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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN TECHNOLOGIES, INC.,
Petitioner,

v.

NOVEN PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2018-00173
Patent No. 9,724,310

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,724,310

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I. INTRODUCTION

Mylan Technologies, Inc. ("Mylan") requests review of U.S. Patent No. 9,724,310 to Mantelle ("the '310 patent," EX1001), which issued on August 8, 2017. PTO records indicate that the '310 patent is assigned to Noven Pharmaceuticals, Inc. (Patent Owner, "PO"). This Petition demonstrates that there is a reasonable likelihood that claims 1-15 of the '310 patent are unpatentable for failure to distinguish over the prior art asserted herein. An additional petition is being filed simultaneously to address similar claims of related U.S. Patent No. 9,730,900, also assigned to PO.

These patents are directed to a monolithic (single drug-containing layer) transdermal drug delivery system (*i.e.*, a transdermal patch) for the administration of estradiol, and to conventional methods of making and administering them. The patch comprises a backing layer, and a single drug-containing adhesive polymer matrix, and optionally a release liner. The claims specify parameters for coat weight, drug loading (dose per-unit-area), and estradiol flux (permeation over time) that were each known in the prior art.

The art of transdermal delivery of estradiol using monolithic patches was well developed by the time of the '310 patent's earliest claimed priority in July, 2008. In fact, PO had obtained FDA approval for one patch system, termed Vivelle®, as early as 1994. EX1008 (Vivelle® Label); EX1034 (Orange Book

Listing), 0175. In 1999, PO received FDA approval for a second-generation patch system with higher estradiol flux, termed Vivelle-Dot®, which permitted the delivery of the same amount of estradiol as Vivelle®, but in smaller patches. EX1006 (Vivelle-Dot® Label); EX1034, 0175. The art made clear that smaller adhesive patches were desirable for a number of reasons, both aesthetic and practical (*e.g.*, reduced skin irritation, better adhesive properties, improved patient satisfaction, improved compliance, and reduced packaging costs).

Thus, before July, 2008, it was well recognized in the art that one could deliver a drug more efficiently, and reduce the patch size for a given dose, by increasing the flux of a patch. The prior art described several methods for increasing the flux of monolithic transdermal patches, including for estradiol. For example, the prior art taught that higher flux can be achieved by increasing the amount of hydrophiles within the adhesive polymer matrix, or by using increased amounts of penetration enhancers. EX1005, ¶¶3, 5, 17-18, 27, 31; EX1007 (Kanios), ¶¶118-22, 126-28.

The prior art Mueller reference (EX1005) describes a monolithic transdermal estradiol delivery system in Example 3 that satisfies each of the elements of independent claim 1 and its dependent claims 2, 8, and 10-15. The Mueller system comprises a single drug-containing adhesive polymer matrix layer, a backing layer, and a release liner. Mueller teaches that the polymer matrix

comprises greater than 0.156 mg/cm^2 estradiol, acrylic and silicone adhesives, soluble polyvinylpyrrolidone (PVP), dipropylene glycol as a penetration enhancer, and a coat weight above 10 mg/cm^2. Moreover, Mueller teaches that it provides a constant release of estradiol over a period of 72 hours, and achieves an estradiol flux of 0.015 mg/cm^2/day, within the claimed range of "from about 0.0125 to about 0.05 mg/cm^2/day." Mueller Example 3 achieves a higher estradiol flux than was reported for the prior art Vivelle-Dot® patch. Mueller expressly teaches that higher flux permits the use of smaller patches to deliver a given amount of estradiol.

The prior art also teaches that increasing the coat weight of the drug-matrix layer of a patch results in an increased flux per-unit-area. For example, Chien, which was not of record during prosecution, explicitly teaches that increasing estradiol drug loading, or the coat weight of the adhesive polymer matrix of an estradiol patch, directly increased flux. EX1009, FIGS. 4-5. Yet, during prosecution, PO obtained allowance for the '310 patent by repeatedly asserting that it was "surprising and unexpected" that increasing the amount of estradiol per-unit-area (increasing the coat weight) of the drug-containing matrix would increase the flux of the patch. *See*, *e.g.*, EX1004, 0387; *see also id.*, 0013, 0120, 0382-0400, 0416-36.

Additionl references besides Chien, including Kim and Ghosh, which were not of record during prosecution are discussed in this Petition, also teach that

increasing the coat weight of a monolithic transdermal patch increases flux. EX1010, 82; EX1014, 287-88. Moreover, these references provide an explanation for how and why an increased coat weight increases flux, noting that, "as the thickness of the matrix increase[s], the occlusive effect of the matrix increase[s], resulting in the increased flux." EX1010, 82. The art explicitly confirmed that "[o]cclusion significantly ($p < 0.05$) increase[s] the percutaneous absorption of estradiol," and noted that "[o]f the various approaches employed to enhance the percutaneous absorption of drugs," increasing occlusion "is the simplest and most common method in use." EX1026, 86, 89.

Thus, the person of ordinary skill in the art would not have found an resulting increase in flux resulting from increased coat weight surprising or unexpected, contrary to that which was argued by PO during prosecution. The direct relationships between each of drug loading and coat weight with estradiol flux of a matrix-type monolithic patch was already described in the art. PO's evidence of "surprising and unexpected" results merely confirms that, in view of the prior art, the results were entirely expected.

A. Brief Overview of the '310 Patent

The '310 patent has an earliest claimed priority date of July 10, 2008. Claim 1 recites a monolithic transdermal estradiol delivery system, *i.e.*, an estradiol patch. The patch comprises a backing layer and a single adhesive polymer matrix,

wherein the matrix comprises estradiol as the only drug, has a coat weight of "greater than about 10 mg/cm^2," and includes "greater than 0.156 mg/cm^2 estradiol." The patch also "achieves an estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day, based on the active surface area." EX1002, ¶¶14-15. Dependent claims recite minor limitations of the estradiol patch, including the delivery of standard daily doses of estradiol, patch sizes, and known percentages of patch components, as well as flux values that fall within the range recited in claim 1. *Id.*, ¶¶16-17, 19-21.

The '310 patent discloses that its patches may comprise a blend of polymers that "may be immiscible with each other," to entrap a hydrophobic drug, such as estradiol. EX1001, 10:27-33, claims 1-15. This blend of immiscible polymers forms microreservoirs within the single-layer polymer matrix. EX1002, ¶18.

B. Brief Overview of the Prosecution History

U.S. Application No. 14/024,985 ("the '985 application") was filed on September 12, 2013, and issued on August 8, 2017 as the '310 patent. EX1002, ¶22. The '985 patent claims the benefit of U.S. Application No. 12/216,811, filed on July 10, 2008. During prosecution, Applicant amended the claims in response to multiple prior art-based rejections (based on EX1030-33), and further amended the claims after receiving Notices of Allowance. EX1002, ¶¶23-26, 33-44, 53.

On June 15, 2017, Applicant submitted a Rule 132 Declaration signed by Dr. Richard Guy to allege "surprising and unexpected" results. EX1004, 0409-37; EX1002, ¶¶44-53. Dr. Guy presented an "*in vitro* flux study conducted to assess the flux of the estradiol from different systems" using a Franz diffusion cell. EX1004, 0417-18. Dr. Guy also provided "[a]n illustration of the type of experimental data collected with this approach…presented as the average cumulative amounts of drug delivered, and the average drug flux, as a function of time, with the corresponding standard deviations for 4 replicate Franz diffusion cells." *Id.* The standard deviations of the replicate flux measurements provided by Dr. Guy, however, show that measurements of flux of the same patch, in the same experimental set-up can deviate by more than 15%. EX1002, ¶¶49-53. Similarly, additional data submitted by Applicant, and addressed by Dr. Guy in often identical language, demonstrates the routinely high variability associated with flux. For example, Vivelle-Dot® patches were measured in the same Franz system to have flux ranging from 0.00696 to 0.02424 mg/cm^2/day, a variation of more than 242%. *Id.*, ¶52.

The average flux provided in the Guy Declaration was obtained by calculating the slope, or change in average cumulative amount of drug, between each time point. EX1004, 0417-18; EX1002, ¶¶44-48, 113, 144, 158, 183 (*e.g.*, flux at 23.95 hours calculated by taking the difference between drug permeation at

9.92 and 23.95 hours, and dividing by the amount of time passed (10.09 $\mu g/cm^2$/14.03h = 0.72 $\mu g/cm^2$/hr)). This Petition, and supporting expert declaration, discuss flux values defined by slope calculations of drug permeation data, the same definition of flux relied upon by Applicant during prosecution. *Id.*

Dr. Guy also admitted in his declaration that "it was known in the art that the relative amounts of acrylic adhesive and silicone adhesive in an estradiol polymer matrix can impact flux[.]" EX1004, 0417, 0423. Moreover, Applicant did not dispute that transdermal patches with flux values of 0.0125 to 0.05 mg/cm^2/day were known, nor did they dispute that those in the art had motivation and methods by which to improve the flux of a transdermal patch. EX1002, ¶¶31-32, 42, 53, 197, 210 (noting that even Vivelle-Dot® described in EX1004 achieved a flux well within this range). Instead, Applicant and Dr. Guy repeatedly asserted "surprising and unexpected results" were present on the basis that "it was not known or expected that the coat weight of the polymer matrix would impact flux[.]" EX1004, 0423; *see also id.*, 0013, 0120, 0382-0400. The Examiner's June 27, 2017 Notice of Allowance expressly invokes Applicant's assertion of unexpected results made in the declaration of Dr. Guy as a basis for allowance. EX1004, 0531-32. However, neither Applicant nor the Guy declaration accounts for prior art references that were not of record during prosecution and that are discussed in this Petition.

C. Brief Overview of the Scope and Content of the Prior Art

A prior art reference anticipates a claim if it discloses all of the elements of the claim in the claimed combination, *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012). In obviousness cases, *Graham v. John Deere Co. of Kansas City*, requires an evaluation of any differences between the claimed subject matter and the asserted prior art. 383 U.S. 1, 17-18 (1966). As noted in *KSR Int'l Co. v. Teleflex Inc.*, the obviousness inquiry may account for inferences that would be employed by a person of ordinary skill in the art. 550 U.S. 398, 418 (2007). EX1002, ¶¶54-61, 98.

i. *Mueller*

U.S. Patent Application Publication No. US2003/0099695 ("Mueller," EX1005) discloses "transdermal therapeutic systems (TTSs)" for the administration of estradiol. EX1005, ¶¶1, 56-61; EX1002, ¶¶99-102. Mueller's patches comprise an "active substance matrix" that is "a single-layer structure and is self-adhesive," a backing layer, and a "releasable protective layer." EX1005, ¶¶25-26; EX1002, ¶102.

Mueller teaches that patches with increased hydrophile content (*e.g.*, polyacrylate adhesive and PVP) provide "further advantages such as improved or facilitated application…higher therapy safety through stabilization of the delivery

behavior, as well as more efficient use of active substance." EX1005, ¶22; EX1002, ¶¶100-03. Mueller continues:

> By improving the active substance release, the present invention further affords the possibility of broadening the range of applications of transdermal systems which are based on passive diffusion. In addition, the invention enables the manufacture of **transdermal systems which can have a smaller surface area due to the high active substance release rates** which can be achieved with the invention; this in turn is of advantage in manufacture and application.

EX1005, ¶22 (emphasis added); EX1002, ¶101.

