but is not generally understood to impact delivery rate." *Id.* That is, as explained in the '900 Patent and as I discuss in more detail below, "while it is known in the art to increase coat weight to provide delivery over a longer period of time, it was not known that increasing coat weight could increase delivery rate or flux, and thus permit the development of a smaller system while maintaining daily dosage." *Id.* It is this unexpected discovery that permitted the development of Patent Owner's FDA-approved Minivelle® product line, which offers women the same therapeutic efficacy as Vivelle-Dot® products in much smaller sized patches. EX2003, 16; EX1006, 12.

31. The TDSs claimed in the '900 Patent are "monolithic" drug-in-adhesive systems, meaning that they have a single drug-containing polymer matrix layer and consist of (i) a backing layer; (ii) a drug-in-adhesive polymer matrix layer, and, optionally, (iii) a release liner that is removed prior to use. EX1001, Claims 1, 16. The claims recite that the adhesive polymer matrix has a coat weight of greater than about 10 $mg/cm^2$ and includes greater than 0.156 $mg/cm^2$ of estradiol, and that the TDS achieves an estradiol flux of from about 0.0125 to about 0.05 $mg/cm^2/day$, based on the active surface area of the system. *Id.*

32. The '900 patent has 23 claims, including independent claims 1 and 16. Claim 1 of the '900 patent recites:

> A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system consisting of (i) a backing layer and (ii) a single adhesive polymer matrix layer defining an active surface area and comprising an adhesive polymer matrix comprising estradiol as the only drug, wherein the polymer matrix has a coat weight of greater than about 10 $mg/cm^2$ and includes greater than 0.156 $mg/cm^2$ estradiol, and the system achieves an estradiol flux of from about 0.0125 to about 0.05 $mg/cm^2/day$, based on the active surface area.

33. Claim 16 of the '900 patent recites:

> A method of making a monolithic transdermal drug delivery system for administering estradiol consisting of (i) a backing layer, (ii) a single adhesive polymer matrix layer and, optionally, (iii) a release liner, comprising forming an adhesive polymer matrix comprising estradiol as the only drug and a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble PVP, and applying the adhesive polymer

matrix to a support layer to form a single adhesive polymer matrix layer such that the adhesive polymer matrix layer has a coat weight of greater than about 10 mg/cm$^2$ and includes greater than 0.156 mg/cm$^2$ estradiol, wherein the system achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm$^2$/day, based on the active surface area.

34. For the purposes of this declaration, I have focused primarily on independent claims 1 and 16 and dependent claim 3 of the '900 Patent.

**B. Brief Overview of the Prosecution History**

35. U.S. Application No. 13/553,972 ("the '972 Application"), which issued as the '900 Patent, was filed on July 20, 2012, and is a continuation of the application that issued as U.S. Patent No. 8,231,906 ("the '906 Patent") (EX1004), which I understand has been and is the subject of litigation. Paper 4, 2.

36. During prosecution of the '972 Application, the claims were rejected as allegedly anticipated by U.S. Patent Application Publication No. 2006/0078601 (EX1029; "Kanios '601"); allegedly obvious over Kanios '601 in view of U.S. Patent No. 6,638,528 (EX1030; "Kanios '528"); allegedly obvious over Kanios '601 in view of U.S. Patent No. 4,624,665 (EX1031; "Nuwayser"); allegedly obvious over Kanios '528 in view of Nuwayser; and allegedly obvious over Kanios

'528 and Nuwayser further in view of U.S. Patent Application Publication No. 2009/0041831 (EX1032; "Miller"). EX1004, 99-103, 147-151, 251-254.

37. Patent Owner overcame these rejections with arguments and clarifying claim amendments. As acknowledged by the Examiner in the Notice of Allowance mailed October 2, 2015 (EX1004, 296-303), "[t]he prior art does not teach nor reasonably suggest a method for administering estradiol with the claimed monolithic transdermal drug delivery system. Further, the prior art does not teach nor reasonably suggest a method for making the claimed monolithic transdermal drug delivery system." *Id.*, 302.

38. Following receipt of the October 2015 Notice of Allowance, Patent Owner filed an Amendment Under 37 CFR § 1.312 seeking to amend the allowed claims to recite specific embodiments with regard to the amount of estradiol per unit area and flux. EX1004, 314-319. When the Examiner would not enter the amendments after final, Patent Owner filed a requests for continued examination ("RCE") to pursue similar claim amendments. *Id.*, 330-331. Once agreement was reached on revised claim language, another Notice of Allowance was issued in August 2016. *Id.*, 412- 418.

39. Thereafter, Patent Owner filed additional RCEs in order to obtain consideration of information disclosure statements ("IDSs"). EX1004, 433-441, 475-480. After consideration of each IDS, the Examiner issued a Notice of

Allowance with similar reasons for allowance. *Id.*, 446-452, 481-487. With the final RCE, Patent Owner presented new dependent claims that were granted as claims 15 and 23. *Id.*, 524-532.

40. After the final RCE, Patent Owner conducted an interview with the Examiner and submitted the Declaration Under 37 CFR § 1.132 of Dr. Richard H. Guy.[1] EX1004, 538-540, 564-601. In his declaration, Dr. Guy explained the state of the art and presented experimental data of unexpected results. Dr. Guy attested that "a person of ordinary skill in the art would not have thought of coat weight as a parameter to be adjusted to affect the flux of a drug from a transdermal patch" and that none of the art of record "suggests that increasing coat weight would increase flux." EX1004, 599-600" . Dr. Guy also attested that the only predictable way to increase drug flux from a TDS is to increase the size of the TDS. *Id.*, 600. Dr. Guy also presented experimental data showing the unexpected result embodied

[1] Dr. Guy is a professor of Pharmaceutical Sciences at the University of Bath (UK) in the Department of Pharmacy & Pharmacology and has more than 30 years' research experience in the field of topical and transdermal drug delivery, including the study of drug absorption into and through the skin. He has co-authored more than 350 peer-reviewed articles and over 70 book chapters, and served as the Associate Editor of the Journal of Pharmaceutical Sciences from 2002-2007.

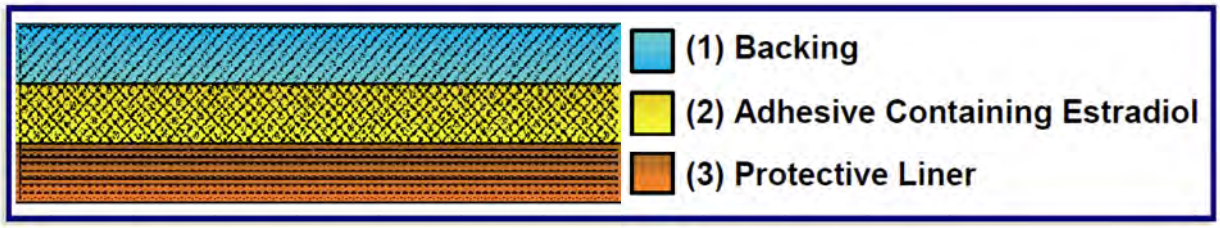
in the claimed subject matter, that increasing the coat weight of the drug-containing polymer matrix of the monolithic estradiol TDS increased flux. *Id.*, 587-596.

41. Thereafter, the Examiner issued the final Notice of Allowance. EX1004, 684-691. The Examiner reiterated her finding that "[t]he prior art does not teach nor reasonably suggest the claimed monolithic transdermal drug delivery system," and separately noted that "Applicant's arguments of unexpected results … are persuasive." *Id.*, 689.

## VI. TECHNOLOGICAL BACKGROUND

### A. Transdermal Drug Delivery and Drug Flux

42. As noted above, the '900 Patent generally relates to TDSs for the delivery of estradiol, methods of administering estradiol to a patient using the claimed transdermal drug delivery systems, methods of delivering estradiol using them, and methods of making them. As also noted above, the claims recite TDSs that are "monolithic" drug-in-adhesive systems that consist of (i) a backing layer; (ii) a drug-in-adhesive polymer matrix layer, and, optionally, (iii) a release liner that is removed prior to use, as illustrated below. EX1001, Claims 1, 16.



43. The claims recite that the adhesive polymer matrix of the TDS has a coat weight of greater than about 10 mg/cm$^2$ and includes greater than 0.156 mg/cm$^2$ of estradiol, and that the TDS achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm$^2$/day, based on the active surface area of the system. EX1001, Claims 1, 16.

44. The flux of a drug is the rate at which it diffuses through the skin. As of July 10, 2008, a POSA understood that the passive flux of a drug can be quantitatively described and modelled by Fick's 1st law of diffusion. *See, e.g.*, J. Hadgraft and R. Guy, *Feasibility Assessment in Topical and Transdermal Delivery*, *in* TRANSDERMAL DRUG DELIVERY 3-4 (R. Guy & J. Hadgraft eds., 2d ed. 2003) (EX2004, 3-4). Fick's 1st law is often used to describe drug delivery (in units of amount per time, *e.g.*, mg/day or µg/hour) from a transdermal patch across the skin:

$$J = A \times k_p \times \Delta C$$

In this formula:

A is the active surface area of the patch.

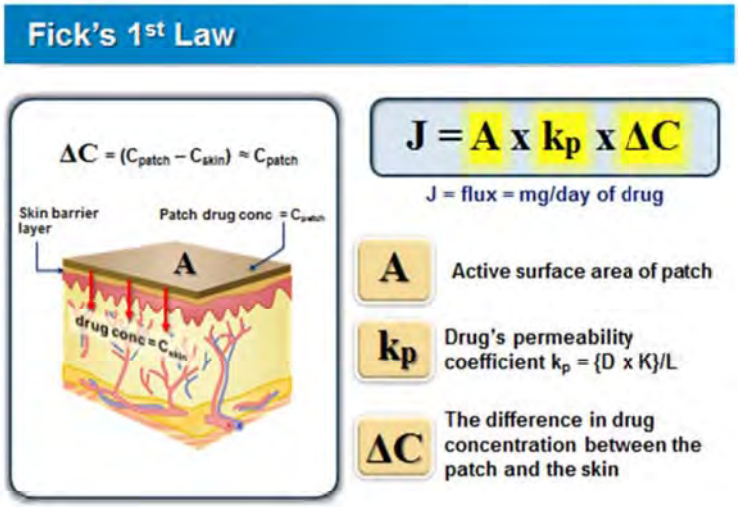
$k_p$ is the drug's permeability coefficient across the skin, and can be defined as $k_p = \{D \times K\}/L$, where D is the drug's diffusivity through the skin barrier, K is its partition coefficient between the skin barrier

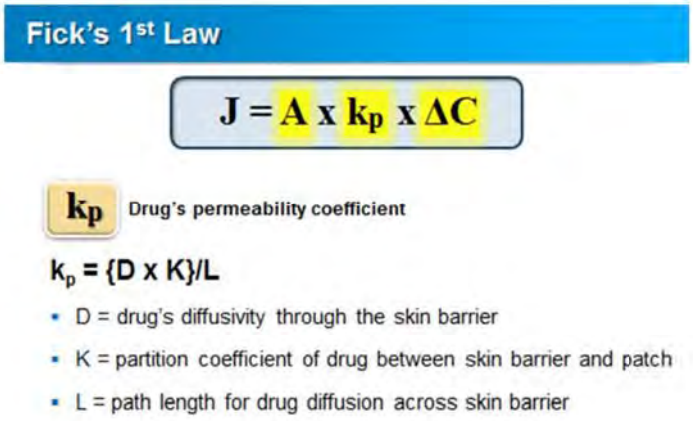
and the patch, and L is the path length for diffusion across the skin barrier.

ΔC is the difference in concentration of the drug between that in the patch ($C_{patch}$) and that on the "downstream" side of the skin barrier ($C_{downstream}$). In many examples of transdermal delivery, when depletion of drug from the patch is limited, drug concentration in the patch greatly exceeds that on the downstream side so that ΔC can be approximated to $C_{patch}$.

EX2004, 4; EX1007, ¶¶70, 71.

45. The following images illustrate these factors:






46. Fick's 1st law indicates that there are four general ways to increase flux:

(1) Increase the active surface area of the patch to cause a proportional change in flux.

(2) Increase the drug concentration in the patch until it reaches its limiting solubility.

(3) Adjust the formulation for a given drug loading such that the drug reaches its limiting solubility.

(4) Introduce a penetration enhancer into the formulation to increase D and/or alter the value of K.

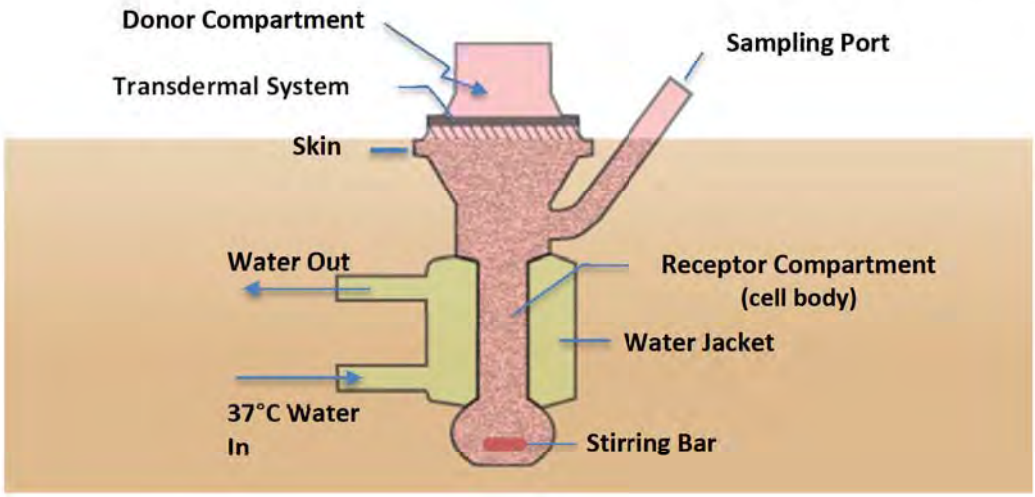
*See, e.g.*, J. Hadgraft, *Passive enhancement strategies in topical and transdermal drug delivery*, 184 Int'l J. Pharmaceutics 1, 2-5 (1999) (EX2005, 2-5). Nothing in Fick's 1st law indicates or predicts that increasing the coat weight (thickness) of a

polymer matrix would increase flux. This is because no factor in Fick's 1st law embodies or includes coat weight. EX2004, 4.

47. Dr. Brain states in EX1002, ¶59 that "those in the art understood that increasing coat weight can increase a drug's diffusivity through the skin barrier, and thereby, increase flux." That is incorrect, however. Diffusivity (often expressed as a "diffusion coefficient") is a fundamental property of the drug being delivered in a given membrane, and so is inherent to the specific drug and membrane (*e.g.*, skin) at issue under fixed conditions such as temperature. B. Barry, *Transdermal Drug Delivery*, *in* AULTON'S PHARMACEUTICS – THE DESIGN AND MANUFACTURE OF MEDICINES 577 (Michael E. Aulton ed., 3d ed. 2007) (EX2006, 577). As such, the coat weight of a drug-containing polymer matrix would not alter the diffusivity of the drug through the membrane at issue.

