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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 IPR2018-00174
Patent 9,730,900 B2

Before JAMES T. MOORE, SUSAN L. C. MITCHELL, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Mylan Technologies, Inc. ("Petitioner") requests an *inter partes* review of claims 1–23 of U.S. Patent No. 9,730,900 B2 ("the '900 patent," Ex. 1001). Paper 2 ("Pet."). Noven Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018).

Applying those standards, and upon consideration of the information presented in the Petition and the Preliminary Response, we determine that Petitioner has not demonstrated a reasonable likelihood of success in proving that any claim of the '900 patent is unpatentable. We, therefore, deny the Petition and do not institute an *inter partes* review.

II. BACKGROUND

A. Related Matters

Petitioner identifies *Noven Pharmaceuticals, Inc. v. Alvogen Pine Brook LLC*, No. 1:17-cv-01429-LPS (D. Del.) as a related matter under 37 C.F.R. § 42.8(b)(2). Pet. 20. Petitioner also petitioned for an *inter partes* review of U.S. Patent 9,724,310 B2 ("the '310 patent"), owned by Patent Owner, which has been designated Case IPR2018-00173. *Id.* at 20. Petitioner states that the '310 and the '900 patents both claim the benefit of

priority to U.S. Application No. 12/216,811, filed on July 10, 2008, now U.S. Patent No. 8,231,906 ("the '906 patent"). Petitioner identifies both pending and terminated litigations involving the '906 patent. *See id.* at 20–21 (identifying *Noven Pharmaceuticals Inc. v. Mylan Technologies Inc.*, No. 1:15-cv-00328 (D. Del.) (terminated); *Noven Pharmaceuticals Inc. v. Mylan Technologies Inc.*, 1:15-cv-00069 (N.D.W.V.) (terminated), *Noven Pharmaceuticals Inc. v. Actavis Laboratories UT, Inc*., Nos. 1:15-cv-00249-LPS and 1:16-cv-00465-LPS (D. Del.) (pending); *Alvogen Pine Brook LLC v. Noven Pharmaceuticals, Inc.*, No. 1:16-cv-00395-LPS (D. Del.) (pending)).

B. The '900 Patent

The '900 patent, titled "Transdermal Estrogen Device and Delivery," issued on August 15, 2017. Ex. 1001, [45]. The '900 patent relates to transdermal drug delivery systems for the transdermal administration of estrogen, and to methods of making and using such systems. *Id.*, Abstract. In one embodiment, the transdermal drug delivery system is a patch comprising a single adhesive polymer matrix layer of adhesive polymer matrix and estradiol. *Id.* at 2:12–18.

According to the '900 patent, "a patch comprising a pressure-sensitive adhesive containing a drug, as a means of delivering drug through the skin is well known." *Id.* at 1:21–23. But formulation of viable commercial embodiments has been difficult, in part due to patient preference for patches having a small surface area. *Id.* at 1:56–2:7. The '900 patent explains that "size, e.g., surface area at the site of application, is often dictated and limited by other physical and pharmacokinetic requirements, such as desired drug delivery rates and daily dosages." *Id.* at 1:58–61. Thus, "it is easier to

develop a relatively 'large' transdermal drug delivery system that will achieve drug delivery at target therapeutic levels over an intended duration of therapy, than it is to develop a smaller transdermal drug delivery system that still exhibits acceptable pharmacokinetic properties." *Id.* at 1:61–66.

The '900 patent refers to the target delivery rate of a drug as "flux," *id.* at 3:41, and explains that "Applicant surprisingly discovered 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" to larger patches, *id.* at 3:58–62. Although "it was known in the art to increase coat weight to provide delivery over a longer period of time," the '900 patent continues, "it was not known that increasing coat weight could increase delivery weight or flux, and thus permit the development of a smaller system while maintaining daily dosage." *Id.* at 3:65–4:2.

The '900 patent provides an example of a polymer matrix composition comprising, *inter alia*, acrylic adhesive, silicone adhesive, povidone (PVP), and estradiol. *Id.* at 15:8–19 (Example 1). In one example, the polymer matrix was applied to a release liner at a coat weight of 12.5 mg/cm^2 (Example 1), and in a second sample, at a coat weight of 15 mg/cm^2 (Example 1a). *Id.* at 15:21–22. Human cadaver permeation studies were then performed to compare the estradiol flux of these samples to that of commercial embodiment Vivelle-Dot®. *Id.* at 15:23–43. As shown in Figure 1, below, "the systems according to the invention have a greater flux than the Vivelle-Dot® product and are able to achieve therapeutic daily dosages despite their significantly smaller size." *Id.* at 15:44–47.