Mueller teaches that patches with stabilizing hydrophile additives achieve higher flux than those without hydrophile additives. EX1005, FIGS. 1-3. Example 3 ("Monolithic Transdermal System (TTS) Based on Silicone Adhesives With Hydrophile Additives") achieves the highest estradiol flux in Mueller. EX1005, FIGS. 1-3; EX1002, ¶109. Figures 1-3 present the cumulative amount of estradiol delivered (in $\mu g/cm^2$) over time. EX1005, FIGS. 1-3; EX1002, ¶¶109-15. The slope at each time point in Mueller Figure 3 provides the flux that was achieved by the patches of Example 3:

Time (hours)	Estradiol Permeation ($\mu g/cm^2$)	Flux ($\mu g/cm^2$/hour)	Flux (mg/cm^2/day)
8	3.2	0.400	0.010
24	11	0.488	0.012
32	16	0.625	0.015
48	25	0.563	0.014
72	33.8	0.365	0.009

EX1005, FIG. 3; EX1002, ¶¶109-15; *see also* EX1004, 0416-18 (Applicant defining flux the same way).

The percent of each component in the dried Example 3 patch is provided below, as is the initial mass of the patch, and the mass after drying (derived from solids content). EX1005, ¶¶56-57; EX1002, ¶¶104-07.

Component	Initial Mass (g)	Mass after Drying (g)	Percent Total Dried Product
Estradiol hemihydrate			
Estradiol	1.16	1.16	1.50%
Water	0.04	0.04	0.05%
		(1.2 Total)	(1.55% Total)
Dipropylene glycol	9.0	9.0	11.62%
Hydroxypropyl cellulose	0.26	0.26	0.34%
Silicone adhesive	88.0	61.6	79.52%
Polyacrylate adhesive	10.0	5.1	6.58%

Component	Initial Mass (g)	Mass after Drying (g)	Percent Total Dried Product
Kollidon 90F (PVP)	1.2	0.3	0.39%
Total Mass	109.66 g	77.46 g	100%

Once coated onto a backing layer and dried, the patches of Example 3 have a polymer matrix "coating weight of 115 g/m^2," (*i.e.*, 11.5 mg/cm^2). EX1005, ¶57; EX1002, ¶108. This coat thickness affords the patches of Example 3 with an estradiol dose per-unit-area of ~0.1725 mg/cm^2, calculated by multiplying coat weight with weight percent of estradiol. EX1005, ¶¶56-57; EX1002, ¶108; *see also* EX1035, 0126 (Applicant defining dose per-unit-area the same way).

Mueller was published on May 29, 2003 and is prior art to the challenged claims of the '310 patent under 35 U.S.C. §102(b). Mueller was cited in an Information Disclosure Statement (IDS), but not discussed during prosecution.

ii. *Vivelle-Dot® Label*

Vivelle-Dot® Label (EX1006) describes a second-generation monolithic transdermal estradiol patch, Vivelle-Dot®. EX1002, ¶¶117, 119-21. Vivelle-Dot® was approved for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, vulvar and vaginal atrophy, and hypoestrogenism, as well as the prevention of postmenopausal osteoporosis. EX1006, 0016, 0018; EX1002, ¶122. Vivelle-Dot® Label describes "Vivelle-Dot [as a] revised formulation with smaller system sizes," that "was shown to be bioequivalent to the

original formulation, Vivelle[.]" EX1006, 0014; EX1002, ¶117. Vivelle-Dot® "provide[s] nominal *in vivo* delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day" in patches that are "2.5, 3.75, 5.0, 7.5, or 10.0 cm^2" in size. EX1006, 0012; EX1002, ¶118.

Vivelle-Dot® Label was publicly available at least as early as April 14, 2006 and is prior art to the challenged claims of the '310 patent under 35 U.S.C. §102(b). EX1006, 0001 (affidavit from Freedom of Information Services confirming public availability from FDA at least as early as this date). EX1002, ¶116.

iii. *Kanios*

U.S. Patent Application Publication No. US2006/0078602 ("Kanios," EX1007) discloses transdermal patches in which "the drug delivery rates, onset and profiles of at least one active agent are controlled by selectively manipulating the monomeric make up of an acrylic-based polymer in the transdermal drug delivery system." EX1007, Abstract; EX1002, ¶124.

The patches of Kanios comprise "(a) one or more acrylic based polymers…; (b) one or more silicone-based polymers; and (c) one or more active agents[.]" EX1007, Abstract; EX1002, ¶125. The patches further comprise one or more penetration enhancers, including oleyl alcohol and dipropylene glycol. EX1007, ¶¶106,131-33; EX1002, ¶126. Figure 1 provides "average flux profiles" of the patches of Examples 1-3. EX1007, FIG. 1; EX1002, ¶¶127-28. The Figure 1 flux

values are shown in the table below. For example, Figure 1 teaches that Example 1 achieves an estradiol flux of 0.875 µg/cm^2/hr (equivalent to 0.021 mg/cm^2/day) at 11 hours. EX1007, FIG. 1; EX1002, ¶¶127-28. At 24 hours, both Examples 1 and 2 achieve estradiol flux of 0.672 µg/cm^2/hr (0.016 mg/cm^2/day). EX1007, FIG. 1; EX1002, ¶¶127-28.

Estradiol Flux µg/cm^2/hour (mg/cm^2/day)	**11 hours**	**24 hours**
Example 1	0.875 (0.021)	0.672 (0.016)
Example 2	0.641 (0.015)	0.672 (0.016)
Example 3	0.562 (0.013)	0.531 (0.013)

Kanios was published on April 13, 2006 and is prior art to the challenged claims of the '310 patent under 35 U.S.C. §102(b). Kanios was cited in an IDS but was not discussed during prosecution. EX1002, ¶123.

iv. *Chien*

U.S. Patent No. 5,145,682 ("Chien," EX1009) discloses "[t]ransdermal absorption dosage units… which comprise a backing layer, an adjoining adhesive polymer layer," and an optional release liner, comprising "at least minimum effective daily doses of an estrogen[.]" EX1009, Abstract, 2:45-3:2; EX1002, ¶130. The patches of Chien comprise "estradiol or other estrogenic steroids used in

formulating the polymer matrix," wherein the estradiol is "suitably dispersed in the adhesive polymer." EX1009, 3:14-17, 3:53-8, 4:5-6; EX1002, ¶¶130-31; *see also* EX1001, 10:27-33 (polymers that "may have different solubility parameters for the drug and which may be immiscible with each other, may be selected"); EX1002, ¶18 ("The effect of using immiscible polymers with a hydrophobic drug such as estrogen is to encapsulate the drug and form microreservoirs of estrogen"). The estradiol-containing adhesive polymer layer comprises "suitable polyacrylic adhesive polymers, silicone adhesive polymer[s]" and a "transdermal absorption enhancing agent." EX1009, 3:23-25, 3:53-60; EX1002, ¶¶130-31. These patches "deliver at least minimum daily doses of the estrogen for at least one day or for multiple days, such as for one week." EX1009, Abstract.

Chien teaches the desirability of using penetration enhancers, the effect of drug loading in a dosage unit, and the effect of coating thickness in a dosage unit on the skin penetration rate of estradiol achieved by the patches. EX1009, 5:20-28, FIGS. 3-5; EX1002, ¶¶132-33. Figures 3-5 demonstrate that increasing the amount of penetration enhancer, estradiol loading, and coat weight (thickness) of the polymer matrix layer each increase flux. *Id.*

Chien issued on September 8, 1992 and is prior art to the challenged claims of the '310 patent under 35 U.S.C. §102(b). Chien was not cited by Applicant or

Examiner, and was not of record during prosecution of the ’310 patent. EX1002, ¶129.

D. Brief Overview of the Level of Skill in the Art

A person of ordinary skill in the relevant field as of July 10, 2008, would likely have an advanced degree, for example a Ph.D., in pharmaceutical chemistry, physical chemistry, bioengineering, or a drug delivery related discipline. EX1002, ¶¶62-63. Alternatively, one could have a bachelor’s degree plus two to five years’ experience in the transdermal delivery industry. *Id.* The skilled artisan 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, including those discussed in this Petition. *Id.*

This Petition is supported by the declaration of Dr. Keith Brain. EX1002; *see also id.*, ¶¶12-13; EX1003 (Dr. Brain’s *curriculum vitae*, providing a summary of his education, training, and experience). Dr. Brain is a pharmaceutical scientist with over 50 years of experience whose research career focused on transdermal drug delivery systems. *Id.*, ¶¶1-11. Dr. Brain has the scientific background and technical expertise to provide detailed analysis of the references discussed herein in relation to the challenged claims and to explain the level of ordinary skill in the art as of July 10, 2008. *Id.*

E. Background Knowledge in the Art Prior to July 10, 2008

The following background publications document knowledge a skilled artisan would bring to bear in reading the prior art. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015); EX1002, ¶75. This knowledge assists in understanding why one of ordinary skill would have been motivated to combine or modify the references asserted in the Grounds of this Petition to arrive at the claimed invention. As *KSR* established, the knowledge of such an artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013) (citing 550 U.S. at 406).

Monolithic transdermal drug delivery systems were known to be useful for the administration of estradiol many years prior to July 10, 2008. EX1018 (Müller), Abstract, 1:4-9; EX1002, ¶76. Indeed, many monolithic estradiol patches had been described in the art. EX1018, 1:10-19; *see also*, *e.g.*, EX1011 (Miranda), 4:44-47; EX1019 (Rovati), 1:10-44; EX1002, ¶77. Such patches were known to be useful for the treatment of a variety of disorders in postmenopausal women. EX1019, 1:17-22. By 2008, several monolithic matrix-type transdermal estradiol delivery systems were approved by FDA for hormone replacement therapy ("HRT"). EX1034 (Orange Book), 0175; EX1008 (Vivelle® Label), 0012; EX1015 (Climara® Label), 0005-6; EX1016 (Alora® Label), 0018; EX1017 (Menostar®

Label), 0010; EX1002, ¶¶78-83. The daily doses approved for HRT prior to July 2008 included 0.025, 0.0375, 0.05, 0.075, and 0.1 mg/day. *See* EX1008, 0012; EX1015, 0005-06; EX1016, 0018 ; EX1017, 0010; EX1002, ¶¶78-83. The Vivelle® patch, for example, is a monolithic matrix-type transdermal estradiol delivery system that provides these nominal daily doses in "an active surface area of 7.25, 11.0, 14.5, 22.0, or 29.0 cm^2," respectively. EX1008, 0012; EX1002, ¶¶79-82.

To determine the dose of estradiol delivered by a patch, the amount of estradiol delivered per-unit-time and per-unit-area of the patch (*i.e.*, flux) is measured. U.S. Patent No. 6,521,250 teaches a method of measuring flux in which a skin sample from a hairless mouse or from a human cadaver is placed in a Franz diffusion cell. An estradiol-containing patch is applied to the skin and the active substance release is measured at 37˚C." EX1020 (Meconi), 7:6-10 -57, Table 2; EX1002, ¶¶84-85, 92; *see also* EX1004, 00417-18; EX1002, ¶¶49-53.

Those in the art understood prior to 2008 that the patch size, dose, and flux of a patch for transdermal drug delivery are interdependent variables. EX1025 (van der Bijl), 507; EX1002, ¶93. For example, if patch size is held constant, increased flux provides a proportional increase in the amount of drug delivered (dose). *Id.* If dose is held constant, increased flux allows for a proportional decrease in patch size. *Id.* It was well established in the art that smaller patches for a given dose were

desirable because they reduce skin irritation, provide better patch adhesion, improve patient compliance, and reduce packaging costs. EX1012 (Fotinos), 15:31-16:1; EX1013 (Bevan); EX1002, ¶¶94-97.