48. While the flux of a transdermal drug delivery system is an *in vivo* property, it is measured by *in vitro* methodology, such as human cadaver skin permeation studies, as illustrated in Example 1 of the '900 Patent.

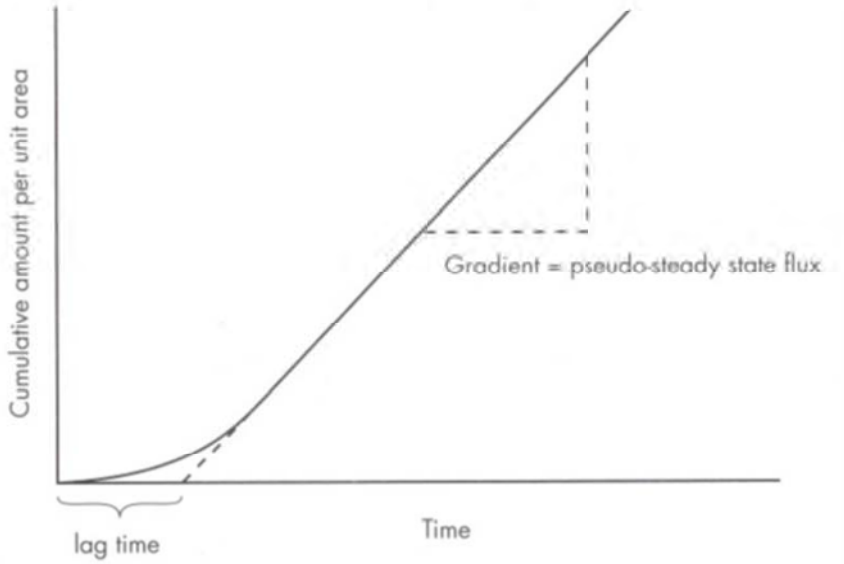
49. The use of *in vitro* skin permeation studies was well-known and conventional to a POSA. Such flux studies often are conducting using a Franz cell apparatus as illustrated below:




As illustrated in this figure, the main elements of the apparatus include a donor compartment, a means for retaining a skin sample, and a receptor compartment. In use, the receptor compartment is filled with a receptor fluid in which the drug is suitably soluble. The receptor compartment may be maintained at a selected temperature, such as 37°C (body temperature), such as by means of a water jacket as illustrated in this figure. The skin surface temperature in such an experimental design is usually around 32°C, to mimic the *in vivo* situation. The receptor compartment is typically equipped with stirring means, such as a stirring bar as illustrated in the figure. A TDS is placed on top of the skin sample in what is referred to as the donor compartment. Receptor fluid is sampled periodically over the study period (such as via a sampling port as illustrated), and analyzed for drug content.

50. The drug content of a given sample of receptor fluid taken at a given time reflects the cumulative amount of drug that passed through the skin by that

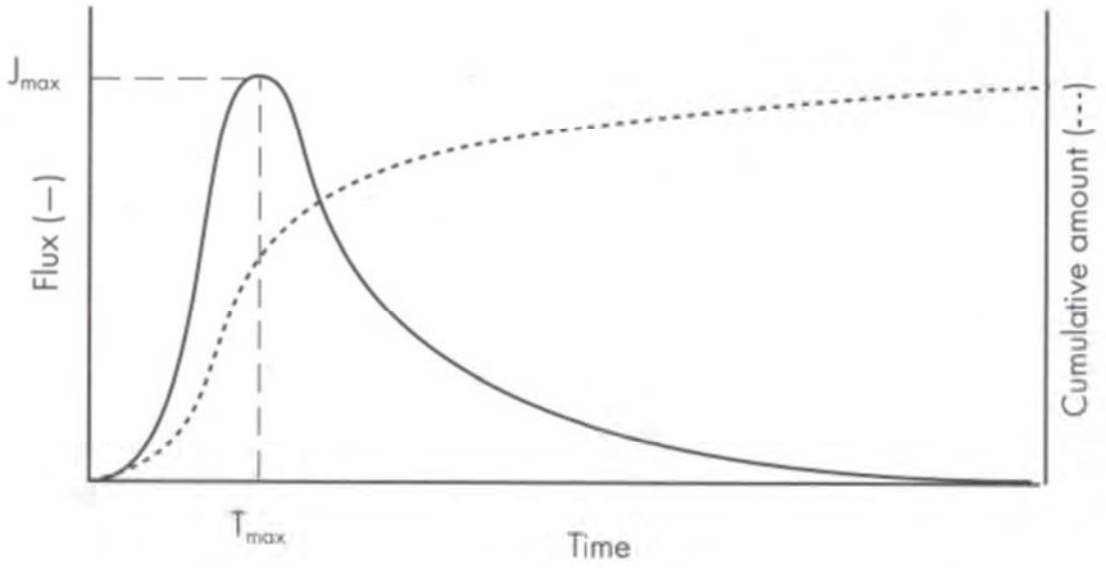
time. That data can be used to plot the cumulative amount of drug that is delivered across the membrane with time. An ideal plot is illustrated below:




As shown in the above figure, there is usually a short time delay, the "lag time", before the drug appears in the receptor solution because the applied drug molecules must pass through the skin barrier. The length of the lag time depends on the physical and chemical properties of the drug. EX2006, 571-572. For lipophilic molecules such as estradiol passing through human skin, the lag time is typically in the order of few hours, whereas for hydrophilic molecules, or molecules that bind to skin components, the lag time may be up to 10 hours or more. A. Williams & B. Barry, *Urea analogues in propylene glycol as penetration enhancers in human skin*, 36 INT'L J. PHARMACEUTICS 43-50 (1989) (EX2007, 47-48). Thereafter, drug delivery from a constant infinite dose of drug in a formulation – *i.e.*, one with continual drug delivery – will be linear with time. This constant rate of drug

delivery is referred to as "zero-order" or "pseudo zero-order" drug delivery. *See, e.g.*, EX2006, 571-572; EX1007, ¶11. The data from the linear portion of the curve can be used to calculate the steady state flux of the drug through the skin membrane, providing the amount of drug permeating through the membrane with time. This is indicated by the "Gradient" in the figure above.

51. When a finite dose of drug is applied to the skin, then the profile changes as illustrated below. Again after a lag time, there is an increase in flux (amount transported per unit area with time) to a maximum value beyond which flux falls as the drug concentration in the donor phase declines, resulting in a drop in the concentration gradient across the membrane. This is referred to as "first-order" drug delivery. *See, e.g.*, EX1007, ¶7. The cumulative amount of drug passing through the membrane thus reaches a plateau. *Id.*



A TDS intended to be applied for an extended period, such as for 3 days, ideally would exhibit a zero order profile over the intended application period, reflecting delivery of a uniform dose over time. *See, e.g.*, EX1007, ¶11.

52. When assessing the flux of TDS, it is essential to account for variations in skin permeability, because there can be a large variation in permeability between different skin samples. The impact of skin permeability on flux and the use of well-known and accepted techniques to account for this factor is illustrated in the Guy Declaration. EX1004, 433-435. The data presented in ¶¶40-42 of the Guy Declaration show a significant variation in flux when the very same formulations were tested on different human cadaver skin samples. (Dr. Brain discusses the Guy Declaration in EX1002, ¶¶44-53.) As Dr. Guy explained, in the flux experiments at issue, Vivelle-Dot® systems were used as a control because the flux of estradiol form Vivelle-Dot® was well characterized by Noven. EX1004, 435. In particular, the nominal flux of estradiol from Vivelle-Dot® was reported in the Vivelle-Dot® Label to be 0.4 $\mu g/cm^2/h$ (calculated from the dose delivered per day per unit area), EX1006, 12; *Id*. However, the values observed in these flux studies for the Vivelle-Dot® control were 1.5 to 2.5-fold higher. This is seen in the table set forth in ¶41 of the Guy Declaration (highlighting added):

| Study # | Formulation Components (% by weight) | | | | | | Coat Wt. ($mg/cm^2$) | Drug Flux ($\mu g/cm^2 \cdot h$) |
|---|---|---|---|---|---|---|---|---|
| | Acrylate | Silicone | DPG | OAlc | PVP | Estradiol | | |
| | | | | | | | | |
| 1323 | 10 | 66.9 | 8 | 6 | 7.5 | 1.6 | 15 | 1.42 |
| | 10 | 66.9 | 8 | 6 | 7.5 | 1.6 | 12.5 | 1.11 |
| Control (flux): Vivelle-Dot® (0.77 $\mu g/cm^2 \cdot h$) | | | | | | | | |
| Control (flux): Vivelle® (0.23 $\mu g/cm^2 \cdot h$) | | | | | | | | |
| | | | | | | | | |
| 1214 | 10 | 66.9 | 8 | 6 | 7.5 | 1.6 | 15 | 1.25 |
| | 10 | 66.9 | 8 | 6 | 7.5 | 1.6 | 10 | 1.02 |
| Control (flux): Vivelle-Dot® (0.7 $\mu g/cm^2 \cdot h$) | | | | | | | | |
| | | | | | | | | |
| 1293 | 10 | 66.9 | 8 | 6 | 7.5 | 1.6 | 15 | 1.09 |
| | 10 | 66.9 | 8 | 6 | 7.5 | 1.6 | 10 | 1.02 |
| Control (flux): Vivelle-Dot® (0.66 $\mu g/cm^2 \cdot h$) | | | | | | | | |
| Control (flux): Vivelle® (0.22 $\mu g/cm^2 \cdot h$) | | | | | | | | |
| | | | | | | | | |
| 1233 | 10 | 66.9 | 8 | 6 | 7.5 | 1.6 | 15 | 1.59 |
| | 10 | 66.9 | 8 | 6 | 7.5 | 1.6 | 10 | 1.50 |
| Control (flux): Vivelle-Dot® (1.01 $\mu g/cm^2 \cdot h$) | | | | | | | | |

That is, instead of exhibiting a flux of 0.4 $\mu g/cm^2/h$, Vivelle-Dot® exhibited an estradiol flux of 0.77, 0.7, 0.66 or 1.01 $\mu g/cm^2/h$ in these flux studies. As Dr. Guy explained, the higher estradiol flux from Vivelle-Dot® "indicat[ed] that the donor skin had a higher permeability than usual." *Id.* Thus, the estradiol flux observed from Vivelle-Dot® in these studies was not characteristic of Vivelle-Dot® *per se*, but reflected the higher than usual permeability of the skin samples used in the study.

**B. Developing Transdermal Drug Delivery Systems**

53. The field of transdermal drug delivery is a highly unpredictable art. Indeed, Dr. Brain himself has said that the fact that "[s]kin absorption of chemicals is a passive process…does not mean that the process of dermal absorption is simple and highly predictable, as there are a diverse range of factors that can affect the rate and extent to which a chemical is absorbed." K. Brain & R. Chilcott, *Physicochemical Factors Affecting Skin Absorption, in* PRINCIPLES AND PRACTICE OF SKIN TOXICOLOGY 83 (R. Chilcott and S. Price eds., 2008) (EX2008, 83). Indeed, Dr. Brain went so far as to say:

> [O]ne could even imagine that the services of an astrologer may be a useful adjunct to predicting skin absorption!

*Id.* at 84.

54. One reason the field is so unpredictable, is that out of the four general ways to increase flux that are embodied in Fick's 1st law, the only predictable way to increase flux is to increase the active surface, *i.e.*, increase the size of the patch. This is because out of all the factors embodied in Fick's 1st law, only active surface area has a direct and directly proportional impact on flux. EX2004, 4; EX2005, 2-5. The predictability of increasing flux by increasing patch size is reflected in commercial TDS products, where different doses of the same product are provided by different patch sizes. For example, the Vivelle-Dot® products deliver 0.025,

0.0375, 0.05, 0.075 or 0.1 mg/day from a patch size of 2.5, 3.75, 5.0, 7.5 or 10.0 $cm^2$, respectively (EX1001, 3:41-45; EX1006, 12); the Alora® products deliver 0.025, 0.05, 0.075 or 0.1 mg/day from a patch size of 9, 18, 27 or 36 $cm^2$, respectively. (EX1016, 18), and the Climara® products deliver 0.025, 0.05, 0.075 or 0.1 mg/day from a patch size of 6.5, 12.5, 18,75 or 25 $cm^2$, respectively (EX1015, 5).

55. Other ways of trying to increase flux are unpredictable, and must be tested experimentally. This is illustrated in several references cited by Petitioner, including Kanios (EX1007), and U.S. Patent No. 5,656,286 (EX1011) and U.S. Patent No. 6,024,976 (EX1033) (collectively, the "Miranda Patents"). For example, it is generally expected that increasing the concentration of drug in the composition will have some positive impact on flux up to a point, but the precise impact cannot be predicted *a priori*. FIG. 17 of the Miranda Patents shows how increasing estradiol concentration can increase flux. EX1011, FIG. 17; EX1033, FIG. 17. However, this approach only is useful until the saturation concentration of the drug is reached. EX2005, 2. On this point, Kanios warns that "[h]igh drug concentrations, on the other hand, frequently affect the adhesion properties of the adhesives, and tend to promote unwanted crystallization." EX1007, ¶13. Rovati (EX1019) includes a similar warning. EX1019, 2:55- 3:4. Another countervailing consideration to increasing drug concentration is unnecessary drug waste. That is, a

POSA would not increase drug concentration beyond that required to achieve the desired drug delivery profile because the excess drug would go to waste, representing an unnecessary expenditure and increasing the risks associated with disposal of the TDS, such as risks of unintended consumption and risks to the environment.

56. The other approaches are even more unpredictable. When adjusting the composition to cause the drug concentration to more closely approach its limiting solubility, it takes trial and error to determine what adjustments can be made without undermining other properties of the composition or changing the shape of the drug delivery profile curve. This is illustrated in Mantelle, *et al.*, *Effect of Silicone/Acrylic PSA Blends on Skin Permeation*, 26 PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS 415-16 (Rev. July 1999) (the "Mantelle Article") (EX2010).