Methods for increasing flux were known to those of skill in the art. For example, increasing polyacrylate content and including a penetration enhancer in the polymer matrix were each methods known to increase flux. EX1011 (Miranda), Figures 12, 16; EX1021 (Heiber), 10:1-14; EX1022 (Bucks), TABLE I-II, 32; EX1002, ¶92. Kim teaches inclusion of penetration enhancers, such as oleyl alcohol and hydrophobic glycols, to improve drug permeation across skin thereby increasing flux. EX1010 (Kim), 83; EX1002, ¶¶86-87.

Kim also teaches that increasing the coat weight (thickness) of the adhesive polymer matrix of a monolithic, matrix-type patch increases flux. EX1010, 79, 82; EX1002, ¶87; *see also* EX1014 (Ghosh), 287, and Chien (EX1009), discussed above. Kim further notes that "it seemed that the occlusive effect of adhesive matrix increased. The occlusive effect is usually provided by [a] backing membrane, however, as the thickness of the adhesive matrix increased, the matrix also contributes to [the] occlusive effect[.]" EX1010, 82. Kim teaches that "[a]s the thickness of the matrix increased, the occlusive effect of the matrix increased, resulting in the increased flux[.]" EX1010, 82; EX1002, ¶¶86-87.

As explained by Dr. Brain, the positive effect of occlusion on drug flux observed by Kim was well-known in the art prior to 2008. EX1002, ¶¶88-91 (discussing EX1026 (Bronaugh), 86, 89). In fact, Bronaugh teaches that "[o]f the various approaches employed to enhance the percutaneous absorption of drugs, occlusion (defined as the complete impairment of passive transepidermal water loss at the application site) is the simplest and most common method in use." EX1026, 86, 89; *see also* EX1022 (of which Dr. Richard Guy, proponent of the Rule 132 declaration during prosecution of the '310 patent, is a co-author), 32; EX1004, 0120 (noting "the area of skin subject to occlusion"). Bronaugh further teaches that, while "occlusion does not necessarily increase the percutaneous absorption of all chemicals," it "significantly increase[s] the percutaneous absorption ($p<0.01$) of the steroids," including estradiol. EX1026, 86, 89 ("[o]cclusion significantly ($p<0.05$) increased the percutaneous absorption of estradiol"); EX1002, ¶¶89-90.

II. GROUNDS FOR STANDING

Petitioner certifies under 37 C.F.R. § 42.104(a), that the '310 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the '310 patent on the grounds identified.

III. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

Real Parties-in-Interest (37 C.F.R. §42.8(b)(1)): Mylan Technologies, Inc. and Mylan Pharmaceuticals Inc., each a wholly owned subsidiary of Mylan Inc., an indirectly wholly-owned subsidiary of Mylan N.V., and Mylan N.V. are the real-parties-in-interest.

Related Matters (37 C.F.R. §42.8(b)(2)): A petition for *inter partes* review of related U.S. Patent No. 9,730,900 ("the '900 patent") is also being filed by the present Petitioner as IPR2018-00174. The '310 and the '900 patents both claim the benefit of U.S. Application No. 12/216,811, filed on July 10, 2008, now U.S. Patent No. 8,231,906.

Litigation concerning the '310 patent to which Petitioner is not a party is currently pending in the District of Delaware: *Noven Pharmaceuticals, Inc. v. Alvogen Pine Brook LLC*, No. 1:17-cv-01429-LPS.

Petitioner and other entities were previously involved in litigation concerning the related parent U.S. Patent No. 8,231,906 ("the '906 patent") in an action styled *Noven Pharmaceuticals Inc. v. Mylan Technologies Inc., et al.*, Nos. 1:15-cv-00328 (D. Del.); 1:15-cv-00069 (N.D.W.V.), which terminated in February 2016. Litigation concerning the '906 patent, to which Petitioner is not a party, apparently remains pending in the District of Delaware: *Noven Pharmaceuticals Inc. v. Actavis Laboratories UT, Inc.*, Nos. 1:15-cv-00249-LPS;

1:16-cv-00465-LPS – consolidated; *Alvogen Pine Brook LLC v. Noven Pharmaceuticals, Inc.* No. 1:16-cv-00395-LPS.

Lead and Back-Up Counsel (37 C.F.R. §42.8(b) (3)):

Lead Counsel: Steven W. Parmelee (Reg. No. 31,990)

Back-Up Counsel: Michael T. Rosato (Reg. No. 52,182)

Back-Up Counsel: Jad A. Mills (Reg. No. 63,344)

Service Information – 37 C.F.R. §42.8(b)(4):

Petitioner hereby consents to electronic service.

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IV. STATEMENT OF THE PRECISE RELIEF REQUESTED

A. Asserted Grounds of Unpatentability

Petitioner requests review of claims 1-15 of the '310 patent under 35 U.S.C. §311 and AIA §6 as follows:

GROUND	CHALLENGED CLAIMS	DESCRIPTION
1	1-2, 8, 10-15	Anticipated under §102 by Mueller
2	1-2 and 8-15	Obvious under §103 over Mueller and Vivelle-Dot® Label
3	3-7	Obvious under §103 over Mueller, Vivelle-Dot® Label, and Kanios

4	1-15	Obvious under §103 over Mueller, in view of Vivelle-Dot® Label, Kanios, and Chien

B. Evidence of Unpatentability Not Considered in Prosecution

During prosecution of the patent, the Examiner never rejected any claim based on the Mueller reference or discussed Mueller or a comparable disclosure from another reference in any substantive manner. The Examiner did not consider that Mueller anticipates the claims challenged in Ground 1 using the same definition of flux relied upon by Applicant during prosecution. Nor did the Examiner consider that Mueller renders the claims challenged in Ground 2-4 obvious in view of the other references asserted in Grounds 2-4. Moreover, Dr. Brain's testimony provides new evidence further supporting the arguments that Mueller anticipates and/or renders obvious the challenged claims. *See Hospira, Inc. v. Genentech, Inc.*, IPR2017-00739, Paper 16 at 17-18 (informative) (recognizing Office's policy favoring institution to correct "errors by the Office in allowing the patent" and to permit petitioners to be heard, but exercising discretion under Section 325(d) not to institute because petitioner failed to present new argument or evidence indicating Examiner had erred during prosecution).

Moreover, Applicant obtained allowance of the challenged claims by arguing that there were "unexpected results based on the coat weight of the polymer to achieve the claimed flux of drug delivery." EX1004, 0154, 0531. However, these results are not unexpected, as addressed in detail below and in the

supporting expert declaration. EX1002, ¶¶28-32, 44-48, 53, 86-92, 132-33, 234-36, 238-42. Several prior art references that were not of record during prosecution each teach that an increase in coat weight results in increased flux. EX1009 (Chien); EX1010, 82 (Kim), EX1014, 287-88 (Ghosh); *see also, e.g.*, EX1026, 86, 89 (Bronaugh not listed on face of patent or on any IDS); EX1002, ¶¶31-32, 42, 44, 86-91 (discussing references not evaluated during prosecution);

Because this petition and its supporting declaration present new evidence demonstrating the unpatentability of the challenged claims, the Examiner's allowance based on the limited disclosure and discussion presented by Applicant during prosecution should not receive deference by the Board. *See Unified Patents Inc. v. Berman*, IPR2016-01571, Paper 10 at 13 (informative) (petitioner reliance on reference not listed on face of the patent, much less used by Examiner as a ground of rejection, overcomes owner's Section 325(d) argument for non-institution).

V. CLAIM CONSTRUCTION

An unexpired claim subject to *inter partes* review receives the broadest reasonable construction in light of the specification of the patent. 37 C.F.R. §42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. ---, 136 S. Ct. 2131, 2146 (2016). Claim terms are also "generally given their ordinary and customary meaning," which is the meaning that the term would have to a person of ordinary

skill in the art at the time of the invention in view of the specification. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under either standard, there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claims. A few pertinent terms are discussed below. EX1002, ¶64.

A. "About"

Claim 1 refers to "an estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day." Claim 9 recites that estradiol delivery is "about" 0.025, 0.0375, 0.05, 0.075 or 0.1 mg/day. Claims 10-14 respectively recite that the estradiol flux is about 0.0125 mg/cm^2/day, about 0.0133 mg/cm^2/day, about 0.015 mg/cm^2/day, about 0.0167 mg/cm^2/day, and about 0.0175 mg/cm^2/day. Claim 15 recites that the adhesive polymer matrix comprises about 1.6% by weight estradiol, based on the total dry weight of the adhesive polymer matrix.

As defined by the specification of the '310 patent:

> 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 in the context in which it is used, **"about" will mean up to plus or minus 10% of the particular term.**

EX1001, 4:42-52 (emphasis added).

Thus, values falling within 10% of a claimed numerical value or that are substantially within the upper and lower bounds of a claimed range satisfy the claimed numerical value or range. *Id.*; EX1002, ¶¶65-67. Thus, for example, an "estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day" encompasses a range of 0.01125-0.055 mg/cm^2/day.

B. "Coat weight"

Claim 1 of the '310 patent recites an adhesive polymer matrix that has "a coat weight of greater than about 10 mg/cm^2." As defined by the '310 patent specification, "'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; EX1002, ¶¶68-70. During prosecution, the term "coat weight" was used by PO to describe the "drug-containing adhesive layer" and "polymer matrix." EX1004, 0379-81, 0386-87; EX1002, ¶69; *see also* EX1035, 0126. PO also stated that increasing the coat weight is the same as increasing the thickness of a polymer matrix. EX1004, 0386-87; EX1002, ¶70. PO also argued in the related prosecution of the '900 patent that coat weight was a proxy for the amount of estradiol per-unit-area where the concentration of the estradiol in the matrix material is held constant. EX1035, 0169.

Under the broadest reasonable interpretation, the phrase "coat weight" includes the dry weight per-unit-area of the "adhesive polymer matrix layer defining an active surface area and comprising an adhesive polymer matrix comprising estradiol as the only drug." Thus, the skilled artisan would understand the term coat weight to include the dry weight of the drug-containing adhesive layer per-unit-area and could use it as a proxy for the amount of estradiol per-unit-area. EX1002, ¶70.

C. "Flux"

Claim 1 of the '310 patent recites a monolithic transdermal drug delivery system, which achieves "an estradiol flux of from about 0.0125 to about 0.05 $mg/cm^2/day$, based on the active surface area." The '310 patent specification states:

> 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. The '310 patent, however, is silent on how flux is measured and does not require the system to "achieve an estradiol flux of from about 0.0125 $mg/cm^2/day$ to about 0.05 $mg/cm^2/day$" for any particular time. EX1002, ¶¶71-73. Under the broadest reasonable interpretation, flux may include flux for any time period when the system is applied to the skin. *Id.*

Following the definition applied by Applicant during prosecution of the '310 patent, flux can be calculated as the change in permeation (mg/cm^2 or $\mu g/cm^2$) over change in time (days or hours). EX1004, 0416-18; EX1002 ¶¶44-48, 71-73. This can be calculated from permeation and time values provided in prior art references, including in tables or graphs. EX1004, 0383-84, 0416-18; EX1002 ¶¶44-48, 71-73. Flux values also may be expressly disclosed. EX1004, 0383-84; EX1002 ¶¶44-48, 71-73.

D. "Therapeutically Effective Amount"

The '310 patent specification states that a "therapeutically effective amount of estradiol is from about 0.025-0.1 mg/day, including about 0.025 mg/day, about 0.0375 mg/day, about 0.05 mg/day, about 0.075 mg/day, or about 0.1 mg/day, such as 0.025-0.1 mg/day, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day." EX1001, 11:64-12:3. As described in the '310 patent specification, doses within this range are therapeutic levels of estrogen for adult human subjects. *Id.*, 4:64-5:11; EX1002, ¶74. Thus, in view of the '310 patent specification, as well as the definition of the term "about," discussed above, under the broadest reasonable interpretation the term "therapeutically effective amount" as used in claim 8 includes, but is not limited to, daily doses of 0.0225-0.11 mg/day (*i.e.*, ±10% of 0.025-0.1 mg/day). EX1002, ¶74; EX1001, 4:42-52, 4:64-5:11.

VI. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. [Ground 1] Claims 1-2, 8, and 10-15 are Anticipated under 35 U.S.C. §102 by Mueller.

This Ground establishes that Mueller (EX1005) describes as part of a single embodiment each element of the challenged claims. EX1002, ¶134. For this comparison, claim 1 is addressed in its component clauses, and examples of where each element appears in the reference are shown below in bold (*see also*, the claim chart at the end of this Ground for additional examples).

1. Claim 1

A monolithic transdermal drug delivery system for estradiol, consisting of…

Mueller describes **transdermal therapeutic systems** (TTSs) which provide "a sufficient active substance flow through the skin." EX1005, ¶¶1-3; EX1002, ¶¶135-36. Mueller teaches that the patches "maintain[] therapeutically useful plasma levels over a period of up to 7 days" following application to the skin. EX1005, ¶3. Mueller's Example 3, entitled "Monolithic Transdermal System (TTS) Based on Silicone Adhesives with Hydrophile Additives," teaches providing "a constant release rate" of estradiol for at least 72 hours after administration to human epidermis. EX1005, ¶¶56-61; EX1002, ¶137. Mueller, thus, teaches a monolithic (single-layer) transdermal estradiol delivery system.

…(i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iiii) a release liner, wherein the single adhesive polymer matrix layer comprises an adhesive polymer matrix comprising estradiol as the only drug,…

The monolithic TTS of Example 3 comprises one "**active substance matrix**" layer that is "a **single-layer** structure and is self-**adhesive**." EX1005, ¶26; EX1002, ¶¶136-37. The adhesive polymer matrix layer is made by admixing 1.2 g estradiol hemihydrate (1.16 g **estradiol**, 0.04 g water), 0.26 g hydroxypropyl cellulose, 88.0 g silicone adhesive, 10.0 g polyacrylate adhesive, and 1.2 g Kollidon 90F (soluble PVP). EX1005, ¶¶56-57; EX1002, ¶¶138-41 (estradiol hemihydrate is 97% estradiol and 3% water, by weight). After the "mass is coated in a thickness of 250 μm onto a film which has been rendered abhesive," (*i.e.*, a **backing layer**), it is dried to produce a monolithic film. EX1005, ¶¶56-57; EX1002, ¶¶138-41. Mueller further describes the backing layer as being "active-substance impermeable." EX1005, ¶25; EX1002, ¶137. Mueller also teaches that the transdermal delivery system of Example 3 comprises a "**releasable protective layer** to be removed prior to application." EX1005, ¶25; EX1002, ¶137.

…wherein the polymer matrix has a coat weight of greater than about 10 mg/cm^2…

Following drying, the "dried film [of Example 3] having a **coating weight of 115 g/m^2** is then covered with a suitable film (e.g. Scotchpak 1220; 3M), and the

finished patches are punched out of the total laminate." EX1005, ¶¶56-57; EX1002, ¶138. A coat weight of 115 g/m^2 is **11.5 mg/cm^2**, which is "greater than about 10 mg/cm^2." EX1005, ¶¶56-57; EX1002, ¶138.

…and includes greater than 0.156 mg/cm^2 estradiol,…

As noted above, the adhesive polymer matrix of Example 3 comprises estradiol hemihydrate, hydroxypropyl cellulose, silicone adhesive (with a 70%-wt solids content), polyacrylate adhesive (51%-wt solids content), and Kollidon 90F (soluble PVP, 25%-wt solids content). EX1005, ¶¶56-57; EX1002, ¶¶139-42. Volatile solvents within the mixture are removed by drying the film. EX1002, ¶¶140-41. The initial mass, mass after drying (derived using solids content), and percent of the total dried product of each component of Example 3 is provided in the table below. EX1005, ¶¶56-57; EX1002, ¶¶139-42.

Component	Initial Mass (g)	Mass in Dried Product (g)	Percent Total Dried Product
Estradiol hemihydrate			
Estradiol	1.16	1.16	1.50%
Water	0.04	0.04	0.05%
		(1.2 Total)	(1.55% Total)
Dipropylene glycol	9.0	9.0	11.62%
Hydroxypropyl cellulose	0.26	0.26	0.34%
Silicone adhesive	88.0	61.6	79.52%

Component	Initial Mass (g)	Mass in Dried Product (g)	Percent Total Dried Product
Polyacrylate adhesive	10.0	5.1	6.58%
Kollidon 90F (PVP)	1.2	0.3	0.39%
Total Mass	109.66 g	77.46 g	100%

Estradiol accounts for 1.50% of the total mass of the final dried TTS of Example 3. EX1005, ¶¶56-57; EX1002, ¶¶141-42. Coat weight multiplied by the percentage estradiol in the final dried product provides an **estradiol dose per-unit-area of 0.1725 mg/cm^2**, which is "greater than 0.156 mg/cm^2 estradiol." EX1005, ¶¶56-57; EX1002, ¶¶141-42; *see also* EX1035, 0126 (similar definition used in prosecution of the '900 patent to determine dose per-unit-area from % mass and coat weight).

> *…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.*

Mueller Figure 3, reproduced below, provides "the results of a comparative permeation study between samples without hydrophilic additives ([Example] 2a) and samples with hydrophilic additives ([Example] 3)." EX1005, ¶¶56-61, FIGS. 1-3; EX1002, ¶¶143-47. These results show an **estradiol flux achieved by Example 3 of 0.015 and 0.014 mg/cm^2/day** when measured at 32 and 48 hours, respectively, both flux values being well within the range recited in the claim.

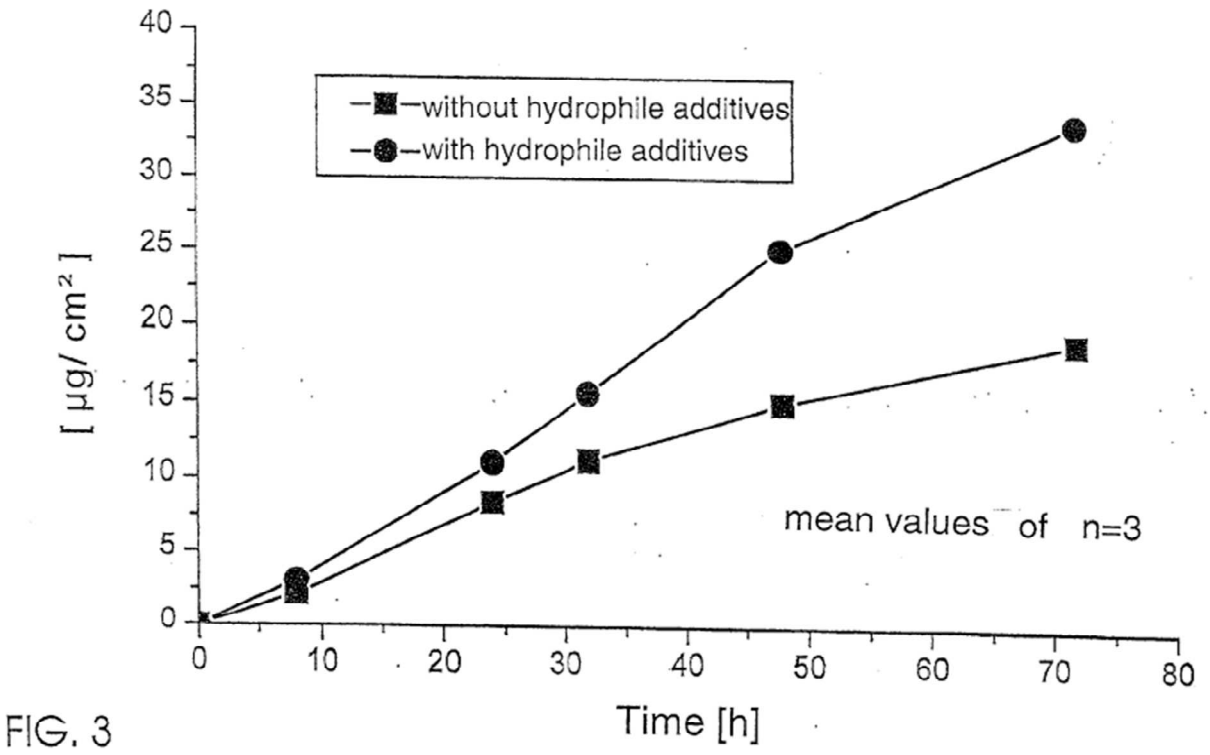


FIG. 3

EX1005, FIG. 3 (circles denote flux data points of Example 3). The slope of the permeation for each time point provides flux in units of µg/cm^2/hr, which may be converted to units of mg/cm^2/day by dividing by 1000 µg/mg and multiplying by 24 hours/day. EX1002, ¶¶47, 143-47; *see also* EX1004, 0384 (Applicant applying the same definition of flux during prosecution). The data from Figure 3 for Example 3, provided in units of per hour and per day, and the flux calculated from the slope for each permeation data point, is summarized below.

Time (hours)	Estradiol Permeation ($\mu g/cm^2$)	Flux ($\mu g/cm^2$/hour)	Flux (mg/cm^2/day)
8	3.2	0.400	0.010
24	11	0.488	0.012
32	16	0.625	**0.015**
48	25	0.563	**0.014**
72	33.8	0.365	0.009

EX1005, FIG. 3; EX1002, ¶¶144-45; *see also* EX1001 at FIG. 1 (reporting flux of less than 0.3 $\mu g/cm^2$/hour around 10 hours, equal to less than 0.007 mg/cm^2/day); EX1004, 0384.

The system of Mueller Example 3, thus, achieves an estradiol flux of **0.015 mg/cm^2/day** at 32 hours and **0.014 mg/cm^2/day** at 48 hours. EX1005, ¶¶56-58, FIG. 3; EX1002, ¶¶144-45. Mueller explains, "[t]he time course of the permeation in FIGS. 1 to 3 clearly shows that in the case of the TTSs according to the present invention a constant release rate, and thus a stabilization, is achieved for a period of at least 72 h[.]" EX1005, ¶61.

Even over multiple days, Mueller Example 3 achieves a flux that falls well within the range recited in the claim. EX1002, ¶¶146-47. For example, over the first 48 hours, Example 3 achieves an average flux of **0.013 mg/cm^2/day**, as shown in the table below. EX1005, FIG. 3; EX1002, ¶¶146-47. In other 24 hour periods,

e.g., 8-32 hours and 24-48 hours, Example 3 achieves an average estradiol flux of **0.013 and 0.014 mg/cm^2/day**, respectively, values within the range recited in the claim. EX1005, FIG. 3; EX1002, ¶¶146-47.

Time (hours)	Average Flux (μg/cm^2/hour)	Average Flux (mg/cm^2/day)
0-48	0.521	**0.013**
8-32	0.533	**0.013**
24-48	0.583	**0.014**

Thus, Mueller teaches a monolithic transdermal estradiol patch that not only achieves estradiol flux within "of from about 0.0125 to about 0.05 mg/cm^2/day," as recited in claim 1, but also that maintains this flux over the course of one or more full days. EX1002, ¶¶147-48.