57. The Mantelle Article describes the effects of varying the silicone to acrylic ratio of a pressure-sensitive adhesive used in a drug-in-adhesive transdermal drug delivery system, *i.e.*, the drug-containing polymer matrix of a TDS. The Mantelle Article reports experiments using two different drugs: selegeline and estradiol. The estradiol composition was formulated with 1.6% estradiol, 7.5% kollidon-30 (a soluble PVP), 8% dipropylene glycol and 6% oleyl alcohol, with the acrylic polymer content varied between 10 and 20% and the

silicone polymer content varied between 66.9 and 56.9% (all by dry weight in the finished product). EX2010, 2, right column. The Mantelle Article states that the examples were prepared as 10 $cm^2$ systems, but does not describe the coat weight of the examples. *Id.*

58. As reported in the Mantelle Article, "varying the silicone to acrylic ratio…resulted in an average flux rate increase from 1.01 to 1.09 to 1.25 $\mu g/cm^2/hr$ with the additional effect of having altered the initial burst effect and subsequent sustenance of the pseudo-zero-order delivery profile." EX2010, 3, right column. As seen in Figure 2, a "higher silicone to acrylic … ratio resulted in a shift of the permeation profile from a pseudo-zero-order to a first order delivery system incapable of sustaining the targeted 84 hour delivery." *Id.* (emphasis added). That is, increasing the relative amount of silicone increased the initial flux of estradiol from the system, but the increased flux was not sustained over the targeted delivery timeframe. The flux from the high silicone formulation decreased, and fell below the flux of the 20% acrylic/56.9% silicone formulation by 72 hours. These results illustrate the unpredictable effects of adjusting one parameter of a TDS, and also illustrate the balance and tension between increasing drug flux and sustaining drug flux.

59. The Miranda Patents cited by Petitioner further illustrate the high level of unpredictability in this regard. The Miranda Patents relate to using blends

of different polymers to adjust the solubility of a drug in the polymer matrix of a TDS and thereby affect drug delivery, and also describe the use of soluble polyvinylpyrrolidone ("PVP") to increase the amount of drug that can be solubilized in a polymer matrix. EX1011, Abstract; EX1033, Abstract. The Miranda Patents report with reference to FIG. 6 that when estradiol was formulated in a polymer matrix with acrylic and silicone polymers, increasing the silicone polymer content increased estradiol flux "during the first 22 hours of delivery, but was affected to a much lesser degree during the remainder of the study (22 to 99 hours)." EX1011, 40:66-41:3; EX1033, 40:43-47. The Miranda Patents also note that "the formulation of Example 10 [with 18% polysiloxane and 65% acrylate] delivers drug at approximately the same rate over time whereas the formulation of Example 13 [with 58% polysiloxane and 15% polyacrylate] delivers more quickly in the early phase than the latter." EX1011, col. 41:9-12; EX1033, 40:53-56.

60. The Miranda Patents report with reference to FIG. 19 that when estradiol/norethindrone acetate systems were formulated in a polymer matrix with 0, 2.5, 5, or 10% PVP "essentially the same flux" was achieved, even though "the incidence of crystal formation was reduced as the [PVP] concentration increased. EX1011, 50:65-51:5; EX1033, 50:66-51:6. This indicates that an approach that improves a drug's solubility in the polymer matrix may not always impact flux.

61. While penetration enhancers are specifically used to increase flux, the "best" enhancer for a given composition usually is assessed empirically, and can depend on the drug being formulated, the desired pharmacokinetic profile, and other components present in the composition. A. Williams & B. Barry, *Chemical Permeation Enhancement*, *in* ENHANCEMENT IN DRUG DELIVERY 233, 248-50 (E. E. Touitou & B. Barry eds., 2007) (EX2011, 248-50) ("It is difficult to select rationally a penetration enhancer for a given permeant…the level of enhancement expected for these agents is unpredictable."). This is illustrated by the examples of the Miranda Patents which use different enhancers for different drugs. EX1011, 38:3-60:40; EX1033, 37:54-60:54; *see also* A. Williams & B. Barry, *The enhancement index concept applied to terpene penetration enhancers for human skin and model lipophilic (oestradiol) and hydrophilic (5-fluorouracil) drugs*, 74 INT'L J. PHARMACEUTICS 157-168 (1991) (EX2012, 165-66) (reporting that the terpene enhancers had different activities for estradiol versus 5-fluorouracil).

62. All of these adjustments can impact not just the magnitude of the drug flux curve, but also its shape. That is, increasing drug concentration, adjusting the composition components, and using an enhancer can impact not only the dose of drug delivered, but also whether drug delivery is essentially zero order over the target delivery period or shifts to first-order delivery and declines, as illustrated in the Mantelle Article (EX2010) and Miranda Patents discussed above.

63. Still further complicating the development process is the fact that the components of a polymer matrix can interact in unpredictable and undesirable ways. Previous writings by Dr. Brain highlight this problem. *See* K. Walters & K. Brain, *Dematological Formulation and Transdermal Systems, in* DEMATOLOGICAL AND TRANSDERMAL FORMULATIONS 338-43 (K. Walters, ed., 2002) (EX2013). For example, Dr. Brain explains that when the drug is mixed with the adhesive (as it is in a drug-containing polymer matrix), "the potential for interaction between drug and adhesive, which can lead to either a reduction of adhesive effectiveness, or the formation of a new chemical species, must be fully assessed." EX2013, 339. He also cautions that "residual monomers, catalysts, plasticizers, and resins may react to give new chemical species," and that "the excipients, including enhancers, or their reaction products, may interfere with adhesive systems." *Id.* He identifies "three critical considerations in the selection of a particular system: adhesion to skin, compatibility with skin, and physical or chemical stability of total formulation and components." *Id.* Yet, he considered none of these factors in his proposed modifications of Mueller.

64. With regard to monolithic systems in particular, Dr. Brain noted that their design "simplicity is, however, deceptive and several factors, involving potential interaction between drug or enhancer and the adhesive, need to be considered," including "chemical interactions resulting in interference with

adhesive performance, breakdown of the active species, or formation of new chemical entities." *Id.* at 340. That he considered none of these factors in his obviousness analysis shows that his analysis does not reflect the perspective of a POSA.

### C. Coat Weight Was Not Known To Impact Flux

65. Dr. Brain is just plain wrong when he alleges that it was "understood that increasing the thickness, or coat weight, of the adhesive polymer matrix layer would result in an increase in flux." EX1002, ¶101. While Dr. Brain cites several papers (*e.g.*, EX1009, EX1010, and EX1014) as allegedly supporting that premise, none of those citations stand up to scrutiny, and none stand for the general proposition for which Dr. Brain and Petitioner rely on them. Furthermore, the references contain internal inconsistences that would prevent a POSA from taking their conclusions at face value. Indeed, Dr. Brain's willingness to generalize references that relate to different drugs contradicts his own scholarly writings that emphasized that "[a] major determinant of skin absorption relates to the physicochemical properties of the applied chemical." EX2008, 84; *see also* Walters & Brain, *Dematological Formulation and Transdermal Systems* in DEMATOLOGICAL AND TRANSDERMAL FORMULATIONS (Walters, ed.) (Marcel Dekker Inc., 2002) (EX2013, 342). A POSA certainly would not extrapolate the

dubious conclusions of these papers into a general rule, as Dr. Brain and Petitioner have seen fit to do; nor do they evidence a supposedly well-accepted rule.

66. Even more remarkably, the main reference that Petitioner relies on to challenge the '900 Patent, Mueller (EX1005), proves that there was no understanding in the art that increasing coat weight would increase flux, because Mueller fails to take into account the different coat weights of its comparative examples. EX1005, ¶¶49-61. Further, at least one other reference cited by Petitioner supports the explanation in the '900 Patent that it was known to increase coat weight to provide delivery over a longer period of time, but it was not known that increasing coat weight would increase flux.

### *1. Kim (EX1010)*

67. Petitioner alleges that Kim (EX1010) "teaches that increasing the coat weight of a monolithic matrix-type transdermal patch increases flux." *See, e.g.*, Petition, 4, 63, 65. There are many reasons why I disagree with Petitioner. For at least these reasons, a POSA would not have understood Kim to teach that increasing coat weight of an estradiol TDS would lead to increased estradiol flux.

#### a. A POSA Would Not Rely On Kim

68. A POSA would not rely on the cited portions of Kim for several reasons. First, a POSA would note that the manuscript was submitted on March 15, 2003, and accepted on April 21, 2003. This means that the entire review process

was barely a month long, which suggests that little, if any, substantive peer review occurred. Second, a POSA would have noted glaring internal inconsistencies in Kim that would have prevented a POSA from finding its reports credible.

69. Significantly, the data depicted in Figure 4 does not correspond to the data described for Figure 4 in the text. This is the very portion of Kim that Petitioner and Dr. Brain rely upon, but neither Dr. Brain or Petitioner even acknowledge these discrepancies, let alone attempt to explain them.

70. In this regard, I note that while the text corresponding to Figure 4 states that after 30 hours the total amount of tulobuterol delivered from the 30 μm matrix was 34.5 ± 3.9 μg/cm$^2$, Fig. 4 shows a cumulated amount permeated of about 100 μg/cm$^2$ for the 30 μm matrix at 30 hours. EX1010, 82. There are similar mismatches for the data reported/depicted for the 50, 60 and 70 μm matrices (all of the matrices). That is, while the text states that after 30 hours the total amount of tulobuterol delivered from the 50, 60 and 70 μm matrices was 77.1 ± 9.3 μg/cm$^2$, 101.1 ± 8.4 μg/cm$^2$, and 131.1 ± 10.1 μg/cm$^2$, respectively, Fig. 4 shows a cumulated amount permeated of about 135 μg/cm$^2$, 140 μg/cm$^2$, and 170 μg/cm$^2$, respectively. EX1010, 82. Given these significant discrepancies, a POSA would not rely on the results reported in Kim for any purpose, let alone to draw any general conclusions as to the effect of coat weight on flux.

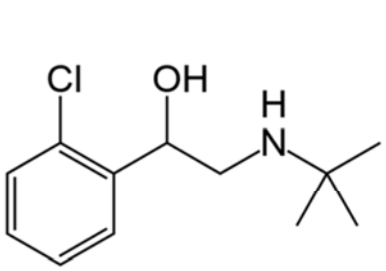
71. Further, Kim was published in the Journal of Korean Pharmaceutical Sciences. I was not aware of this journal prior to being asked to review the paper, and as far as I can ascertain the journal is no longer published. Kim is entitled "Penetration Enhancement of $\beta_2$ Selective Agonist, Tolobuterol, Across Hairless Mouse skin." I do not believe that a POSA looking to develop a TDS to deliver estradiol across human skin would have considered the content of Kim as being relevant to that pursuit. Indeed, a Google Scholar search on March 8, 2018 (EX2014) revealed that Kim only has been cited five times, and only one of those times was in a scientific publication by a third party. Even then it was not cited for the teaching that Petitioner relies. That publication, A. Ghosh *et al.*, *Current Pharmaceutical Design on Adhesive Based Transdermal Drug Delivery Systems*, 21 CURR. PHARM. DESIGN 2771-2783 (2015) (EX2015), cites Kim for the proposition that "[r]ecent development in new adhesives for transdermal drug delivery aims at enhancing the rate of drug transport, achieving a high physicochemical compatibility of adhesives with drugs, permeation enhancers and skin, and having adhesives able to accommodate high drug loads without their adhesive property being negated." EX2015, 2775. The remaining citations to Kim include three subsequent self-citations in publications by HK Choi, the lead author on Kim, and one citation on the face of U.S. Patent No. 8,029,820, entitled "Patches containing tulobuterol" (EX2016). The number of times a publication has

been cited by others in scientific literature is a measure of the publication's credibility. That Kim has only been cited one such time in the 15 years since it was published indicates that it was not widely read, and shows that it is not credible evidence of a general understanding in the art.

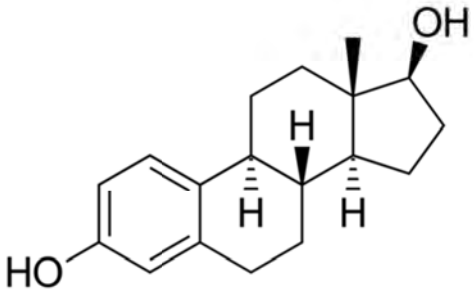
b. A POSA Would Not Extrapolate Kim To Estradiol TDSs

72. A POSA would not have extrapolated Kim's results to estradiol TDSs or generalized Kim's results to all TDSs. Instead, a POSA would note that Kim relates to only one drug, tulobuterol, and assessed flux using hairless mouse skin, not human skin. This is of note because (i) tulobuterol is physiochemically distinct from estradiol, and, as discussed below (ii) hairless mouse skin is not an accurate predictor of flux through human skin.

73. Tulobuterol and estradiol belong to different classes of drugs, with tulobuterol being a β2-adrenoreceptor agonist and estradiol being a steroid hormone. Nor are these drugs structurally similar. As shown below, they have different physicochemical properties, including size, molecular weight, solubility, hydrogen bonding capacity, and functional groups.




Tulobuterol




Estradiol

These differences are significant in the context of transdermal drug delivery. According to Dr. Brain, "[t]he primary factors affecting skin absorption are concerned with the physicochemical properties of the penetrant. The most important physicochemical parameters are arguably molecular weight, solubility, charge and hydrogen bonding capacity." EX2008, 84. Thus, a POSA would not expect such different drugs to behave similarly in a transdermal context.

74. Accordingly, even if Kim convincingly showed that increasing the coat weight of its tulobuterol TDS increased flux—which I do not believe it does, as explained below—a POSA would not have extrapolated the results reported in Kim to any and all TDSs for any and all drugs, or to estradiol TDSs in particular.

75. With regard to the type of skin used, a POSA knew that performance of a particular TDS on hairless mouse skin is not necessarily predictive of performance of a TDS on human skin. Indeed, Godin and Touitou warn that "human skin should be used in skin permeation studies and not hairless mouse or snake skin; otherwise, misleading results may be obtained." B. Godin & E.

Touitou, *Transdermal skin delivery: Predictions for humans from in vivo, ex vivo and animal models*, ADV. DRUG DELIV. REVIEWS, 59(11): 1152-1161 (2007) (EX2017, 1156). Rather, it was very well known that hairless mouse skin is less robust than human skin and is liable to substantial degradation of its stratum corneum barrier if simply bathed by water in a donor and receptor compartment for periods beyond 24 hours, as concluded in R. Hinz *et al.*, *In vitro percutaneous penetration: evaluation of the utility of hairless mouse skin*, 93(1) J. INVEST. DERMATOL. 87-91 (1989) (EX2018, 88-89). Additionally, it was well known that hairless mouse skin was a poor model to predict the activity of penetration enhancers in human skin. In a comparison between human and hairless mouse skin, "after penetration enhancer pretreatment, the hairless mouse model was misleading," and the authors "conclude that hairless mouse skin cannot be used as a reliable model for human percutaneous absorption as modified by accelerant treatment." J. Bond & B. Barry, *Hairless mouse skin is limited as a model for assessing the effects of penetration enhancers in human skin*, 90(6) J. INVEST. DERMATOL. 810-813 (1988) (EX2019, 812). Even Petitioner's own reference, Ghosh (EX1014), reported that "[s]kin permeation rate across human cadaver skin was found to be lower than that of hairless mice." EX1014, Abstract.