As discussed above in Claim Construction (Section V), an estradiol flux range of from "about 0.0125 to about 0.05 mg/cm^2/day" as recited in claim 1 of the '310 patent "is not limited to the exact number[s] set forth." The '310 patent notes that, if unclear, the term "'about' will mean up to plus or minus 10% of the particular term." EX1001, 4:42-52. Thus, an "estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day" as intended by the use of the modifier "about" for each endpoint encompasses ±10%, *i.e.*, 0.01125-0.055 mg/cm^2/day. EX1002, ¶¶65-67. The estradiol flux of Example 3 at 24 hours (0.012 mg/cm^2/day), as well as the

average flux achieved from 0-72 hours (0.0113 mg/cm^2/day), fall within the range of flux values recited in claim 1.

As demonstrated above, Mueller Example 3 describes a single embodiment comprising each element of claim 1 of the ’310 patent. EX1002, ¶148.

2. Claim 2

Claim 2 recites that the adhesive polymer matrix of claim 1 comprises an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP). The adhesive polymer matrix of Mueller Example 3 comprises a polymer blend of a **silicone adhesive** (BIO-PSA 4301), a **polyacrylate (acrylic) adhesive** (Durotak 387-2287), and **soluble polyvinylpyrrolidone** (PVP; Kollidon 90F). EX1005, ¶56; EX1002, ¶¶149-51. Mueller Example 3 thus discloses a single embodiment comprising each element of claim 2 of the ’310 patent.

3. Claim 8

Claim 8 depends from claim 1 and recites that “the adhesive polymer matrix comprises an amount of estradiol effective to deliver a therapeutically effective amount of estradiol over a period of time selected from the group consisting of at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days.”

Mueller describes transdermal therapeutic systems that “maintain…**therapeutically useful** plasma levels **over a period** of up to **7 days**.”

EX1005, ¶3; EX1002, ¶¶152-53. Example 3 is taught to deliver "a constant release rate [of estradiol]…for a period of **at least 72 h**." EX1005, ¶¶58-61; EX1002, ¶¶152-53; *see also* EX1005, ¶21. Mueller Example 3 thus anticipates claim 8 of the '310 patent.

4. Claims 10-14

Claims 10-14 depend from claim 1 and recite specific estradiol flux values of about 0.0125, about 0.0133, about 0.015, about 0.0167, and about 0.0175 $mg/cm^2/day$, respectively. Neither the patent nor the prosecution history identifies any particular advantage, criticality, or unexpected result of these specific flux values over the range recited in claim 1. EX1002, ¶¶154-55.

As discussed above in Sections V.A and V.C, "about 0.0125," as recited in claim 10, as well as the flux values recited in claims 11-14, are "not limited to the exact number[s] set forth." EX1001, 4:42-52. As noted in the specification of the '310 patent, when unclear, the term "'about' will mean up to plus or minus 10% of the particular term." *Id.*; EX1002, ¶¶65-67. Thus, "about 0.0125 $mg/cm^2/day$" as recited in claim 10, encompasses flux values of 0.0113-0.0138 $mg/cm^2/day$, as shown in the table below. EX1002, ¶¶156-57. Indeed, as demonstrated by the data presented by Dr. Guy during prosecution, the standard deviation associated with replicate flux measurements routinely exceeded 15%. *Id.*, ¶¶49-53.

Claim	Recited Flux (mg/cm^2/day)	±10% Range (mg/cm^2/day)
10	"about 0.0125"	0.0113-0.0138
11	"about 0.0133"	0.0120-0.0146
12	"about 0.015"	0.0135-0.0165
13	"about 0.0167"	0.0150-0.0184
14	"about 0.0175"	0.0158-0.0193

The system of Mueller Example 3 achieves a flux of **0.012 mg/cm^2/day** at 24 hours, and an average flux of **0.013 mg/cm^2/day** from 0-48 hours and 8-32 hours, each of which is well within 10% of 0.0125 mg/cm^2/day and thus clearly meets the limitation of "about 0.0125 mg/cm^2/day" recited in claim 10. EX1002, ¶¶158-60; EX1005, FIG. 3.

Regarding claim 11, the other time periods of Example 3 achieve flux of **0.012 mg/cm^2/day** at 24 hours, **0.014 mg/cm^2/day** at 48 hours, an average flux of **0.013 mg/cm^2/day** between 0-48 and 8-32 hours, and **0.014 mg/cm^2/day** at 24-28 hours, each of which are within 10% of 0.0133 mg/cm^2/day and thus meet the limitation of "about 0.0133 mg/cm^2/day." EX1002, ¶161; EX1005, FIG. 3.

Regarding the flux of claim 12 of "about 0.015 mg/cm^2/day," the flux achieved by Example 3 at 48 hours (**0.014 mg/cm^2/day**), at 32 hours (**0.015 mg/cm^2/day**), and the average flux between 24-48 hours (**0.014 mg/cm^2/day**) are

all within 10% of 0.015 mg/cm^2/day and thus meet the limitation of "about 0.015 mg/cm^2/day." EX1002, ¶162; EX1005, FIG. 3.

The flux recited in claim 13 is "about 0.0167 mg/cm^2/day." Mueller Example 3 achieved a flux at 32 hours of **0.015 mg/cm^2/day**. EX1002, ¶163. This flux is within 10% of 0.0167 mg/cm^2/day as shown in the table above. The flux of Mueller Example 3 at 32 hours also anticipates claim 14 because 0.015 mg/cm^2/day is substantially within the flux range encompassed by "about 0.0175 mg/cm^2/day" recited in claim 14. EX1005, FIG. 3; EX1002, ¶164. Thus, Mueller Example 3 anticipates each of claims 10-14.

5. Claim 15

Claim 15 depends from claim 1 and recites that "the adhesive polymer matrix comprises about 1.6% by weight estradiol, based on the total dry weight of the adhesive polymer matrix." As described above in Section V, the term "about" indicates a range of ±10% of the recited 1.6% (1.44-1.76%). EX1002, ¶165.

Example 3 has a total dry mass of 77.46 g, and comprises 1.16 g of estradiol, and thus has an **estradiol content of 1.50%** (1.16 g estradiol / 77.46 g total mass x 100 = 1.50%). EX1002, ¶165; EX1005, ¶¶56-58. Thus, Mueller's Example 3 describes a polymer matrix comprising "about 1.6% by weight estradiol," based on the total dry weight of the polymer matrix, as recited in claim 15 of the '310 patent. EX1002, ¶165.

As shown above, each of claims 1-2, 8, and 10-15 of the '310 patent is described in Mueller, and thus anticipated under 35 U.S.C. § 102. EX1002, ¶166. The claim chart below identifies exemplary locations in Mueller where the elements of claims 1-2, 8, 10-15 are described.

CHALLENGED CLAIMS	ANTICIPATED BY MUELLER (EX1005)
1. A monolithic transdermal drug delivery system for estradiol, consisting of…	"EXAMPLE 3 Monolithic Transdermal System (TTS) Based on Silicone Adhesives With Hydrophile Additives" EX1005, ¶56; EX1002, ¶136.
…(i) a backing layer, (ii) a single adhesive polymer matrix layer defining an active surface area and, optionally, (iii) a release liner, wherein the single adhesive polymer matrix layer comprises an adhesive polymer matrix comprising estradiol as the only drug,…	"The structure of the TTSs according to the invention comprises an active substance-impermeable backing layer and a releasable protective layer to be removed prior to application, apart from the mentioned active substance-containing matrix." EX1005, ¶¶25, 57; EX1002, ¶¶137-38. "In the simplest case, the active substance matrix of the systems according to the invention has a single-layer structure and is self-adhesive." EX1005, ¶26. "Monolithic Transdermal System …[comprising] 1.2 g of estradiol hemihydrate…" EX1005, ¶56.
…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,…	"1.2 g of estradiol hemihydrate…The dried film having a coating weight of 115 g/m^2…" EX1005, ¶56; EX1002, ¶¶138-41.

CHALLENGED CLAIMS	ANTICIPATED BY MUELLER (EX1005)
…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. **Claims 10-14.** The method of claim 1, wherein the system achieves an estradiol flux of about 0.0125 mg/cm^2/day, 0.0133 mg/cm^2/day, 0.015 mg/cm^2/day, 0.0167 mg/cm^2/day and 0.0175 mg/cm^2/day, based on the active surface area.	EX1005, ¶¶58-61, FIG. 3; EX1002, ¶¶142-47, 154-64.
2. The transdermal drug delivery system of claim 1, wherein the adhesive polymer matrix comprises a polymer blend comprising an acrylic adhesive, a silicone adhesive, and soluble polyvinylpyrrolidone (PVP).	"1.2 g of estradiol hemihydrate are dissolved …to this solution are added 88.0 g of silicone adhesive (BIO-PSA 4301; Dow-Corning; solids content: 70%-wt.), 10.0 g of a polyacrylate adhesive (Durotak 387-2287; solids content 51%-wt.; National Starch) and 1.2 g of a solution of Kollidon 90F in ethanol (solids content 25%-wt)…" EX1005, ¶56; EX1002, ¶¶150-51.
8. The transdermal drug delivery system of claim 1, wherein the adhesive polymer matrix comprises an amount of estradiol effective to deliver a therapeutically effective amount of estradiol over a period of time selected from the group consisting of at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days.	"Transdermal therapeutic systems (TTSs)…general advantages lie in preventing the so-called first-pass effect and in maintaining therapeutically useful plasma levels over a period of up to 7 days." EX1005, ¶3; EX1002, ¶153. "[A] constant release rate, and thus a stabilization, is achieved for a period of at least 72 h…." EX1005, ¶¶58-61.
15. The transdermal drug delivery system of claim 1, wherein the adhesive polymer matrix comprises about 1.6% by weight estradiol, based on the total	"EXAMPLE 3…1.2 g of estradiol hemihydrate…." EX1005, ¶56; EX1002, ¶165.

CHALLENGED CLAIMS	ANTICIPATED BY MUELLER (EX1005)
drug weight of the adhesive polymer matrix.	

B. [Ground 2] Claims 1-2 and 8-15 are Obvious under 35 U.S.C. §103 over Mueller in view of Vivelle-Dot® Label.

Ground 1 explains how each of claims 1-2, 8, and 10-15 is described in Mueller. EX1002, ¶167. The same claims, as well as claim 9, are obvious in view of Mueller and Vivelle-Dot® Label (EX1006).

1. Claims 1-2

Mueller teaches an estradiol delivery system (Example 3), which comprises a backing layer, a single adhesive polymer matrix layer defining an active surface area, and a release liner. EX1005, ¶¶56-58; EX1002, ¶¶168-69. Example 3 contains estradiol as the only drug within the adhesive polymer matrix layer, which is formed from a polymer blend of an acrylic and silicone adhesives and soluble PVP. EX1005, ¶¶56-58; EX1002, ¶¶170, 177-79. Mueller Example 3 has a coat weight of 11.5 mg/cm^2 and comprises 1.50% estradiol by weight, and thus has an estradiol content per-unit-area of 0.1725 mg/cm^2. EX1005, ¶¶56-58; EX1002, ¶¶177- 81. As shown in Figure 3, Example 3 achieves an estradiol flux of about 0.0125 to about 0.05 mg/cm^2/day" at multiple time points over a 72-hour time period. EX1005, FIG. 3; EX1002, ¶¶172-76, 182-85.

2. Claims 8-9

Claim 8 depends from claim 1 and recites that "the adhesive polymer matrix comprises an amount of estradiol effective to deliver a therapeutically effective amount of estradiol over a period of time selected from the group consisting of at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days and at least 7 days." EX1002, ¶186. Claim 9 depends from claim 1 and recites that the amount of estradiol delivered by the system is "selected from the group consisting of about 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day." *Id.*, ¶191.

Mueller teaches monolithic transdermal estradiol delivery systems for "maintain[ing]…therapeutically useful plasma levels over a period of up to 7 days." EX1005, ¶3. Example 3 delivers "a constant release rate [of estradiol]…for a period of at least 72 h." EX1005, ¶¶58-61; *see also id.*, ¶21; EX1002, ¶190. Indeed, prior to 2008, many FDA-approved estradiol patches were known to deliver therapeutically effective amounts of estradiol over 1-7 days. For example, Vivelle-Dot® Label teaches Vivelle-Dot®, which can deliver between 0.025-0.1 mg estradiol/day, could be "applied to the skin twice weekly." EX1006, 0026, 0030; EX1002, ¶¶187-90.

The doses recited in claim 9 are merely standard daily doses, well known in the art before 2008. Vivelle-Dot® Label, for example, teaches the exact same doses: "[f]ive dosage strengths…of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per

day[.]" EX1006, 0012. These doses are also the same as those used in the art for other estradiol transdermal patches. EX1002, ¶¶78-83, 186-87, 191-92; EX1015, 0005; EX1016, 0018; EX1017, 0010. Thus, given the prevalence of these doses in the art, the skilled artisan would have had reason to use the patch of Mueller Example 3 to deliver the same estradiol doses as described by, *e.g.*, Vivelle-Dot® Label.

Thus, the patches of Mueller Example 3 would deliver standard daily doses of estradiol, for a period of, *e.g.*, two days, in patches that are smaller than those taught by Vivelle-Dot® Label. EX1006, 0012; *see also* EX1001, 11:64-12:3. For example, Mueller Example 3 delivers an average flux of 0.013 mg/cm^2/day from 0-48 hours, *i.e.*, the first two days of use. EX1002, ¶184. This average flux value means that Mueller Example 3 provides a therapeutic dose of estradiol, *i.e.*, the standard respective doses of 0.025, 0.0375, 0.05, 0.075, and 1 mg, taught by Vivelle-Dot® Label, in patches that are ~2 cm^2, ~3 cm^2, ~4 cm^2, ~6 cm^2, and ~8 cm^2, respectively. In view of the teachings of Mueller and Vivelle-Dot® Label, the person of ordinary skill in the art would thus have had a reasonable expectation of successfully delivering a therapeutically effective amount of estradiol as described above.

Thus, each element of claims 8 and 9 is taught by and obvious over the combined teachings of Mueller and Vivelle-Dot® Label.

3. Claims 10-14

Claims 10-14 each recite that the monolithic transdermal estradiol system achieves a certain flux as provided in the table below. EX1002, ¶¶193-95.

Claim	Recited Flux ($mg/cm^2/day$)	±10% Range ($mg/cm^2/day$)
10	"about 0.0125"	0.0113-0.0138
11	"about 0.0133"	0.0120-0.0146
12	"about 0.015"	0.0135-0.0165
13	"about 0.0167"	0.0150-0.0184
14	"about 0.0175"	0.0158-0.0193

As discussed above, Example 3 of Mueller teaches patches with a higher estradiol flux than that of Vivelle-Dot®. EX1002, ¶¶196-97. Figure 3 of Mueller discloses flux values for the patch system of Example 3 at various hourly time points. EX1005, FIG. 3; EX1002, ¶¶182-84. The patches of Example 3 also maintain this high flux of estradiol over multiple days, as presented in Ground 1. EX1002, ¶¶182-84, 195. All of the recited flux values of claims 10-14 are achieved by Mueller Example 3, as described in Ground 1.

In addition, Mueller provides the express motivation to make even smaller patches, noting, "a smaller surface area … is of advantage in manufacture and application" of transdermal systems. EX1005, ¶22; EX1002, ¶¶196-97. As

discussed above, the art recognized many benefits to reducing patch size, *e.g.*, less discomfort, aesthetic appearance, etc. *See, e.g.*, EX1013, 1:28-33; EX1012, 15:31-16:1; EX1023; EX1024; EX1002, ¶¶94-97, 174-76, 196. Mueller teaches that smaller surface areas are possible "due to the high active substance release rates," *i.e.*, high estradiol flux. EX1005, ¶22. Indeed, prior to 2008, the skilled artisan understood that a decrease in patch size could be accomplished by a proportional increase in flux. EX1002, ¶¶172-73. Thus, a person of ordinary skill in the art would have had reason to increase the flux of the Mueller Example 3 system to provide for even smaller patches. *Id.*, ¶¶196-97.

Mueller teaches flux may be increased, and patch size can be decreased by, *e.g.*, incorporating penetration enhancers into the patch formulation. EX1005, ¶¶3-5, 56-57 (Example 3 comprises dipropylene glycol); *see also* EX1006, 0012 (Vivelle-Dot® comprises both dipropylene glycol and oleyl alcohol); EX1002, ¶¶196-97.

Mueller also teaches increasing the hydrophile content of the polymer matrix increases flux. EX1005, ¶¶21, 27-32; EX1002, ¶¶196-97; *see also* EX1004, 0390 (Applicant admitted during prosecution that "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"), 0392, 0422-23, 0427. In view of these teachings, the skilled artisan would have had a reasonable expectation of

successfully increasing the flux of the patches of Example 3, and thereby achieving smaller transdermal patches. EX1002, ¶197.

Thus, in view of the teachings of Mueller and Vivelle-Dot® Label, the skilled artisan would have found it obvious to improve upon the composition taught by Mueller in Example 3 to achieve higher flux values. Thus, the flux values recited in claims 10-14 of the '310 patent would have been obvious.

4. Claim 15

Claim 15 recites that "the adhesive polymer matrix comprises about 1.6% by weight estradiol, based on the total dry weight of the adhesive polymer matrix." As described above in Claim Construction (Section V), the term "about" includes a range of ±10% of the recited 1.6% (1.44-1.76%). EX1002, ¶198.

The patches of Mueller's Example 3 have a total dry mass of 77.46 g, and comprises 1.16 g of estradiol. EX1005, ¶¶56-57. Thus, these patches have an estradiol content of 1.50% (1.16 g estradiol / 77.46 g total mass x 100 = 1.50%). EX1002, ¶¶199-200. 1.5% is within 10% variance of 1.6% (1.44-1.76%). Thus, Mueller Example 3 comprises "about 1.6% by weight estradiol, based on the total dry weight of the polymer matrix," as recited in claim 15 of the '310 patent. EX1002, ¶200.

Moreover, Mueller teaches that an increased concentration of estradiol within the polymer matrix can lead to an increase in flux. The skilled artisan would

thus at least have maintained the 1.50% estradiol content while pursuing other options for increasing flux, such as adding a second penetration enhancer. *Id.*; EX1005, ¶¶9-12. Based on the teachings of Mueller, a skilled artisan would have had reason to prepare patches containing this amount of estradiol to deliver the standard daily doses taught in the Vivelle-Dot® Label.

In view of the discussion above, each of claims 1-2 and 8-15 of the '310 patent are obvious under 35 U.S.C. § 103 over Mueller and the Vivelle-Dot® Label.

C. [Ground 3] Claims 3-7 are Obvious under 35 U.S.C. §103 over Mueller, Vivelle-Dot® Label, and Kanios.

As discussed in Ground 2, each of claims 1-2 and 8-15 is obvious in view of the teachings of Mueller and Vivelle-Dot® Label. Claims 3-7 are obvious in view of Mueller and Vivelle-Dot® Label, in further view of Kanios. EX1002, ¶201.

1. Claim 3

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, all based on the total dry weight of the adhesive polymer matrix." As discussed in Claim Construction (Section V), a value that falls within 10% of the ranges recited in claim 3 satisfies the claimed numerical value. EX1001, 4:42-52; EX1002, ¶¶202-03.

Mueller Example 3 contains 1.50% estradiol, 11.62% dipropylene glycol (penetration enhancer), 0.34% hydroxypropyl cellulose, 79.52% silicone adhesive, 6.58% polyacrylate adhesive, and 0.39% soluble PVP. EX1005, ¶¶56-57; EX1002, ¶203 (79.52% silicone adhesive operates substantially the same as 70-77% silicone adhesive (+10% of the 45-70% range recited in claim 3)).

Mueller teaches that hydrophile polymers, *i.e.*, polyacrylate and PVP, actively stabilize the estradiol within the transdermal drug delivery system. EX1005, ¶18; EX1002, ¶¶203-04, 208-10. For example, Figures 1-3 of Mueller show that transdermal patches with hydrophile polymers achieve higher estradiol flux compared to those without hydrophile polymers. EX1005, ¶¶18, 31, FIGS. 1-3; EX1002, ¶¶203-04. This stabilization prevents the recrystallization of estradiol both before and after release from the system, and allows for high flux values to be achieved. EX1005, ¶¶18, 58-61, FIGS. 1-3; EX1002, ¶¶208-10. Thus, the skilled artisan would have had reasons to modify Mueller's Example 3 to increase the amount of hydrophiles (polyacrylate and PVP), to increase flux, and thereby decrease patch size. EX1002, ¶¶205, 208-10. As silicone adhesives merely serve as "the base polymers of the active substance matrix," the skilled artisan would have decreased the amount of silicone adhesive to accommodate the increase in hydrophiles. EX1005, ¶27; EX1002, ¶¶204-07.

Kanios is directed to transdermal drug delivery systems with adhesive polymer matrices that are similar to those of Mueller Example 3. EX1007, ¶¶127-28; EX1002, ¶¶211, 225. Comparatively, the compositions of Examples 1-3 of Kanios contain more hydrophile polymer (polyacrylate and PVP content are 30% by weight of the total dry weight) and, consequently, less silicone polymer than that of Mueller Example 3. EX1005, ¶¶56-57; EX1007, ¶¶118-22, 126-27; EX1002, ¶¶212-14. Examples 1-3 of Kanios also achieve comparatively higher flux than Mueller Example 3, as shown in the table below. EX1007, FIG. 1; EX1002, ¶¶212-14. Indeed, Examples 1-3 of Kanios achieve an estradiol flux that is within 90% of the 0.0125, 0.0133, 0.015, 0.0167, and 0.0175 mg/cm^2/day flux limitations recited in claims 10-14 at 24 hours. At 11 hours, Example 1 of Kanios also achieves a flux of 0.021 mg/cm^2/day, which is higher than each of 0.0125, 0.0133, 0.015, 0.0167, and 0.0175 mg/cm^2/day. Because this flux value reported by Kanios is higher than each of the claimed flux values, each of the claimed flux values must have been achieved on the way to achieving the higher flux in Kanios Example 1.