76. Accordingly, even if Kim convincingly showed that increasing coat weight of its tulobuterol TDS increased flux across hairless mouse skin—which I

do not believe it does —a POSA would not have expected to see the same effect with human skin, let alone have expected to see the same effect with a completely different TDS for a completely different drug. There is simply nothing in Kim that supports a general proposition that increasing coat weight will increase flux.

c. Other Publications By The Same Author Report Different Results

77. Two later publications by Choi, the other author of Kim (EX1010), do not support a general proposition that increasing coat weight will increase flux.

78. R . Subedi *et al.*, *Influence of formulation variable in transdermal drug delivery system containing zolmitriptan*, 419 INT'L J. PHARMACEUTICS 209-214 (2011) (EX2020), relates to a TDS for zolmitriptan. The authors found that "[t]he penetration rate of zolmitriptan increased when matrix thickness increased [from 25 μm] up to 95 μm" but then "remained similar up to 130 μm." EX2020, 211. Moreover, "[f]urther increase in the thickness resulted in lower permeation rate." *Id*. (emphasis added). Thus, for the zolmitriptan system studied in this paper, increasing coat weight apparently increased flux up to a point, while further increases had no effect, and then decreased flux.

79. R. Subedi *et al.*, *Formulation and in vitro evaluation of transdermal drug delivery system for donezil*, 42 J. PHARMA. INVEST. 1-7 (2012) (EX2021) relates to a TDS for donepezil. The authors found that the "[p]ermeation profile of donepezil was unchanged when matrix increased from 65 to 85 μm." EX2021, 4.

On the other hand, they found that "further increase in matrix thickness resulted in lower permeation profile of donepezil." *Id.* (emphasis added). Thus, for the donepezil system studied in this paper, increasing coat weight resulted in no change in flux up to a certain thickness, beyond which point further increasing the coat weight decreased flux.

d. Drug Depletion, Not Coat Weight *Per Se*, Is A More Likely Explanation For Kim's Results

80. Collectively, these results suggest that the effect Kim (EX1010) attributed to coat weight actually relates to drug depletion. That is, the observed differences in flux can be attributed to differences in the absolute amounts of drug present. As I explained at ¶¶50 and 51 above, with zero-order (constant) drug delivery, a plot of the cumulative amount of drug permeated over time will show a linear relationship, the slope of which provides the flux. When the drug delivery profile falls off, as in Figure 4 of Kim, that indicates depletion of the drug from the dosage form.

81. The amount of drug present in a matrix limits the amount of drug available to leave the matrix and flux through the skin sample. Thus, when only a relatively small amount of drug is present, or delivery is relatively rapid, flux may be limited by drug depletion. Increasing the thickness of the matrix increases the absolute amount of drug present. Thus, when flux is limited by drug depletion, providing more drug, such as by applying a thicker matrix, may partially

compensate for that limitation—*i.e.*, a smaller fraction of the total drug content is delivered from a thicker matrix, so depletion is proportionately less. Figure 4 of Kim is consistent with a drug depletion effect, as explained below.

82. Looking at the shape of the flux curves in Figure 4 of Kim, it is seen that the slopes of the curves are linear for a time and then tail off. EX1010, 82. As I explained earlier, the linear portion of the flux curves represents the flux at pseudo-steady state. In Figure 4, the flux at steady state (gradient from approximately 5 to 10 hours) appear to be superimposed and are indistinguishable for the 50 and 60 μm matrices. This indicates that the difference in coat weight between those matrices did not impact flux at steady state. Because the flux at steady state was identical, the separation between the flux curves for the 50 and 60 μm matrices as time goes on likely is due to differences in the absolute amount of drug present and the drug depletion effect. For the 30 μm matrix, the profile suggests depletion at earlier time points and for the 70 μm matrix, depletion appears to occur slightly later, after approximately 14h, based on a crude extrapolation of the data in the figure. Depletion at later times is expected with the higher amount of drug present in the thicker matrix. Thus, a POSA reviewing Kim would believe that the effect Kim attributed to coat weight actually relates to drug depletion.

83. Whether drug depletion will be a limiting factor depends on the absolute amount of drug present as well as the transdermal flux (which in turn is

influenced by the drug diffusion coefficient and the partition coefficient of the drug between the skin barrier and the patch). By way of explanation, if a patch contained 1 mg of a drug but only 0.01 mg was delivered over 24 h, then the initial drug concentration will have fallen by only 1% which would be unlikely to significantly affect the concentration gradient and hence flux of the drug over a subsequent 24 hour period. In contrast, if a patch contained 10 mg of drug and 5 mg was delivered over 24 h hours, then the initial drug concentration will have depleted by 50% and so the concentration gradient will fall and hence drug flux over a subsequent 24 hour period will consequently fall. In this regard, I note that the Ghosh reference (EX1014) cited by Petitioner discusses the impact of drug depletion on flux, and concludes that, for its methadone systems, "a minimum of 40% of the initial loaded dose needed to be retained by the patch to maintain a single steady-state skin permeation rate of methadone across the hairless mouse skin." EX1014, 290.

84. Drug depletion is not a factor limiting drug flux in a system that achieves sustained flux over an extended period of time while delivering only a relatively small fraction of the drug present (such as with Vivelle-Dot®, which achieved therapeutically effective delivery over 3.5 days while delivering only about 22% of the drug present). *See also* EX1014, 290. Consequently in such systems where drug depletion is not a factor, increasing the amount of drug present

by increasing the coat weight would not be expected to increase flux. Petitioner has not established any reason for a POSA to expect any deviation from Fick's first law in the context of the claimed invention. Rather, as discussed in the '900 Patent and confirmed in Wong (EX1028) discussed below, increasing the coat weight of such a system was expected to extend the duration of the delivery period, not increase flux.

85. Contrary to Petitioner's and Dr. Brain's assertions, the effect Kim observed in Figure 4 is not likely due to occlusion. This is because Kim's matrix already had a backing layer. EX1010, 80. Indeed, TDSs generally have a backing layer that externally protects the drug matrix. EX1006, 13; EX1015, 5; EX1016, 18; EX 2009, 2. Various backing layers are known for this purpose, and generally are occlusive—that is, they prevent or reduce Transepidermal Water Loss from the skin to the external environment. In so doing, they allow the stratum corneum of the skin (which is the main barrier to drug delivery) to hydrate, which in consequence promotes delivery of most drugs through the tissue. Kim does not identify the specific backing layer it used, but does acknowledge that the backing provides occlusivity to the system. EX1010,82. Thus, a POSA would not expect that incrementally increasing the thickness of the matrix, would have any further impact on the occlusivity of the system, let alone that it would have such an impact

on occlusivity that it would impact flux. There is simply no data in Kim to support such a conclusion.

86. If Kim wanted to know whether increasing the matrix thickness increased occlusivity, Kim could have readily determined that experimentally. That is, Kim could have directly assessed the occlusivity of its matrices, such as by taking measurements of Transepidermal Water Loss (TEWL) when a thinner or thicker patch was applied to skin in a Franz cell. Without such data, a POSA would not agree with Kim's conjecture that "it seemed that the occlusive effect of the adhesive matrix increased" with increasing thickness.

### *2. Ghosh (EX1014)*

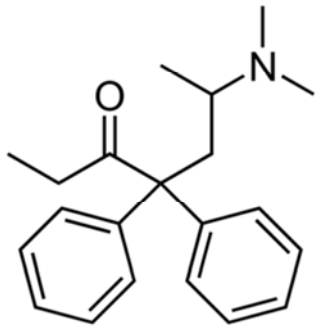
87. Petitioner alleges that Ghosh (EX1014) also "teach[es] that increasing the coat weight of a monolithic matrix-type transdermal patch increases flux." (*see, e.g.*, Petition, 4, 63, 65). Again, there are many reasons why I disagree that a POSA would have understood Ghosh to teach that increasing coat weight of an estradiol TDS would lead to increased estradiol flux.

#### a. A POSA Would Not Extrapolate Ghosh To Estradiol TDSs

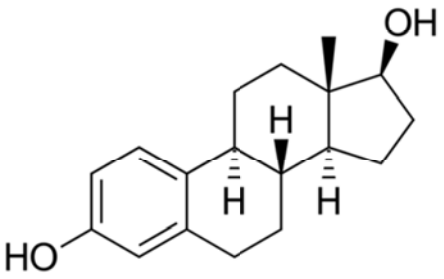
88. As with Kim, a POSA would not have extrapolated Ghosh's results to estradiol TDSs or generalized Ghosh's results to all TDSs. Instead, a POSA would note that Ghosh relates to only one drug, methadone, and used hairless mouse skin to assess flux of systems having different coat weights. There is simply no

scientific basis for Petitioner's sweeping generalizations of Kim and Ghosh. Indeed, Dr. Brain contradicts his own work which emphasizes that the drug being delivered is "[a] major determinant of skin absorption relates." EX2008, 84.

89. Methadone and estradiol belong to different classes of drugs, with methadone being an opioid and estradiol being a steroid hormone. Nor are these drugs structurally similar. As shown below, they have different physicochemical properties, including size, molecular weight, solubility, hydrogen bonding capacity, and functional groups.




Methadone




Estradiol

As noted above, these differences are significant in the context of transdermal drug delivery. EX2008, 84. Thus, a POSA would not expect such different drugs to behave similarly in a transdermal context.

90. Accordingly, even if Ghosh convincingly showed that increasing the coat weight of its methadone TDS increased flux—which I do not believe it does,

as explained below—a POSA would not have extrapolated the results reported in Ghosh to any and all TDSs for any and all drugs, or to estradiol TDSs in particular.

91. With regard to the type of skin used, as discussed above, a POSA knew that performance of a particular TDS on hairless mouse skin is not necessarily predictive of performance of a TDS on human skin. Indeed, Ghosh itself reported that "[s]kin permeation rate across human cadaver skin was found to be lower than that of hairless mice." EX1014, Abstract. Accordingly, even if Ghosh convincingly showed that increasing coat weight of its methadone TDS increased flux across hairless mouse skin—which I do not believe it does—a POSA would not have expected to see the same effect with human skin, let alone have expected to see the same effect with a completely different TDS for a completely different drug . There is simply nothing in Ghosh that supports a general proposition that increasing coat weight will increase flux.

b. Petitioner and Dr. Brain Misinterpreted Ghosh

92. Petitioner and Dr. Brain also have misinterpreted Ghosh. For example, Dr. Brain states in EX1002, ¶91:

> As shown in Table 1, as film thickness increased from 1.0 to 2.0 mm, flux increased from 94.04 to 136.81 μg/cm$^2$/hr in a Phase I trial, and from 36.71 to 53.02 μg/cm$^2$/hr in a Phase II trial.

However, Ghosh expressly states that "no inference on statistical difference could be drawn" between the 1.0 mm thick matrix and the others, because of the "differences in time intervals between phase I and phase II." EX1014, 288, left col. Thus, Petitioner and Dr. Brain rely on a comparison of data that Ghosh itself expressly states should not be compared.

93. Moreover, Dr. Brain's reference to a "Phase I trial" and "Phase II trial" is incorrect, if not misleading. The data reported in Table I of Ghosh was obtained from a single *in vitro* permeation study. EX1014, 288, col. 1. Ghosh's reference to "phase I" and "phase II" pertains to the unusual biphasic nature of the observed flux profiles, where all matrices exhibited an initial steady state flux ("phase I") followed by reduced flux ("phase II"). *Id.* Ghosh is not referring to Phase I and Phase II clinical trials.

c. Ghosh Acknowledges Drug Depletion Is A Factor

94. Consistent with the discussion of depletion included above, Ghosh itself discusses drug depletion as a factor that impacts flux. As noted above, Ghosh specifically discusses the impact of drug depletion on flux, and concludes that, for its methadone systems, "a minimum of 40% of the initial loaded dose needed to be retained by the patch to maintain a single steady-state skin permeation rate of methadone across the hairless mouse skin." EX1014, 290.

95. Collectively, Kim (EX1010), EX2020, EX2021, and Ghosh (EX1014) do not support a general proposition or understanding in the art that increasing coat weight is a predictable way to increase flux.

### *3. Bronaugh (EX1026)*

96. Petitioner and Dr. Brain also rely on Bronaugh (EX1026) to support their theory that it was known that increasing coat weight would increase flux, but Bronaugh barely mentions TDSs and does not mention coat weight at all! Bronaugh's data showing an impact of "occlusion" on drug flux does not pertain to TDSs, but rather was obtained using liquid compositions, which are inherently non-occlusive. *See, e.g.*, EX1026, 95. In particular, Bronaugh reports studies where the percutaneous absorption (absorption into the skin) of volatile liquid compounds or steroids dissolved in a volatile liquid solvent (*e.g.*, acetone) was assessed. *See, e.g.*, EX1026, 87-95. In that context, Bronaugh reports that using a covering over the application site can increase flux, although the effect is reported to be drug-specific. *Id.* For example, in one study Bronaugh assessed the impact of covering the application site with a glass cylinder capped with Parafilm, covering the application site with plastic wrap, or leaving the application site unprotected. EX1026, 87-88.

97. I do not disagree with Bronaugh's conclusion that increasing occlusion can enhance percutaneous absorption; nor do I disagree with Bronaugh's

explanation that occlusion may promote hydration of the stratum corneum which in turn may promote percutaneous absorption. What I do disagree with is that these teachings of Bronaugh somehow relate to the coat weight of a polymer matrix of a TDS that already has a protective backing. To the contrary, as discussed above, since a TDS already includes a backing layer that provides considerable occlusivity to the system (similar to a covering as used in Bronaugh), a POSA would not expect increasing the thickness of the polymer matrix to have a further impact on occlusivity, let alone on flux.

98. The only evidence that Petitioner cites that associates polymer matrix thickness with occlusivity is Kim (EX1010). For the reasons I explained above, however, a POSA would not agree with Kim's conjecture that increasing the thickness of its matrix increased the occlusivity of its system.

99. Thus, a POSA would not find Bronaugh or any other reference cited by Petitioner to indicate that increasing the polymer matrix coat weight of a TDS would increase the occlusivity of the TDS and thereby increase flux.

#### *4. Chien (EX1009)*

100. Petitioner alleges that "Chien expressly teaches that increasing the coating thickness (or coat weight) of the adhesive polymer matrix increases estradiol flux." Petition, 60. It most certainly does not.

101. Petitioner and Dr. Brain solely rely on Figure 5 of Chien, which Petitioner alleges "expressly" provides such a teaching. Petition, 60; EX1002, ¶148. However, contrary's to their assertions, Chien does not describe the figure as relating to "coating thickness (or coat weight) of the adhesive polymer matrix" of a monolithic TDS, as recited in the claims of the '900 Patent. Nor does Chien refer to this figure as providing evidence that increasing the coat weight of the drug-containing polymer matrix of a monolithic system increases estradiol flux. Indeed, the reference is completely devoid of any additional information on or discussion of this figure or the experiments used to obtain the depicted results.