Estradiol Flux mg/cm^2/day	11 hours	24 hours
Kanios Example 1	0.021	0.016
Kanios Example 2	0.015	0.016
Kanios Example 3	0.013	0.013
Mueller Example 3	**0.010 (at 8 hours)**	**0.012 (at 24 hours)**

To achieve higher flux, in view of the teachings of Kanios the skilled artisan would have reason to increase the polyacrylate adhesive and the soluble PVP content beyond that of Mueller Example 3 to achieve the 30% by weight hydrophile content disclosed in Kanios Examples 1-3. EX1002, ¶¶213-15. Increasing the hydrophile components by adopting the polyacrylate adhesive and soluble PVP percentages of Kanios Examples 1-3 would yield a polymer matrix with 20% acrylic adhesive, 10% soluble PVP, and 56.5% silicone adhesive, further comprising the 1.50% estradiol, 11.62% dipropylene glycol, and 0.34% hydroxypropyl cellulose taught by Mueller. *Id.* This is consistent with the teachings of Mueller, which specify the patches of Example 3 can be modified to have a hydrophile content between 10%-40% wt. relative to the total matrix. EX1005, ¶¶29-32, claims 4-7; EX1002, ¶¶214-17.

Moreover, the skilled artisan would have had a reasonable expectation of successfully increasing the flux of Mueller Example 3 by increasing the hydrophile content, and decreasing the silicone adhesive content, as taught by Kanios. EX1002, ¶¶214-17; *see also* EX1004, 0390, 0392, 0421-23, 0427 (Applicant 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"); EX1035, 0549-60 (Applicant admitted this effect was understood by those skilled in the art to be due to "estradiol's solubility in acrylic adhesives").

Thus, a monolithic transdermal estradiol delivery system having the components as recited in claim 3 would have been obvious to the person of ordinary skill in the art in view of the combined teachings of Mueller, Vivelle-Dot® Label and Kanios. EX1002, ¶218.

2. Claims 4-6

Claims 4-6 depend from claim 3 and respectively recite that the penetration enhancer comprises oleyl alcohol, dipropylene glycol, or both of them. EX1002, ¶219. Mueller and Kanios each disclose the use of penetration enhancers in transdermal estradiol delivery systems. EX1005, ¶¶3-5 (dipropylene glycol); EX1007, ¶¶106 (oleyl alcohol and dipropylene glycol, both alone and in

combination), 127 (Examples 1-3), 131-34 (Examples 7-11); EX1002, ¶¶216, 220-22.

Vivelle-Dot® Label similarly teaches the use of dipropylene glycol, as well as dipropylene glycol in combination with oleyl alcohol. EX1006, 0012; EX1002, ¶220. As discussed above, the skilled artisan would have recognized that incorporating oleyl alcohol into the composition of Mueller Example 3 as a second penetration enhancer would have resulted in an increase in flux, permitting a proportional decrease in patch size. EX1002, ¶¶94-97, 174, 189, 222; EX1013, 1:28-33, 2:66-3:9, 3:27-39; EX1012, 15:31-16:1; EX1023; EX1024. The skilled artisan thus would have had a reasonable expectation of successfully increasing estradiol flux by combining oleyl alcohol with dipropylene glycol in a transdermal estradiol patch such as Mueller Example 3. EX1002, ¶¶221-22.

Each of claims 4-6 is thus obvious over the combined teachings of Mueller, Vivelle-Dot® Label, and Kanios.

3. Claim 7

Claim 7 depends from claim 3 and recites that "the acrylic adhesive and silicone adhesive are present in a ratio of from about 1:2 to about 1:6, based on the total weight of the acrylic and silicone adhesives."

As taught by Kanios, a person of ordinary skill in the art would have reason to increase the hydrophile content of the patch matrix of Mueller Example 3 to

30% by weight (20% acrylic adhesive + 10% PVP), resulting in a concomitant decrease in the total amount of silicone adhesive. EX1002, ¶223. The resulting percentage of acrylic and silicone adhesive are respectively 20% and 56.5%, thus providing a polymer matrix having an acrylic adhesive to silicone adhesive ratio of 1:2.8. This value clearly falls within claim 7's recited range of about 1:2 to about 1:6. Thus, for the reasons discussed above, claim 7 of the '310 patent would have been obvious to the person of ordinary skill in view of the combined teachings of Mueller, Vivelle-Dot® Label, and Kanios. EX1002, ¶224.

Challenged Claim	**Obvious over Mueller (EX1005), Vivelle-Dot® Label (EX1006), and Kanios (EX1007)**
3. The transdermal drug delivery system of claim 1, wherein 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, all based on the total dry weight of the adhesive polymer matrix.	"1.2 g of estradiol hemihydrate are dissolved in 9 g of dipropylene glycol…[with] 0.26 g of hydroxypropyl cellulose… 88.0 g of silicone adhesive (BIO-PSA 4301; Dow-Corning; solids content: 70%-wt.), 10.0 g of a polyacrylate adhesive (Durotak 387-2287; solids content 51%-wt.; National Starch) and 1.2 g of a solution of Kollidon 90F in ethanol (solids content 25%-wt)" EX1005, ¶56. EX1007, ¶¶109, 127; EX1002, ¶¶202-03, 211-17.
4. The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises	*See above, claim 3.*

Challenged Claim	Obvious over Mueller (EX1005), Vivelle-Dot® Label (EX1006), and Kanios (EX1007)
oleyl alcohol. **5.** The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises dipropylene glycol. **6.** The transdermal drug delivery system of claim 3, wherein the penetration enhancer comprises oleyl alcohol and dipropylene glycol.	"Vivelle-Dot is comprised of…an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, povidone and dipropylene glycol" EX1006, 0012; EX1002, ¶¶220-22. "… the transdermal drug delivery system can also contain …penetration enhancers… such as dipropylene glycol…oleyl alcohol…" EX1007, ¶¶106, 127, Examples 7-11; EX1002, ¶¶220-22.
7. The transdermal drug delivery system of claim 3, wherein the acrylic adhesive and silicone adhesive are present in a ratio of from about 1:2 to about 1:6, based on the total weight of the acrylic and silicone adhesives.	"The portion of the polyacrylate polymer admixed to the hydrophobic matrix [of silicone adhesive] is preferably 40%-wt. at the most, relative to the total matrix…the polyacrylate should be at least about 10%-wt., better still at least about 15%-wt., relative to the matrix layer." EX1005, ¶29. EX1007, ¶¶109, 127, 131-33, Examples 7-11; EX1002, ¶¶223-24.

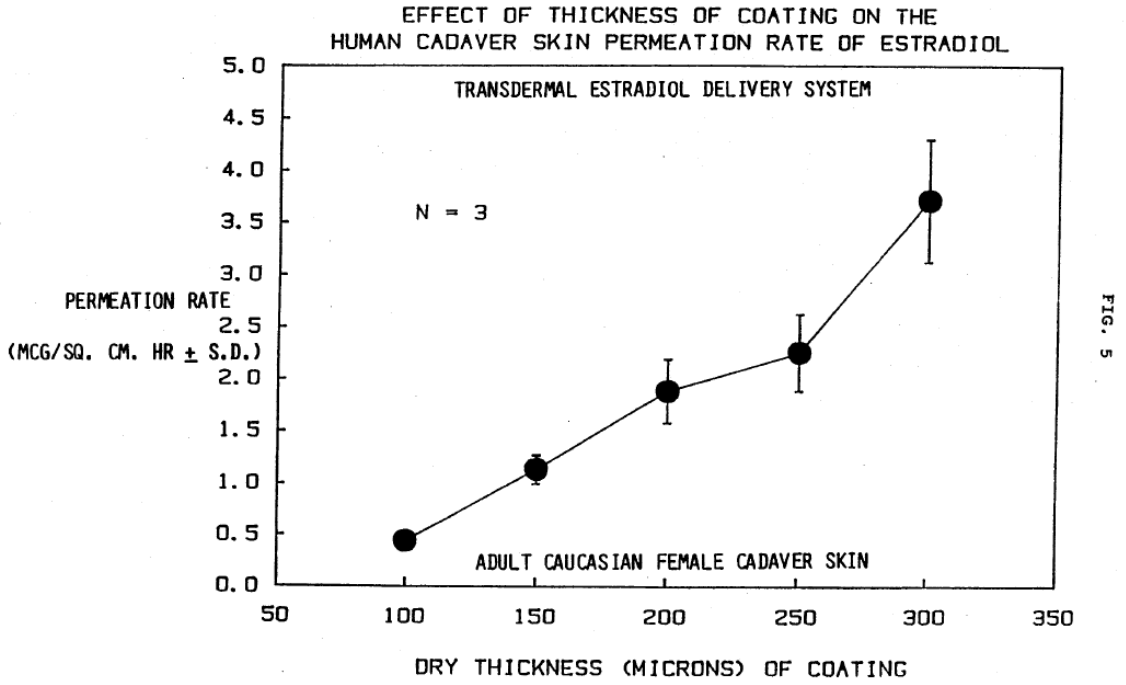
D. [Ground 4] Claims 1-15 are Obvious under 35 U.S.C. §103 over Mueller, Vivelle-Dot® Label, Kanios, and Chien.

As discussed above in Ground 2, each of claims 1-2 and 8-15 of the '310 patent is obvious in view of the combined teachings of Mueller and Vivelle-Dot® Label. EX1002, ¶¶226-32. As discussed in Ground 3, each of claims 3-7 is obvious

in further view of Kanios. *Id.* And, as discussed above in the Brief Overview of the Prosecution History (Section I.B), during prosecution, Applicant argued that increasing coat weight unexpectedly increased the estradiol flux of the systems recited in claims 1-15. However, this means for increasing estradiol patch flux was already expressly taught in the prior art. Thus, each of claims 1-15 is obvious in further view of Chien.

Chien, for example, teaches monolithic transdermal drug delivery systems that are similar to those of Mueller and that comprise an adhesive polymer matrix layer containing estradiol, a backing layer, and a release liner. EX1009, 2:45-3:2, 3:41-4:36, 7:28-39, 8:36-41; EX1002, ¶¶233-35, 237 (also discussing EX1019, 1:38-44, 2:18-30 (describing "'monolithic' systems [wherein]…the active ingredient is dissolved or dispersed in a 'matrix,' which becomes the drug reservoir")). Figure 5 of Chien expressly teaches that increasing the coating thickness (or coat weight) of the adhesive polymer matrix increases estradiol flux. EX1009, 5:20-22-28, FIG. 5; EX1002, ¶233; *see also* EX1022, 32; EX1010, 82; EX1035, 0169-70 (identifying increased coat weight as a "proxy" for increased drug loading); EX1004, 0387, 0415-16, 0426 (increasing coat weight is the same as increasing the thickness of a polymer matrix); *id.*, 0120-21 ("unexpected that increasing the amount of drug per unit area would impact drug delivery rate"); EX1009, FIG. 4 (increasing estradiol drug loading increases flux).

Figure 5 of Chien (shown below) demonstrates that increasing coat thickness from, *e.g.*, 150 μm to 200 μm, almost doubles the flux of the system (~1 mg/cm^2/h to ~1.8 mg/cm^2/h). Increasing coat thickness from 250 μm to 300 μm results in a similarly heightened estradiol flux (~2.25 mg/cm^2/h to ~3.75 mg/cm^2/h). EX1002, ¶234.



The adhesive polymer matrix of Mueller Example 3 is "coated in a thickness of 250 μm onto a film" prior to drying, equivalent to a dry thickness of ~50-175 μm. EX1005, ¶¶56-57; *see also* EX1002, ¶234, citing EX1027 (Jenkins), 6:43-54, EX1028 (Wong), 7:9-14.

As the delivery systems of Chien have compositions similar to those of Mueller, and of a similar thickness, a person of ordinary skill in the art would have

known that increasing the coat weight or drug loading of a polymer matrix as described in Mueller Example 3 would increase the estradiol flux of the resulting patch. EX1002, ¶¶234-35. The skilled artisan would have had a reasonable expectation of successfully increasing flux by simply coating the drug-containing polymer matrix onto the backing layer more thickly than as described by Mueller. EX1002, ¶¶235-36, EX1005, ¶¶27-31; EX1009, 3:14-16, 3:41-4:4, 7:43-64, 8:36-41.