102. Chien describes various different embodiments of estradiol TDSs. Chien describes many TDSs that may include (i) an estrogen-containing polymer adhesive layer, (ii) an "additional adhesive layer," and (iii) "another layer…between the estrogen-containing adhesive polymer layer and the adhesive layer." EX1009, 2:45-3:40. In other words, the TDSs described in Chien have varying compositions, and some are multi-layer systems with more than one adhesive polymer layer in addition to the drug-containing adhesive layer. More particularly, while the legend and figure labels of Figure 5 refer to "thickness of coating," nowhere does Chien describe the actual identity or composition of the particular "coating" or the system that is the subject of Figure 5. Thus, a POSA would not know from Chien the identity of the "coating" that purportedly was

studied for Figure 5. In other words, a POSA reading Chien would not know if the "coating" of Figure 5 is the estrogen-containing polymer adhesive layer, or the "additional adhesive layer," or the "another layer … between the estrogen-containing adhesive polymer layer and the additional adhesive layer," or some combination of the above, and would not know if the system was a monolithic system or a multi-layer system.

103. The sole discussion of Figure 5 in the entirety of Chien is in the "Brief Description of the Drawings" section, where it states:

> FIG. 5 is a graph showing the effect of thickness of coating in a dosage unit on the human cadaver skin permeation rate of estradiol.

EX1009, 5:26-28. Chien provides no description of the "coating" at issue, no description of the "dosage unit" at issue, and no description of how the data was obtained. Because Chien does not provide any pertinent information relating to Figure 5, a POSA reviewing Chien would not draw any conclusions from the figure.

104. Petitioner's and Dr. Brain's speculation that Figure 5 relates to the "coating thickness…of the adhesive polymer matrix" is merely that—speculation. Chien does not explain Figure 5, what the data pertains to, or how the data was generated. A POSA could not reasonably interpret Chien as teaching that

"increasing the coating thickness (or coat weight) of the adhesive polymer matrix increases estradiol flux" because Chien fails to provide any basis whatsoever for reaching such a conclusion.

### *5. Mueller (EX1005)*

105. Dr. Brain's discussion of the allegedly known relationship between coat weight and flux glaringly omits Mueller (EX1005), which is the main reference Petitioner relies upon to challenge the '900 Patent. Dr. Brain must have overlooked the fact that Mueller itself does not support this theory. Indeed, not only does Mueller fail to mention that increasing coat weight would increase flux, Mueller thought so little of the impact of coat weight on flux it did not even take coat weight into account or control for coat weight when comparing flux of different systems. Thus, Mueller evidences that neither Mueller nor a POSA following Mueller suspected that coat weight would impact flux.

106. Mueller is directed to "Stabilised Oversaturated Transdermal Therapeutical Matrix Systems," where the systems are stabilized to prevent recrystallization of the drug, which is present at a concentration exceeding its saturation concentration. EX1005, Title; Abstract; ¶1. Mueller's examples compare systems with and without a hydrophilic skin contacting layer or with and without hydrophilic additives in *in vitro* permeation studies. EX1005, ¶¶41-6. The results are reported to show that the systems according to Mueller (*e.g.*, with hydrophile

additives) achieved "a constant release rate" for "a period of at least 72 hours," while the comparative systems (*e.g.*, without the hydrophile additives) did not. EX1005, ¶61.

107. Petitioner relies on Mueller's Example 3, which compares a TDS without hydrophile additives (Mueller's Example 2a system) to a TDS with hydrophile additives (Mueller's Example 3 system). EX1005, ¶58. Mueller expressly refers to the Example 2a system as "a comparison" for the Example 3 system, and expressly describes the study as a "comparative permeation study between samples without hydrophilic additives (2) and samples with hydrophilic additives (3)." EX1005, ¶58. Thus, Mueller likely expected, and a POSA following Mueller would expect, that the only meaningful impact on flux between the examples would be due to the polymer matrix formulation (*e.g.*, the hydrophile additives). Yet, the Example 2a system had a coat weight of 80 g/m$^2$ while the Example 3 system had a coat weight of 115 g/m$^2$.[2] EX1005, ¶¶50, 57. Mueller's failure to keep coat weight constant between the systems used for the comparison indicates that Mueller did not think coat weight would impact flux. Indeed, the coat weight of Example 3 is nearly 1.5 times that of Example 2a ((115 g/m$^2$ / 80 g/m$^2$) =

[2] I note that the Example 2a and Example 3 polymer matrix compositions also differ in other respects.

1.43); yet, Mueller does not even comment on this difference, let alone indicate that it might have impacted the flux reported in Fig. 3. Rather, even though Mueller uses different coat weights for its systems, it does not teach or suggest that coat weight is a result-effective variable for flux, but rather attributes flux differences only to the hydrophilic additives. *See, e.g.*, EX1005 ¶61.

108. I also note that Mueller has a U.S. filing date of March 2001, which is many years after the asserted dates of Chien (EX1009) —(1992), Ghosh (EX1014) —(1996), and Bronaugh (EX1026) —(1991). If those references truly reflected an understanding in the art that increasing coat weight would increase flux, as Petitioner insists, then Mueller would have controlled the coat weight between Example 2a and Example 3 in order to make a valid comparison. The fact that Mueller did not do so shows that, contrary to Petitioner's theory, there was no understanding in the art that increasing coat weight would increase flux.

***6. Wong (EX1028)***

109. Dr. Brain's discussion of the allegedly known relationship between coat weight and flux also omits Wong (EX1028), which he cites for a different purpose. Perhaps this is because Wong supports the explanation in the'900 Patent that, while it was known to increase coat weight to provide delivery over a longer period of time, it was not known that increasing coat weight would increase flux.

110. In this regard, I note that Wong is directed to nicotine patches. EX1028, Abstract. Wong's examples describe patches with a thickness that depends on the intended delivery period. In particular, the patch of Wong Example 3 is 100 microns thick and designed for use "for 16-24 hr," while the same composition is used in Wong Example 4 to make a patch of that is 50 microns thick and designed for use over "8-10hr." EX1028, 10:1-9; 20-24; 20-27. That is, Wong halved the coat weight in order to halve the duration of delivery. Thus, Wong shows that it was known in the art that increasing coat weight could be used to increase the duration of delivery, but does not support Petitioner's theory that there was an understanding that increasing coat weight would increase flux.

### D. Estradiol Transdermal Drug Delivery Systems

111. At the time of the 2008 priority date of the '900 Patent, Patent Owner's Vivelle-Dot® product was by far the smallest FDA-approved estradiol TDS. The standard starting dose of Vivelle-Dot® for treating moderate to severe vasomotor symptoms due to menopause is 0.0375 mg/day, which is provided in a 3.75 $cm^2$ patch. The largest approved dose of Vivelle-Dot® is 0.1 mg/day, which is provided in a 10.0 $cm^2$ patch. Other approved estradiol TDSs were much larger, as reported in the following table from J. Mantelle, *DOT Matrix® Technology, in* MODIFIED RELEASE DRUG DELIVERY TECHNOLOGY 405-14 (Rathbone *et al.* eds., 2d ed. 2008) ("the Mantelle Chapter") (EX2022, 412):

**Table 1** Based on Label Claim for 0.05 mg/day Dose

| Product | Patch size | Estradiol content | % depletion |
|---|---|---|---|
| Vivelle-Dot | 5.0 $cm^2$ | 0.8mg | 22.4 |
| Vivelle | 14.5 $cm^2$ | 4.3mg | 4.0 |
| Climara[c] | 12.5 $cm^2$ | 3.9mg | 9.0 |
| Estraderm | 18.0 $cm^2$[a] | 4.0mg | 4.4 |
| Mylan[c] | 23.7 $cm^2$[b] | 1.9mg | 18.0 |
| Alora | 18.0 $cm^2$ | 1.5mg | 11.6 |
| Esclim | 22.0 $cm^2$ | 10.0mg | 1.8 |

[a]Active area is $cm^2$.
[b]Active area is 15.5$cm^2$.
[c]7-day patch; others are 3.5-day.

112. As described in the Vivelle-Dot® Label, Vivelle-Dot® is a monolithic estradiol TDS, wherein the polymer matrix layer includes estradiol, "acrylic adhesive, silicone adhesive, oleyl alcohol, povidone and dipropylene glycol." EX1016, 13. At the time of the 2008 priority date of the '900 Patent, a POSA would have known that the polymer components of Vivelle-Dot® already had been optimized to maximize estradiol flux. EX2022, 409. This is discussed in the Mantelle Chapter which describes the use of acrylic and rubber (*e.g.*, silicone) polymers for drug-in-adhesive systems (*e.g.*, for drug-containing polymer matrices). *Id.* According to the Mantelle Chapter, the use of these two types of polymers (referred to as "Dot Matrix" technology) balances the drug solubilizing properties of acrylic polymers with the adhesive properties of rubber polymers, to obtain a product with "a delivery optimized thermodynamics matrix system,

which, by design, delivers greater amounts of drug per unit area without the need for…enhancers and provides the comfort and adhesion properties which today's consumers demand." EX2022, 417. As noted in the Mantelle Chapter, the Vivelle-Dot® product embodies the "Dot Matrix" technology. *Id.*

113. Indeed, given the size reduction embodied in Vivelle-Dot® as compared to Vivelle® and other products, a POSA would have believed that the formulation of the Vivelle-Dot® product already had been optimized with regard to estradiol concentration, penetration enhancers, and other formulation considerations, such as the relative amounts of silicone and acrylic polymers and the amount of povidone (also referred to as "polyvinylpyrrolidone" or "PVP").

114. Prior to developing Vivelle-Dot®, Patent Owner had developed Vivelle® estradiol TDS. Vivelle® provided the 0.0375 mg/day dose in an 11.0 $cm^2$ patch, and provided the 0.1 mg/day dose in a 29.0 $cm^2$ patch. EX1008, 12. Although Patent Owner was able to develop progressively smaller estradiol TDSs, not every "new" estradiol TDS was smaller than previously available products. For example, both Alora® and Esclim® were approved after Vivelle-Dot® but provide comparable doses from much larger patches. The Alora® 0.1 mg/day patch is 36 $cm^2$, and the Esclim® 0.1 mg/day patch was 44 $cm^2$, both several times larger than the 10 $cm^2$, 0.1 mg/day Vivelle-Dot® patch. EX1016, 18; EX2009, 2.

115. Neither Petitioner nor Dr. Brain have cited any evidence that there was any desire or need for a product smaller than Vivelle-Dot®. Indeed, although Petitioner and Dr. Brain cite Bevan (EX1013) as allegedly providing a reason to reduce patch size, Bevan states that then-available single-drug systems already satisfied "demands" for "small and comfortable" patches. EX1013, 1:34-37. Bevan therefore is focused on multi-drug systems, and suggests that a system having a total active surface area of 13 $cm^2$ sufficiently addresses the alleged desire to reduce patch size. EX1013, Table V (System V). Fotinos (EX1012) does not discuss a specific target size, but uses 5 $cm^2$ patches in its rabbit skin irritation studies. EX1012, 16. Nor does Mueller indicate what "smaller surface area" its approach might permit. EX1005, ¶22. The other references cited by Petitioner and Dr. Brain on this point use much larger patches. *See, e.g.*, Muller (EX1018, 4:20-21, 4:41-42) (16 $cm^2$); Rovati (EX1019, 4:40-42) (18-20 $cm^2$); Meconi (EX1020, 6:55-58, 7:2-3, 8:25-26) (16 and 20 $cm^2$); Jenkins (EX1027, 6:49-52) (19 or 28.5$cm^2$).

116. The only references that discuss Vivelle-Dot® in particular point out its advantages, but do not indicate that an even smaller patch would be advantageous. Dinger (EX1023) describes Vivelle-Dot® as using Patent Owner's "revolutionary Dot Matrix technology" and states that Vivelle-Dot® "offered drug delivery efficiency and was able to stick to the skin in spite of rigorous activities."

EX1023, 4/6. Butschli (EX1024) discusses the packaging used for Vivelle-Dot®. While Butschli (EX1024) discusses some practical advantages associated with the smaller size of Vivelle-Dot® as compared to previous products, Butschli does not suggest that an even smaller size would offer further advantages, or even indicate that a smaller patch would be packaged in a smaller pouch or carton. EX1024, 4/12.

117. Thus, Petitioner has not cited any evidence that a POSA would have been motivated to try to make an estradiol TDS product smaller than Vivelle-Dot®.

## VII. CLAIM CONSTRUCTION

### A. Legal Standard

118. I understand that a claim undergoing *inter partes* review is given its broadest reasonable construction in light of the patent specification, including any definitions provided in the patent. I also understand that claim terms are generally given their ordinary and customary meaning, as would be understood by a person skilled in the art in the context of the entire disclosure of the patent. I applied these principles in my analysis of the claims of the '900 Patent, including my comments below on the meaning of certain claim terms.

**B. "About"**

119. Claims 1 and 9-16 use the term "about" to qualify some of the recited parameters. The term "about" is defined in the'900 patent as follows:

> The term "about" and the use of ranges in general, whether or not qualified by the term about, means that the number comprehended is not limited to the exact number set forth herein, and is intended to refer to ranges substantially within the quoted range while not departing from the scope of the invention. As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

EX1001, 4:42-52. I applied this definition in my analysis of the '900 Patent.

**C. "Coat Weight"**

120. Claims 1 and 16 recite that the polymer matrix has "a coat weight of greater than about 10 mg/cm$^2$." The term "coat weight" is defined in the'900 patent as follows:

> As used herein, "coat weight" refers to the weight of the drug-containing layer per unit area of the active surface area of the transdermal drug delivery system.

EX1001, 5:16-18.

The term "active surface area" is defined in the'900 patent as follows:

> As used herein, "active surface area" means the surface area of the drug-containing layer of the transdermal drug delivery system.

EX1001, 5:13-15. I applied these definitions in my analysis of the '900 Patent. I also note that the specification of the '900 Patent discusses the "dry weight" of the drug-containing polymer matrix layer. *See, e.g.*, EX1001, 2:18-26. In view of this discussion and usage in the art, a person skilled in the art would understand the term "coat weight" as defined in the '900 Patent with reference to the weight of the drug-containing layer as being the "dry weight" of the drug-containing polymer matrix layer, *i.e.*, the weight of the dry components not including any processing solvents.

121. Dr. Brain cites a statement in the prosecution history where the Patent Owner's representative confounded the amount of estradiol per unit area with coat weight. *See* EX1002, ¶85. Patent Owner's representative subsequently rectified this statement, and clarified that "the amount of drug per unit area of a monolithic

transdermal drug delivery system as claimed depends on both the concentration of the drug in the polymer matrix and the coat weight of the polymer matrix," and that "applying a polymer matrix having a given concentration of drug over a smaller or larger area (or using it to form a smaller or larger system) would result in a smaller or larger amount of drug per unit area." EX1004, 273. Thus, a person skilled in the art would understand from the specification of the '900 Patent, and optionally from the record of the '900 Patent as a whole, that the term "coat weight" as used in the claims of the '900 Patent refers to the dry weight of the drug-containing polymer matrix layer.

**D. "Flux"**

122. Claims 1 and 16 recite that the transdermal drug system achieves "an estradiol flux of from about 0.0125 to about 0.05 mg/cm$^2$/day, based on the active surface area." The term "flux" is defined in the'900 patent as follows:

> As used herein, "flux" (also called "permeation rate") is defined as the absorption of a drug through skin or mucosal tissue, and is described by Fick's first law of diffusion: J = -D(dCm/dx) where J is the flux in g/cm$^2$/sec, D is the diffusion coefficient of the drug through the skin or mucosa in cm$^2$/sec and dCm/dx is the concentration gradient of the drug across the skin or mucosa.

EX1001, 5:24-32. I applied this definition in my analysis of the '900 Patent. I also note that a person skilled in the art would understand that, while the flux of transdermal drug delivery system is an *in vivo* property, it is measured by *in vitro* methodology, typically using donated human cadaver skin, as illustrated in Example 1 of the '900 Patent.

123. I disagree with Dr. Brain's suggestion that a POSA would solely rely on flux values extrapolated from a plot. *See* EX1002, ¶88. Dr. Brain has it in reverse. As I explained above in ¶¶50-51, flux is determined from the cumulative amount of drug that passed through the skin at given time periods, and that data can then be used to plot a curve. This is illustrated in the Guy Declaration from the prosecution history of the '900 Patent, where Dr. Guy presented a table of data showing the cumulative amount of drug delivered at specific time points, and explained that the results "may be plotted graphically." EX1004, 544.

124. Dr. Brain states that because the '900 Patent does not expressly define a time period when the TDS should achieve the claimed flux, the broadest reasonable interpretation would encompass flux "at any point during application to the skin." EX1002, ¶72. Dr. Brain is wrong on this point, however. For example, as I explained above in ¶¶50 and 51, a person skilled in the art would know that there is a lag period from the time of application to the time that steady state or pseudo steady state flux is reached, and a person skilled in the art would know that the flux

observed during this time period is not characteristic of the TDS, but rather reflects the time it takes for the initial amount of drug to begin passing through the skin and for a steady state flux to be reached. Thus, a person skilled in the art assessing the flux achieved by a TDS would not use flux values from the time period before a steady state flux had been reached, but rather would use flux values for a time period once steady state is reached. For at least this reason, I also disagree with Dr. Brain's statement that "if the permeation rate over a set time period is described in text with no additional data points, it is within the broadest reasonable interpretation to calculate the flux by comparing the disclosed permeation rate to a zero permeation rate at a zero hour time point." EX1002, ¶88.

125. Petitioner's and Dr. Brain's construction also ignores the essential need to account for variations in skin permeability, because there can be a large variation in permeability between different skin samples. Dr. Brain acknowledges this "high amount of variability that routinely occurs in flux measurements" (EX1002, ¶50), but fails to take it into account in his construction of flux. A person skilled in the art determining the flux achieved by a TDS would be aware of the impact of skin permeation variability on flux measurements, and would implement one or more well-known and accepted techniques for accounting for skin permeation variability, such as the use of an internal control with known flux

properties, as reflected in Example 1 of the '900 Patent and discussed in the Guy Declaration submitted during prosecution of the '900 Patent. EX1004, 597-99.

126. In summary, in accordance with the definition in the '900 Patent and consistent with the prosecution history of the '900 Patent and general understanding in the art of how flux is measured, the broadest reasonable interpretation of the term "flux" as used in the claims of the '900 Patent is the rate of absorption of drug through skin or mucosal tissue, as may be determined by *in vitro* human cadaver skin permeation studies, appropriately accounting for skin permeation variability, and the flux "achieve[d]" by a TDS would be reflected by flux values for a period when the flux is at steady state or pseudo steady-state.

127. As noted above, Example 1 and the prosecution history of the '900 Patent include further information on flux and how flux can be measured by well-known and conventional *in vitro* methodology, like that described in the Rule 132 Declaration of Dr. Richard H. Guy submitted on June 15, 2017. EX1004, 564-601.

### E. "Therapeutically Effective Amount"

128. Claim 8 recites a "therapeutically effective amount" of estradiol. In the context of the '900 Patent, this term includes doses "from about 0.025-0.1 mg/day." EX1001, 11:64-12:3.

## VIII. GROUNDS OF UNPATENTABILITY

129. Petitioner asserts four grounds of unpatentability which I address in turn below. As shown below, each ground rests on unsupported inferences that go far beyond what a POSA would have understood from the cited references, relies on mischaracterizations of the cited references and the state of the art, and ignores the high level of unpredictability in the art which is demonstrated by the very references Petitioner cites.

### A. Cited References

130. Petitioner's four grounds rely on four references, which I briefly summarize below.

#### *1. Mueller (EX1005)*

131. The main reference Petitioner relies upon is Mueller (EX1005). I understand that Mueller was submitted to the Examiner during prosecution of the '900 Patent, and that the Examiner acknowledged consideration of Mueller when examining the application and deciding to grant the claims. EX1004, 108.

132. As noted above, Mueller is directed to "Stabilised Oversaturated Transdermal Therapeutical Matrix Systems," where the systems are stabilized to prevent recrystallization of the drug, which is present at a concentration exceeding its saturation concentration. EX1005, Title; Abstract; ¶1. Mueller teaches that the use of a hydrophilic skin contacting layer or hydrophilic additives may be used to

stabilize the systems. EX1005, Abstract. Mueller teaches that its stabilized systems thereby can deliver drug "over a prolonged period of time." EX1005, ¶20. Mueller's examples compare systems with and without a hydrophilic skin contacting layer or with and without hydrophilic additives in *in vitro* permeation studies. EX1005, ¶¶41-61. The results are reported to show that the systems according to Mueller achieved "a constant release rate" for "a period of at least 72 hours," while the comparative systems did not. EX1005, ¶61.

133. Petitioner relies on Mueller's Example 3 and Fig. 3 which is said to be "a comparative permeation study between samples without hydrophilic additives (2a) and samples with hydrophilic additives (3)." EX1005, ¶58. Based on the information provided in Mueller, the approximate content of Mueller's Example 3 composition on a dry weight basis would be as follows:

| | |
|---|---|
| Estradiol: | 1.5% |
| Silicone Adhesive: | 79.5% |
| Acrylic adhesive: | 6.6% |
| Kollidon 90F (PVP): | 0.4% |
| Dipropylene glycol: | 11.6 % |
| Hydroxypropylcellulose: | 0.3% |

134. Aside from a description of the systems themselves, the only information Mueller provides on the permeation study of Example 3/Fig. 3 is in two bare sentences:

> These measurements were made using Franz diffusion cells and human epidermis. Each point is the mean of 3 independent measurements.

EX1005, ¶60. This description does not provide sufficient information for a POSA to evaluate the results of Example 3/Fig. 3 in the manner Petitioner has done. For example, Mueller does not explain what is meant by "3 independent measurements," which could mean any of a number of things—measuring the estradiol present in each sample three independent times, running the study on three different skin samples from the same donor, running the study on different skin samples from different donors, *etc.*

135. In addition, although Dr. Brain interpreted Fig. 3 of Mueller as allegedly showing that Mueller's Example 3 system achieved a specific flux, Mueller itself does not report any actual flux values for Example 3 or any of its systems, or even disclose a target flux value that its systems might achieve.

136. Most significantly, Mueller does not report the use of any controls, or otherwise indicate that variations in skin permeability were accounted for. For this

reason alone a POSA would not have read Fig. 3 as disclosing that the systems achieved a specific flux, as discussed above and explained in more detail below.

137. Moreover, as also discussed below, there are several other reasons a POSA would have understood Mueller Fig. 3 to disclose qualitative comparative data, not quantitative data showing that the TDSs achieved a specific estradiol flux. For example, a POSA reviewing Mueller as a whole would have taken note of the absence of numerical data in Mueller, Mueller's lack of a control, Mueller's failure to account for variation in skin permeability, and the imprecision with which Fig. 3 is presented, and would not have understood Fig. 3 to disclose quantitative data showing that the TDS of Example 3 achieved a specific estradiol flux.

### *2. Vivelle-Dot® Label* (EX1006)

138. I understand that a version of the Vivelle-Dot® Label was submitted to the Examiner during prosecution of the '900 Patent, and that the Examiner acknowledged consideration of the Vivelle-Dot® Label when examining the application and deciding to grant the claims. EX1004, 154.

139. The Vivelle-Dot® Label (EX1006) relates to the Vivelle-Dot® product discussed in the '900 Patent. The Vivelle-Dot® Label describes patches that deliver 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day having a size of 2.5, 3.75, 5.0, 7.5, or 10.0 $cm^2$ respectively. EX1016, 12. The Vivelle-Dot® product described by the Vivelle-Dot® Label delivers 0.01 mg/cm2/day of estradiol.

EX1001, 4:9-11; EX1016, 12. As noted above, the Vivelle-Dot® Label indicates that the standard starting dose for treating moderate-to-severe vasomotor symptoms (*e.g.*, "hot flashes") is 0.0375 mg/day, which is provided by the 3.75 $cm^2$ Vivelle-Dot® patch. EX1016, 26. As described in the Vivelle-Dot® Label, Vivelle-Dot® is a monolithic estradiol TDS, wherein the polymer matrix layer includes estradiol, "acrylic adhesive, silicone adhesive, oleyl alcohol, povidone and dipropylene glycol." EX1016, 13. The Vivelle-Dot® Label does not provide any more information on the components, such as the specific acrylic adhesive or specific silicone adhesive used, and does not provide any information on the actual or relative amounts of the components.

### *3. Kanios (EX1007)*

140. I understand that Kanios was submitted to the Examiner during prosecution of the '900 Patent, and that the Examiner acknowledged consideration of Kanios when examining the application and deciding to grant the claims. EX1004, 154.

141. Kanios (EX1007) generally relates to transdermal drug delivery systems (not just estradiol TDSs), and describes selectively manipulating the monomeric make up of an acrylic based polymer used in the drug-containing layer in order to control drug delivery rates, onset and profiles. *See, e.g.*, EX1007, ¶18. With regard to drug flux, Kanios states that "[s]imple diffusion models for

permeation of drugs through the skin suggest that permeation rates are concentration dependent." EX1007, ¶14. Kanios explains further, "[s]ome adhesives, such as, for example, polyacrylate adhesives have a high affinity for many drugs and thus tend to solubilize higher concentrations of drug than do, for example, rubber adhesives. However, the use of polyacrylates alone as the adhesive is not without its drawbacks as polyacrylate adhesives, for example, may tend to cause skin irritation, especially when the transdermal device is used for extended periods of time." *Id.* Kanios refers to Fick's 1st law of diffusion, and states that "[t]he invention resulted from the discovery that the transdermal permeation rate of a drug from the pressure-sensitive adhesive system can be selectively modulated by adjusting the monomeric make-up of the acrylic based polymer in the system." EX1007, ¶¶71-72.

142. Concerning coat weight, Kanios provides a very general description of typical coat weights in transdermal patch systems, as "usually in the range from about 1 mg/cm$^2$ to about 20 mg/cm$^2$, and more preferably in the range of from about 2.5 mg/cm$^2$ to about 15 mg/cm$^2$." EX1007, ¶103. Kanios does not report the coat weight used for its examples.

143. Concerning drug flux, Kanios provides a very general description that "a single dosage "[t]he delivery rate is in the range from 0.01 mg to about 100 mg of active agent per day, and more preferably in the range of from about 0.1 mg to

about 50 mg per day." EX1007, ¶103. A POSA would find these ranges to be very broad, and would not understand them to pertain to estradiol TDSs in particular, especially where the highest approved dose for an estradiol TDS was 0.1 mg/day. *See, e.g.*, EX1016, 12.

144. Kanios has no teaching or suggestion concerning the effect, if any, of coat weight on flux.

145. Concerning patch size, Kanios provides a very general description that "a single dosage unit may have a surface area in the range of 1 to 200 $cm^2$," and notes that "[p]referred sizes are from 5 to 60 $cm^2$." EX1007, ¶114. Kanios has no discussion of whether smaller or larger patches are preferred, or why or when one size might be preferred over another.

146. Petitioner relies on FIG. 1 of Kanios, which is said to present "[t]he average flux profiles of Examples 1-3," which are estradiol systems having the same amounts of different types of acrylic polymers, as set forth in this table from Kanios, ¶127:

Examples 1-3

**[0127]**

| | Example 1 | Example 2 | Example 3 |
|---|---|---|---|
| Acrylic-based polymer (70% soft monomers/30% hard monomers) | 20 | | |
| Acrylic-based polymer (50% soft monomers/50% hard monomers) | | 20 | |
| Acrylic-based polymer (20% soft monomers/80% hard monomers) | | | 20 |
| Silicone-based polymer (BIO-PSA 4503) | 62 | 62 | 62 |
| Oleyl Alcohol | 6 | 6 | 6 |
| PVP (Kollidon 30) | 10 | 10 | 10 |
| 17 β Estradiol | 2 | 2 | 2 |

147. Nowhere does Kanios report flux values for Examples 1-3. For reasons similar to those discussed above and below with reference to Mueller Fig. 3, a POSA would have understood Kanios FIG. 1 to disclose qualitative comparative data, not quantitative data showing that the examples achieved a specific estradiol flux. There is no information whatsoever in Kanios on how the results represented in FIG. 1 were obtained. Thus, a POSA could not know what type of skin samples were used for the study (*e.g.*, human or other animal) or whether any controls were used. While Kanios refers to the results as "the average flux profiles," there is no information on how many replicates were used, no information on standard deviation, and no other information indicating that the results were reproducible. Nowhere does Kanios state that the data points depicted in FIG. 1 were obtained at 11, 24, 46, and 71 hours, as Dr. Brain asserts in ¶143. Also, although Kanios provides information on the formulations of Examples 1-3,

Kanios does not provide any information on how the test systems were prepared, such as the coat weight of the polymer matrix or the size of the systems. EX1007, ¶127. Without knowing how the results were obtained, a POSA would have no way of knowing that the flux values depicted in the figure are meaningful, especially where Kanios itself does not report any specific flux values.

#### *4. Chien (EX1009)*

148. As noted above, Chien (EX1009) discloses various estradiol TDSs, including monolithic and multilayer systems. Petitioner relies on Figure 5 of Chien, but there is no discussion in Chien of the data presented in Figure 5. While the legend and figure labels refer to "thickness of coating," a POSA would not know from Chien the identity of the "coating," especially since Chien describes TDSs that may include several different types of "coatings," such as an estrogen-containing polymer adhesive layer, an "additional adhesive layer," and "another layer … between the estrogen-containing adhesive polymer layer and the adhesive layer." *See, e.g.*, EX1009, 2:45-3:40.