Increasing flux so as to reduce patch size was already routine in the art, as demonstrated by Vivelle-Dot® Label's reduction in patch size by 60% compared to its predecessor patch described in Vivelle® Label. More specifically, Vivelle-Dot® Label describes an estradiol delivery system that is a "revised formulation" that achieves "smaller system sizes… [that are] bioequivalent to the original formulation, Vivelle." EX1006, 0012. The second-generation Vivelle-Dot® provides the same daily doses as described for Vivelle® Label in patches that are ~3-fold smaller. EX1002, ¶¶230-31. For example, the Vivelle® (EX1008, 0012) and Vivelle-Dot® patches for delivering a 0.025 mg/day dose of estradiol have respective sizes of 7.25 cm^2 and 2.5 cm^2, which corresponds to a 2.9-fold reduction in size. *Id.* (also comparing Vivelle® and Vivelle-Dot® patches for estradiol doses of 0.0375, 0.05, 0.075, and 0.1 mg/day, which demonstrate a patch size reduction of 2.93-fold (11.0 cm^2 vs 3.75 cm^2), 2.9-fold (14.5 cm^2 vs 5.0 cm^2), 2.93-fold (22.0

cm^2 vs 7.5 cm^2), and 2.9 (29.0 cm^2 vs 10.0 cm^2), respectively). Thus, the formulation for estradiol patches that are described in Vivelle-Dot® Label achieves a higher flux than its predecessor, *i.e.*, patches described in Vivelle® Label, thereby allowing for the same daily doses, but in a smaller patch size. EX1002, ¶¶230-32.

Because Chien teaches increasing coat thickness as a means of increasing estradiol flux,[1] it would have been obvious to increase the estradiol flux and thereby decrease patch size, as recited in claims 1-15, in view of the combined teachings of Mueller, Vivelle-Dot® Label, Kanios, and Chien. EX1002, ¶236. Based on at least the teachings of Chien, these resulting patch systems would have been neither unexpected nor surprising to the person of ordinary skill in the art.

VII. SECONDARY INDICIA OF NON-OBVIOUSNESS

A *prima facie* case of obviousness may in some instances be rebutted by such "secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc." *Graham v. John Deere Co. of Kansas City,* 383 US 1, 17-18 (1966). These factors are relevant to a determination of obviousness to the

[1] As discussed below in Section VII, Kim, Ghosh and Bronaugh also each teach that increasing the coat weight of a monolithic transdermal patch increases flux and could each be asserted as grounds references in place of Chien. EX1010, 82; EX1014, 287-88; EX1026, 86, 89.

extent that they can be linked to novel and claimed features. *See, e.g., Tokai Corp. v. Easton Enterprises, Inc.*, 632 F. 3d 1358, 1369 (Fed. Cir. 2011) ("If commercial success is due to an element in the prior art, no nexus exists."); *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983) (Claims were obvious because Patent Owner "failed to show that such commercial success … was due to anything disclosed in the patent in suit which was not readily available in the prior art.").

As discussed above, the prior art taught each element of the challenged claims, and suggested each of the claims as a whole. PO cannot establish support for any secondary indicia of non-obviousness that can be attributed to a novel aspect of the claims. EX1002, ¶238.

Moreover, contrary to PO's statements in the '310 patent and repeated assertions during prosecution (EX1004, 0013, 0120, 0381-82, 0387-98), the prior art proves that it was not "surprising and unexpected that increasing the amount of estradiol per unit area resulted in an increased flux per unit area." In fact, the prior art shows that this was a routine and obvious strategy to a person of ordinary skill in the art. EX1002, ¶¶238-42.

For example, Chien, which was not of record during prosecution, teaches that increasing estradiol drug loading or coat weight of the adhesive polymer matrix of an estradiol patch results in increased flux. EX1009, FIGS. 3-5. Thus, the

skilled artisan would not have found the resulting increase in flux surprising or unexpected, as the direct relationship between drug loading and coat weight with estradiol flux of a matrix-type monolithic patch was well-known in the art. *See* Section I.B, I.E, VI.

Furthermore, numerous prior art publications show that flux of various drugs can be increased by increasing the coat weight of the adhesive layer in a monolithic transdermal patch. EX1002, ¶¶239-42. For example, Kim and Ghosh each teach that increasing the coat weight of a monolithic matrix-type transdermal patch increases flux. Moreover, these references describe a potential mechanism for how increased coat weight increases flux, noting, "as the thickness of the matrix increase[s], the occlusive effect of the matrix increase[s], resulting in the increased flux." EX1010, 82. The prior art teaches that "[o]f the various approaches employed to enhance the percutaneous absorption of drugs," increasing occlusion "is the simplest and most common method in use." EX1026, 86. Bronaugh teaches that, that occlusion "significantly increase[s] the percutaneous absorption ($p<0.01$) of the steroids," including estradiol. EX1026, 89. The consistent description of increasing flux by increasing coat weight across a wide range of actives and thicknesses confirms that this was a well-known principle that was not limited to any particular transdermal drug delivery system. EX1002, ¶¶239-42.

Similarly, PO's assertion during prosecution that "[n]othing in Fick's 1st law indicates or predicts that increasing the coat weight (thickness) of a polymer matrix would increase flux" is not indicative of surprising results. EX1004, 0385-87; EX1002, ¶¶43-44. In fact, in view of the teachings above, it is clear that those in the art understood that increasing coat weight increases drug diffusivity (a variable included in Fick's 1st Law), and thereby, increases flux. *Id.*; EX1009, FIGS. 3-5; EX1010, 82; EX1014, 288; EX1026, 86, 95, 105-08.

As such, PO's claimed unexpected and surprising results are not unexpected, but were expressly expected in view of the prior art.

VIII. CONCLUSION

For the reasons set forth above, claims 1-15 of the '310 patent are unpatentable. Petitioner therefore requests that an *inter partes* review of claims 1-15 be instituted and that the challenged claims be canceled.

Respectfully submitted,

Dated: December 4, 2017

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IX. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 12,390 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: December 4, 2017

/ Steven W. Parmelee /
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X. PAYMENT OF FEES UNDER 37 C.F.R. §§42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XI. APPENDIX – LIST OF EXHIBITS

Exhibit No	Description
EX1001	U.S. Patent No. 9,724,310 to Mantelle *et al*.
EX1002	Declaration of Dr. Keith Brain.
EX1003	*Curriculum Vitae* of Dr. Keith Brain.
EX1004	File history of U.S. Patent No. 9,724,310
EX1005	U.S. Patent Application Publication No. US 2003/0099695 to Mueller (published May 29, 2003) ("Mueller")
EX1006	Vivelle-Dot® Transdermal System (Novartis) 05/03/2002 Supplemental Approval [Label Revisions] – FOI Document # 5236149B (2006) ("Vivelle-Dot® Label")
EX1007	U.S. Patent Application Publication No. US 2006/0078602 to Kanios (published April 13, 2006) ("Kanios")
EX1008	Vivelle® Transdermal System (Novartis) 08/16/2000 Approval & Supplemental Approval Letter and Labeling – FOI Document # 5210567A (2004) ("Vivelle® Label")
EX1009	U.S. Patent No. 5,145,682 to Chien *et al.* (issued September 8, 1992) ("Chien")
EX1010	Kim *et al.*, *Penetration Enhancement of β_2-Selective Agonist, Tulobuterol, Across Hairless Mouse Skin*, 33 J. PHARM. INVEST. (2003) 79-84 ("Kim")
EX1011	U.S. Patent No. 5,656,286 to Miranda *et al.* (issued August 12, 1997) ("Miranda")

Exhibit No	Description
EX1012	PCT Application Publication WO 1996/003119 to Fotinos (published February 8, 1996) ("Fotinos")
EX1013	U.S. Patent No. 5,919,477 to Bevan *et al.* (issued July 6, 1999) ("Bevan")
EX1014	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")
EX1015	Climara 0.025mg Transdermal System (Berlex Laboratories) 04/05/2001 Supplemental Approval Letter and Final Labeling – FOI Document # 5243107A ("Climara® Label")
EX1016	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")
EX1017	Menostar (Berlex) 06/08/2004 Approval Letter and Final Labeling – FOI Document # 5228320A ("Menostar® Label")
EX1018	U.S. Patent No. 5,902,602 to Müller *et al.* (issued May 11, 1999) ("Müller")
EX1019	U.S. Patent No. 6,156,335 to Rovati *et al.* (issued December 5, 2000) ("Rovati")
EX1020	U.S. Patent No. 6,521,250 to Meconi *et al.* (issued February 18, 2003) ("Meconi")
EX1021	U.S. Patent No. 5,227,169 to Heiber *et al.* (issued July 13, 1993) ("Heiber")

Exhibit No	Description
EX1022	Bucks *et al.*, *Bioavailability of Topically Administered Steroids: A "Mass Balance" Technique*, 90 J. INVEST. DERMATOL. (1988) 29-33 ("Bucks")
EX1023	Dinger, E., *Noven Pharmaceuticals, Inc.* ENCYCLOPEDIA.COM (2006) http://www.encyclopedia.com/books/politics-and-business-magazines/noven-pharmaceuticals-inc (last accessed: June 29, 2017) ("Dinger")
EX1024	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")
EX1025	van der Bijl, P., *et al.*, *Transmucosal Permeation of Topically Applied Diclofenac and Piroxican*, 3 J. APP. RES. (2003) 505-11 ("van der Bijl")
EX1026	Bronaugh R.L., Maibach H.I. (eds.), *In vitro percutaneous absorption: Principles, fundamentals and applications*. CRC Press, Boca Raton, Florida (1991) 85–114 ("Bronaugh")
EX1027	U.S. Patent No. 5,352,457 to Jenkins (issued October 4, 1994) ("Jenkins")
EX1028	U.S. Patent No. 5,603,947 to Wong *et al.* (issued February 18, 1997) ("Wong")
EX1029	*Intentionally left blank*
EX1030	U.S. Patent No. 6,638,528 to Kanios (issued October 28, 2003) ("Kanios '528")

Exhibit No	Description
EX1031	U.S. Patent No. 4,624,665 to Nuwayser (issued November 25, 1986) ("Nuwayser")
EX1032	U.S. Patent Application Publication No. US 2009/0041831 to Miller *et al.* (published February 12, 2009) ("Miller")
EX1033	U.S. Patent No. 6,024,976 to Miranda *et al.* (issued February 15, 2000) ("Miranda '976")
EX1034	*Approved Drug Products with Therapeutic Equivalence Evaluations*, ORANGE BOOK, 27th Edition (2007) ("Orange Book")
EX1035	File history of U.S. Patent No. 9,730,900
EX1036	U.S. Patent No. 9,730,900 to Mantelle *et al.*

Certificate of Service

Pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for *inter partes* review of U.S. Patent No. 9,724,310 (and accompanying Exhibits EX1001-EX1035) by overnight courier (Federal Express or UPS), on this 4th day of December 2017, on the Patent Owner at the correspondence address of the Patent Owner as follows:

Foley & Lardner LLP
7000 K Street N.W., Suite 600
Washington D.C. 20007-5109

and at other addresses also likely to effect service:

Noven Pharmaceuticals, Inc.
11960 Southwest 144th Street
Miami, Florida 33186

Respectfully submitted,

Dated: December 4, 2017

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990