### B. Ground 1

#### *1. Claims 1, 2, 8, 10-16 and 18-23 are Not Taught By Mueller*

149. Mueller does not set forth each and every element of claims 1, 2, 8, 10-16, and 18-23, either expressly or inherently.

150. Of the claims challenged under Ground 1, claims 1 and 16 are the independent claims. Each of claims 1 and 16 recites a monolithic estradiol TDS that achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm$^2$/day, based on the active surface area. Mueller discloses a monolithic estradiol TDS, but Mueller does not show that its monolithic estradiol TDS achieved the claimed estradiol flux.

### *2. Mueller Does Not Show That Example 3 Achieved The Claimed Estradiol Flux*

151. Petitioner relies on Example 3 of Mueller as allegedly anticipating the challenged claims, but nowhere does Mueller report that the Example 3 TDS achieved an estradiol flux of from about 0.0125 to about 0.05 mg/cm$^2$/day. Petitioner attempts to supplement the teachings of Mueller with Dr. Brain's interpretation of Fig. 3, but Dr. Brain reads far more into Fig. 3 than a POSA would have understood it to disclose.

152. First and foremost, as discussed in ¶¶134-137 above, a POSA would not have understood Fig. 3 to disclose quantitative data showing that the disclosed TDSs achieved a specific estradiol flux, because Mueller did not use any control in Example 3, and did not otherwise account for variation in skin permeability, which can impact flux by several fold. *See., e.g.*, EX1004, 597-99. As discussed above, when assessing flux, it is essential to account for variations in skin permeability; thus, a POSA desiring to obtain quantitative flux data would have been aware of

and implemented one or more well-known and accepted techniques for accounting for skin permeation variability, but Mueller did not do so.

153. Dr. Brain acknowledges the "high amount of variability that routinely occurs in flux measurements, EX1002, ¶65, but fails to take it into account when he interprets Fig. 3 of Mueller as reporting a specific flux even though no control was used, even though Mueller does not indicate that variations in skin permeability were accounted for in some other way, and even though Mueller itself does not state a specific flux.

154. A POSA, however, would not have interpreted Mueller Fig. 3 to disclose that Mueller's system achieved a specific flux, because a POSA would have known that variations in skin permeability can impact flux values by several fold, as illustrated in the Guy Declaration submitted during prosecution of the '900 Patent. EX1004, 597-99. Thus, without a control or other measures for accounting for variations in skin permeability, the depicted flux values *per se* are essentially meaningless, although the figure may provide comparative information, as Mueller intended. That is, since Mueller did not use any controls or otherwise account for variations in skin permeability, it cannot be known from Fig. 3 whether the Example 3 TDS achieved a certain flux. This is further supported by the fact that Mueller does not report a target or expected flux value that its systems might achieve, against which a POSA could evaluate the results reported in Fig. 3.

155. A POSA also would not have read Fig. 3 as disclosing a specific flux because of the manner in which the figure is presented, which supports a qualitative, not quantitative, interpretation.

156. First, Mueller presents the figure only as representative of a comparative study. Mueller states, "The results of a comparative permeation study between samples without hydrophilic additives (2a) and samples with hydrophilic additives (3) are represented in FIG. 3." EX1005, ¶¶58, 60. A POSA therefore would have understood the purpose of the study to be a comparison of the relative permeation of (2a) and (3), not to show that (3) achieves a specific flux. Indeed, nowhere does Mueller report a flux for (3), or even discuss specific flux values. Rather, the only conclusion Mueller draws from its study is comparative, reporting that with "the [TDS] according to the present invention a constant release rate, and thus a stabilisation, is achieved for a period of at least 72 h, whereas in the case of the comparison examples a marked flattening of the permeation profile can be seen already after 32 h." EX1005, ¶61. Nowhere does Mueller discuss a specific "release rate" achieved by its TDS. Unlike Dr. Brain, a POSA would not have interpreted Mueller's figure as conveying more information than Mueller itself did.

157. A POSA also would not have interpreted Fig. 3 as disclosing a specific estradiol flux because Mueller does not describe how the permeation study was performed. As noted above, aside from a description of the systems

themselves, the only information Mueller provides on the permeation study of Example 3/Fig. 3 is that the "measurements were made using Franz diffusion cells and human epidermis," and that each point is the mean of three "independent measurements" of some unspecified type. EX1005, ¶60. The lack of information on this point is significant, because the possible different meanings have a significant impact on the reliability of the data. Did Mueller take three samples at each time point and measure the amount of drug present in each sample? Such measurements would be "independent" but would not account for other sources of variability, such as how the Franz cells were set up or variations in skin permeability. Or, did Mueller use three independent Franz cells fitted with skin from the same donor? Such measurements would be "independent" but would be skewed by the permeability of that donor's skin. Or, did Mueller use three independent Franz cells fitted with skin from three different donors? Such measurements would be "independent" and could partly account for variations in skin permeability. Without more information on how the permeation study was performed, a POSA would not know what was meant by "3 independent measurements," or whether the study was performed in a reliable, scientifically valid manner. Overall, the scant information on how the figure was obtained would prevent a POSA from trying to read specific numerical flux values from the values for any of its systems.

158. Still further, a POSA would take note of the imprecision in which the figure is depicted, and for that reason as well would not have tried to read specific numerical flux values from the figure. Fig. 3 includes a notation "mean values of n=3," but does not include any error bars. The y-axis is marked in increments of 2.5 µg/cm$^2$ and the diameter of each data point is about equal to the y-axis increments. Further, the x- and y-axis of Fig. 3 do not appear to be presented at true right angles. If Fig. 3 is overlaid onto a grid, as shown in the reproduction below, it is evident that the axes are not perpendicular, and therefore the apparent positions of the data points cannot be relied upon for precise measurements.

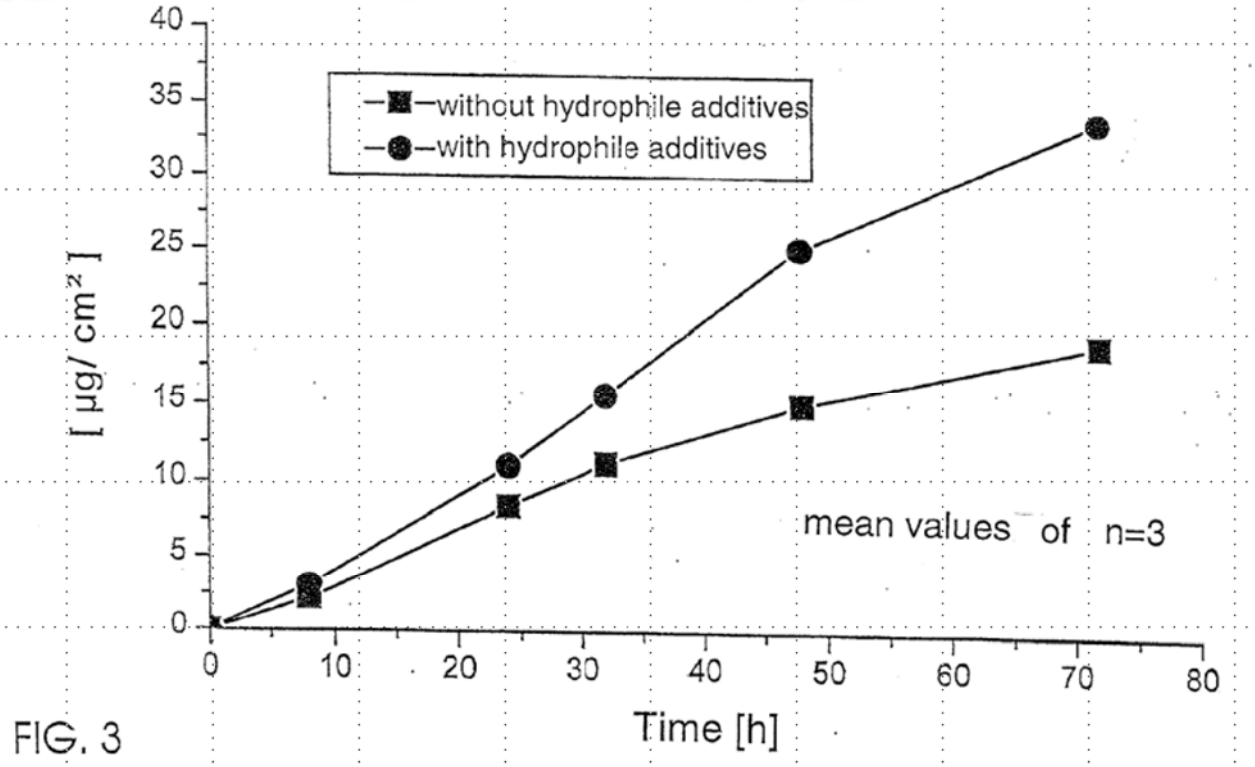



FIG. 3

159. Thus, the imprecision in which Fig. 3 is presented is another reason a POSA would understand Fig. 3 to provide a qualitative representation of a comparative study, not to support a quantitative interpretation of a specific flux. The qualitative purpose of the figure is underscored by the complete absence of any numerical flux data from Example 3.

160. Unlike Dr. Brain, a POSA would not have read flux values from Fig. 3 to the third decimal place, which reflects precision to the fourth decimal place. The size of the data points relative to the y-axis markings do not permit such precision. Dr. Brain did not explain how he was able to measure the figure so precisely, but his measurements could not be scientifically valid. Dr. Brain's flux calculations also depend on the time associated with each data point of Fig. 3 (EX1002, ¶¶125, 127, 158-60), but, unlike Dr. Brain, a POSA would not have interpreted the data points as being as at 8, 24, 32, 48, and 72 hours. There simply is no disclosure in Mueller to indicate that the data were obtained at precisely those times, as opposed to other times.

161. In summary, a POSA reviewing Mueller as a whole would have taken note of the absence of numerical data in Mueller, Mueller's lack of a control, Mueller's failure to account for variation in skin permeability, the imprecision with which Fig. 3 is presented, and the lack of information on how the permeation study was conducted, and would not have understood Fig. 3 to disclose quantitative data

showing that the TDS of Example 3 achieved a specific estradiol flux. Indeed, a POSA would not have assigned precise numerical values to non-numerical data presented in an imprecise format, as Dr. Brain did with Fig. 3. A POSA would have recognized that the qualitative data in Fig. 3 cannot be used to calculate a specific estradiol flux, and does not prove that the TDS of Example 3 necessarily achieved an estradiol flux of from about 0.0125 to about 0.05 mg/cm$^2$/day, as recited in claims 1 and 16. Thus, a POSA reviewing Mueller as a whole would not have found Mueller to disclose that the Example 3 system achieved an estradiol flux of from about 0.0125 to about 0.05 mg/cm$^2$/day, as recited in claims 1 and 16

162. Additionally, in view of the deficiencies discussed above, I believe that it is factually incorrect to conclude that Mueller's Example 3 necessarily achieved a flux of from about 0.0125 to about 0.05 mg/cm$^2$/day, as Petitioner asserts. The information provided in Mueller simply is not adequate to support a conclusion that Mueller's Example 3 necessarily achieved a flux of from about 0.0125 to about 0.05 mg/cm$^2$/day for the many reasons explained above.

### *3. Petitioner's Use of Mueller Fig. 3 is Scientifically Invalid*

163. Petitioner's use of Mueller Fig. 3 is scientifically invalid. Mueller presented the figure as comparative results assessing the relative permeation achieved by its Example 2a and Example 3 formulations, but Petitioner relies Fig. 3 to allegedly show that the Example 3 formulation achieved a specific flux. As a

general rule, a POSA would not rely on comparative data, lacking controls and presented graphically without any author-derived numerical values to derive a specific flux value. Rather, the figure is intended, and allows, only an assessment of relative flux from the two systems. That is, while the lack of a control prevents a determination of absolute flux values, as long as the systems were tested under the same conditions one can make an assessment as to whether one system exhibited a greater or reduced flux as compared to the other.

164. For these reasons, Petitioner's and Dr. Brain's reliance on Mueller Example 3/Fig. 3 is fundamentally scientifically flawed. Indeed, a POSA would not accept Dr. Brain's interpretation of Mueller Fig. 3 as scientifically valid, for each of the reasons discussed above.

#### *4. Mueller Does Not Disclose Applying Its Example 3 TDS To A Person In Need Thereof*

165. Mueller fails to disclose another essential feature of claim 1 of the '900 Patent, namely, "applying [the Example 3 TDS] to the skin or mucosa of a subject in need thereof."

166. From the claim chart at page 42 of the Petition, it appears that Petitioner relies on ¶56 of Mueller for providing such a disclosure, but that paragraph only describes the ingredients used to make the Example 3 formulation. No part of Example 3 could disclose this essential feature of claim 1, because Example 3 was an *in vitro* penetration study "made using Franz diffusion cells and

human epidermis." EX1005, ¶60. There is no disclosure in Mueller that its Example 3 system was "appl[ied] to the skin or mucosa of a subject in need thereof," or even that it was suitable for that purpose.

167. Elsewhere in the Petition, Petitioner cites ¶¶1-4 in Mueller's background section as allegedly corresponding to the active step of claim 1 (Petition, 28-29), but those portions of Mueller do not indicate that the Example 3 system was or should be applied to a subject in need thereof. Indeed, in an attempt to support its position, Petitioner pieces together different statements in Mueller in a way that may be misleading.

168. Petitioner first quotes from paragraph ¶4 of Mueller, but the quoted sentence discusses systems that rely on electric current to drive drug delivery, not the systems that Mueller is directed to, which are passive systems that rely on passive diffusion through the skin. Petitioner also quotes from ¶3, but the quoted sentence discusses "general advantages" of "established" systems; it does not teach that Mueller's systems or the Example 3 TDS in particular is capable of "maintaining therapeutically useful plasma levels over a period of up to 7 days" as the Petitioner suggests.

169. There is no simply disclosure in Mueller that the TDS of Example 3, was or should be applied to the skin or mucosa of a subject in need thereof.

170. Thus, for these many reasons, Mueller does not disclose every feature of claim 1 or claim 16, or, hence of claims 2, 8, 10-15 or 18-23. It therefore is my opinion that Mueller could not anticipate claim 1 or claim 16, or, hence any of claims 2, 8, 10-15 or 18-23.

## C. Ground 2

### *1. Claims 1-2 and 8-23 are not suggested by Mueller and the Vivelle-Dot® Label*

171. Petitioner's Ground 2 rests on the assumption that Mueller Fig. 3 shows that Mueller Example 3 achieves a flux as recited in independent claims 1 and 16. Petition, 44. As discussed above, however, a POSA would not have understood Fig. 3 of Mueller to show that Example 3 achieved a specific flux, nor does Mueller provide sufficient information to permit a conclusion that the claimed flux values were necessarily achieved. EX1005, ¶¶56-61. The Vivelle-Dot® Label does not provide further data or information that would make up for Mueller's failure to meet this feature of independent claims 1 and 16. That is, the Vivelle-Dot® Label does not provide any more information on the flux of Mueller's Example 3 system. EX1006, 1-41.

172. Indeed, Petitioner does not rely on the Vivelle-Dot® Label for teaching or suggesting the claimed flux values. Rather, Petitioner relies on the Vivelle-Dot® Label solely for disclosing allegedly "standard daily doses" of estradiol. Petition, 45, 46, 49. However, the Vivelle-Dot® Label's disclosure of

useful doses of estradiol does not indicate that Mueller's Example 3 system would provide those doses.

173. Thus, the combination of Mueller and the Vivelle-Dot® Label does not teach or suggest every feature of claim 1 or claim 16, or, hence, of claims 2, 8-15, and 17-23. It therefore is my opinion that the combination of Mueller and the Vivelle-Dot® Label do not render obvious claim 1 or claim 16, or, hence, any of claims 2, 8-15 and 17-23.

## D. Ground 3

### *1. Claims 3-7 are not suggested by Mueller, the Vivelle-Dot® Label and Kanios*

174. Claim 3 depends from claim 1 and recites that "the adhesive polymer matrix comprises about 2-25% by weight acrylic adhesive, about 45-70% by weight silicone adhesive, about 2-25% by weight soluble PVP, about 5-15% penetration enhancer, and about 0.1-10% by weight estradiol." Claims 4-7 depend from claim 3. I understand this to mean that claim 3 incorporates all the features of claim 1, and that claims 4-7 incorporate all the features of claim 1 and claim 3.

175. Petitioner's Ground 3 alleges that claims 3-7 are obvious in view of Mueller, the Vivelle-Dot® Label and Kanios, and rests on the assertion that it would have been obvious to modify Mueller Example 3 to arrive at a polymer matrix as recited in claim 3. However, as I explain below, the combination of Mueller, the Vivelle-Dot® Label and Kanios would not suggest to a POSA that he

or she could or, for that matter, should, modify Mueller Example 3 in the manner asserted. Further, as I also explain below, a POSA would not have had a reasonable basis for expecting that such a modified formulation would achieve a flux value within the range recited in claims 1 and 16.

176. As Petitioner admits, Mueller Example 3 includes more silicone adhesive (79.5%) and considerably less PVP (0.39%) than the TDS recited in claim 3. Petition, 54-54; EX1005, ¶56. Petitioner alleges that because Mueller teaches that the acrylic adhesive and PVP stabilize the oversaturated state of its compositions it would have been obvious to increase their content even more in order to increase flux. But Petitioner does not explain why a POSA pursuing such a modification of Mueller would have specifically chosen to increase the PVP content. Moreover, Mueller itself teaches in ¶61 that Example 3 already included enough acrylic adhesive and PVP to provide the "stabilisation" necessary for a constant release rate over 72 hours. Thus, a POSA would not have had any reason to modify Mueller Example 3 to include more PVP. Still further, a POSA would not have reasonably expected that such a modification would result in an increase in flux, since, as discussed above, the Miranda Patents show that adding PVP does not always increase flux, even when it decreases drug crystallization. EX1011, 50: 65-51:5; EX1033, 50:66-51:6.

177. I also disagree with Petitioner's and Dr. Brain's statements that because Mueller describes silicone adhesives as "the base polymers of the active substance matrix," a POSA would have thought the silicone adhesives were somehow unimportant, such that a POSA would have "decreased the amount of silicone adhesive to accommodate the increase in hydrophiles" Petition, 54-54; EX1002, ¶204. Contrary to Petitioner's understanding, a POSA would have understood from Mueller's description of Example 3 as a TDS "Based on Silicone Adhesives With Hydrophile Additives" that the silicone polymer was the most significant component, and that the acrylic polymer and PVP were used in smaller amounts as "additives." Alleging that silicone was insignificant because it was the "base" is akin to saying that the foundation of a building is insignificant because it is just the "base." Contrary to Petitioner's position, Mueller itself warns against preparing matrices with properties that are "excessively determined by the polyacrylate." EX1005, ¶29. Thus, a POSA would understand that the silicone adhesives were the primary component of Mueller's polymer matrix, and would have been wary of decreasing silicone content due to concerns about undermining the essential adhesive properties of the system.

178. Along these same lines, Petitioner incorrectly asserts at page 55 that Mueller teaches that "the patches of Example 3 can be modified to have a hydrophile content between 10-40% wt. relative to the total matrix," citing Mueller

¶¶29-32. Those paragraphs of Mueller do not relate to Example 3 in particular, or even to estradiol TDSs in particular. Moreover, those paragraphs of Mueller do not suggest that the hydrophile content of Example 3 could be increased from about 7% to 30% (as Petitioner alleges in its attempt to reach claim 3) without negatively impacting the adhesive properties or flux profile achieved by Example 3. A POSA would not have any expectation, let alone a reasonable expectation, of maintaining or increasing the flux of the TDS when making such a dramatic change in the matrix components. Rather, as noted above and discussed below, a POSA would have expected that increasing the acrylic polymer content/decreasing the silicone polymer content would decrease flux and would not have expected increasing the PVP content to have a significant impact on flux. Indeed, Kanios (EX1007) FIG. 1 already shows that Examples 1-3 do not achieve the prolonged estradiol flux Mueller emphasizes as a successful result of its Example 3. Thus, a POSA would not have had a reasonable expectation of success in making the modifications Petitioner asserts.

179. Petitioner implies at page 56 that its theory of modifying Mueller by increasing the relative amount of acrylic polymer to increase flux is consistent with statements Patent Owner made during prosecution, but Petitioner has it backwards. Petitioner states at page 56 that Patent Owner "admitted during prosecution 'it was known in the art that the relative amounts of acrylic adhesive and silicone adhesive

used in an estradiol polymer matrix can impact the flux of estradiol.'" Patent Owner did make such a statement during prosecution, but Patent Owner was discussing an effect opposite to what Petitioner contends. That is, Patent Owner was explaining that decreasing the relative amount of acrylic adhesive to silicone adhesive used in the formulation of Examples 1 and 1a of the '900 Patent contributed to the increased flux of these TDSs relative to Vivelle-Dot®. EX1004, 583-585. Thus, the "known" relationship between "the relative amounts of acrylic adhesive and silicone adhesive" that Patent Owner explained would have discouraged a POSA from modifying Mueller Example 3 in the way Petitioner suggests in support of Ground 3.

180. Indeed, contrary to Petitioner's strained reading of Mueller, a POSA would have expected that increasing the relative amount of acrylic adhesive to silicone adhesive in an estradiol polymer matrix would have the effect of decreasing estradiol flux. This is shown in the Miranda Patents (EX1006, 1033) and Mantelle Article (EX2010), discussed above. For example, the Miranda Patents report with reference to FIG. 6 that when estradiol was formulated in a polymer matrix with acrylic and silicone polymers, it was increasing the silicone polymer content that increased estradiol flux "during the first 22 hours of delivery." EX1011, 40:66-41:3; EX1033, 40:43-47. Similarly, the Mantelle Article reports that increasing the silicone to acrylic ratio from 56.9:20 to 61.9:15 to

66.9:10 resulted in an average flux rate increase from 1.01 to 1.09 to 1.25 $\mu g/cm^2/hr$." EX2010, 416. A POSA following the guidance of the Miranda Patents and Mantelle Article would modify Mueller Example 3 in a manner that would lead it even further away from claim 3.

181. Petitioner relies on Kanios for disclosing a formulation with "more hydrophile polymers" and "less silicone polymer" than Mueller Example 3 and alleges that a POSA would have been motivated to modify Mueller Example 3 based on Kanios Examples 1-3. In this regard, Petitioner alleges based on Kanios FIG. 1 that Kanios Examples 1-3 achieve a higher estradiol flux than Mueller Example 3, but a POSA would not have been led by Kanios to modify Mueller for a number of reasons.

182. First, like Petitioner's interpretation of Mueller Fig. 3, Petitioner's interpretation of Kanios FIG. 1 reads far more into the figure than a POSA would have. A POSA would have understood Kanios FIG.1 to disclose qualitative comparative data, not quantitative data showing that the compositions achieved a specific estradiol flux, because Kanios itself presents the data as comparative data and draws only qualitative conclusions. EX1007, ¶135. Nowhere does Kanios report flux values for Examples 1-3. Moreover, Kanios does not provide any information on how the permeation study was performed, what type of skin was used, whether the data is based on more than one sample, or whether any controls

were used. Thus, a POSA would have no basis for concluding that the data was objectively meaningful or reproducible.

183. A POSA would not have interpreted the data in FIG. 1 of Kanios to show the specific flux values Dr. Brain alleges, nor would a POSA have assumed that the reported measurements were taken at 11, 24, 46, and 71 hours, as Dr. Brain asserts in ¶¶142-143 of the Brain Declaration (EX1002). There simply is no disclosure in Kanios to indicate that the data were obtained at precisely those times. Neither Petitioner nor Dr. Brain address these deficiencies of Kanios FIG. 1, but a POSA certainly would have taken note, and would not have interpreted FIG. 1 to disclose that Examples 1-3 achieved a specific estradiol flux.

184. A POSA also would not have concluded that Kanios Examples 1-3 achieved a higher flux than Mueller Example 3. Petitioner reaches this conclusion by taking its extraordinary interpretations of Mueller and Kanios a step further and directly comparing the flux values depicted in the figures of these two completely different references. Petitioner's comparison is not scientifically valid, however. A POSA would not undertake a direct, quantitative comparison of experiments conducted by different groups unless he or she knew that the studies were equivalent, *i.e.*, that both sets of experiments were conducted according to a similar experimental design, under similar conditions, with appropriate controls. *See, e.g.*, J. van de Sandt *et al.*, *In vitro predictions of skin absorption of caffeine,*

*testosterone, and benzoic acid: a multi-centre comparison study*, 39 REG. TOXICOL. PHARMACOL 271–281 (2004) (EX2023) (investigating intra- and inter-laboratory variation in *in vitro* percutaneous absorption methodology). Here, Mueller provides minimal information on Example 3 and Kanios provides even less information on Examples 1-3. Also, the lack of controls in both studies is one factor that would prevent such a direct comparison, as is the lack of information on the type of skin (*e.g.*, human cadaver skin, hairless mouse skin, *etc.*) used by Kanios. Nor would a POSA have drawn conclusions based on figures where no specific values are reported elsewhere in the references. In sum, a POSA would not have directly compared Fig. 3 of Mueller and FIG. 1 of Kanios, and would not have concluded therefrom that Kanios Examples 1-3 achieve a higher flux that Mueller Example 3. Thus, a POSA would not have been motivated to modify Mueller Example 3 based on Kanios.

185. Still further, a POSA trying to achieve Mueller's objective of drug delivery over a prolonged period of time, such as the 72 hour period studied in Mueller (EX1005, ¶¶20, 61), would not want to achieve the flux depicted in Kanios FIG. 1. For example, for Kanios Example 1, the flux falls sharply after only 12 hours, and the flux curves for Example 2 and Example 3 decrease steadily after 24 hours. These results are diametrically opposed to the stated intention of Mueller, which was to achieve drug delivery over a prolonged period of time.

EX1005, ¶20. Thus, a POSA following Mueller would have considered the flux profiles of Kanios FIG. 1 to be worse than the sustained flux reported in Mueller Fig. 3, and would not have wanted to modify the Mueller Example 3 TDS to be more like the Kanios Example 1-3 TDSs.

186. Finally, even if, for the sake of argument, a POSA did think to modify Mueller Example 3 in view of Kanios, he or she would not have made the modifications Petitioner suggests. At the outset, a POSA would have known that the most likely (but still unpredictable) way to modify a formulation to increase flux would be to increase the concentration of the active compound—*i.e.*, increase the estradiol concentration from Mueller's 1.5% to Kanios's 2%. Indeed, Kanios expressly teaches in ¶14 that "permeation rates are concentration dependent." Only if that modification was not successful would a POSA have tried more unpredictable options, such as varying the acrylic adhesive, silicone adhesive, and/or PVP content.

187. Thus, the combination of Mueller, the Vivelle-Dot® Label and Kanios does not teach or suggest every feature of claim 3, or, hence, of claims 4-7. Thus, it is my opinion that the combination of Mueller, the Vivelle-Dot® Label and Kanios does not render obvious claim 3, or, hence, any of claims 4-7.

## E. Ground 4

### *1. Claims 1-23 are not suggested by Mueller, the Vivelle-Dot® Label, Kanios, and Chien*

188. Petitioner's Ground 4 rests on the assertion that Chien discloses information that it does not in fact disclose. In particular, Petitioner asserts that "Figure 5 of Chien expressly teaches that increasing the coating thickness (or coat weight) of the adhesive polymer matrix increases estradiol flux." Petition, 60. However, contrary's to Petitoner's assertion, Chien does not describe the figure as relating to "coating thickness (or coat weight) of the adhesive polymer matrix" of a monolithic TDS as recited in the claims of the '900 Patent. Thus, once again, Petitioner relies on an interpretation of a reference that goes far beyond what a POSA would have understood.

189. Chien discloses various TDSs for estradiol, including monolithic and multilayer systems. Petitioner's reliance on Figure 5 is curious, because, other than the figure legend, there is no discussion in Chien of the data presented in Figure 5. While the legend and figure labels refer to "thickness of coating," a POSA would not know from Chien the identity of the "coating", especially since Chien describes TDSs that may include an estrogen-containing polymer adhesive layer, an "additional adhesive layer," and "another layer … between the estrogen-containing adhesive polymer layer and the adhesive layer." EX1009, 2:45- 3:40. Petitioner's speculation that Figure 5 relates to the "coating thickness … of the adhesive

polymer matrix" is merely that—speculation. Chien provides no description of the "coating" at issue, and no description of how the data was obtained. Because Chien does not provide any pertinent information relating to Figure 5, a POSA reviewing Chien would not draw any conclusions from the figure. A POSA could not reasonably interpret Chien as teaching that "increasing the coating thickness (or coat weight) of the adhesive polymer matrix increases estradiol flux" because Chien fails to provide any basis whatsoever for reaching such a conclusion.

190. Thus, the combination of Mueller, the Vivelle-Dot® Label, Kanios and Chien does not teach or suggest every feature of independent claim 1 and independent claim 16, or, hence, any of claims 2-15 or 17-23. Thus, it is my opinion that the combination of Mueller, the Vivelle-Dot® Label, Kanios and Chien does not render obvious claim 1 or claim 16, or, hence, any of claims 2-15 or 17-23.

CERTIFICATION

191. I declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

192. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on: 13th March 2018 By: A.C. Williams

Dr. Adrian C. Williams