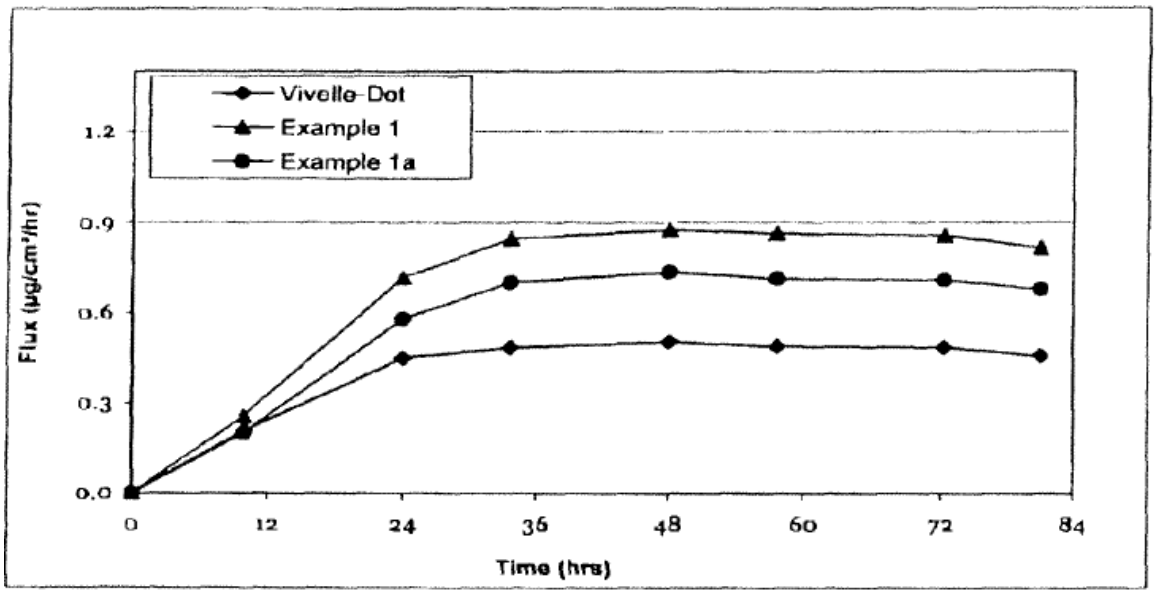

Figure 1 illustrates the estradiol flux (μg/cm^2/hr) over time (0–81 hours) from transdermal delivery systems according to the invention (Examples 1 and 1a) as compared to Vivelle-Dot®. Ex. 1001, 3:26–28.

C. Illustrative Claim

Of the challenged claims, claim 1 is independent and illustrative of the claimed subject matter. Claim 1 recites:

> 1. 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.

Ex. 1001, 15:49–59.

D. The Prior Art

Petitioner advances the following references as prior art on which it relies for the asserted grounds challenging the claims of the '900 patent:

1. Walter Mueller, Patent Application Publication No. US 2003/0099695 A1 (May 29, 2003) ("Mueller," Ex. 1005);

2. Center for Drug Evaluation and Research, Approval Package for Application No. 20-538/S-015, Vivelle-Dot® Transdermal System (Novartis) (May 3, 2002) ("Vivelle-Dot Label," Ex. 1006);

3. David Kanios, Patent Application Publication No. US 2006/0078602 A1 (Apr. 13, 2006) ("Kanios," Ex. 1007); and

4. Yie W. Chien and Te-Yen Chien, U.S. Patent No. 5,145,682 (Sept. 8, 1992) ("Chien," Ex. 1009).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–15 of the '900 patent on the following grounds:

Claims	Basis	References
1, 2, 8, 10–16, and 18–23	35 U.S.C. § 102	Mueller
1, 2, and 8–23	35 U.S.C. § 103	Mueller and Vivelle-Dot Label
3–7	35 U.S.C. § 103	Mueller, Vivelle-Dot Label, and Kanios
1–23	35 U.S.C. § 103	Mueller, Vivelle-Dot Label, Kanios, and Chien

Pet. 21–22. Petitioner also relies on the Declaration of Keith Brain, Ph.D. *See* Pet. 15 (citing Ex. 1002).

Patent Owner disputes that Petitioner's asserted grounds render the challenged claims unpatentable. *See generally* Prelim. Resp. Patent Owner relies on the Declaration of Adrian C. Williams, Ph.D. *See id.* at 7 (citing Ex. 2001).

III. ANALYSIS

We organize our analysis into four sections. First, we address the level of ordinary skill in the art. Second, we turn to claim construction. Third, we provide an overview of the asserted references. Fourth, taking account of the information presented, we consider whether the grounds asserted in the Petition meet the threshold showing for instituting an *inter partes* review under 35 U.S.C. § 314(a).

A. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends and Dr. Brain testifies that, as of July 10, 2008, the earliest filing date in the priority chain for the '900 patent, a person of ordinary skill in the art "would likely have an advanced degree, for example a Ph.D., in pharmaceutical chemistry, physical chemistry, bioengineering, or a drug delivery related discipline," or, alternatively, "a bachelor's degree plus two to five years' experience in the transdermal delivery industry." Pet. 15; Ex. 1002 ¶¶ 77–78. Petitioner also asserts that the ordinarily skilled artisan "would 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 references discussed and presented in the Petition. Pet. 15; *see also* Ex. 1002 ¶¶ 77–78.

At this stage of the proceeding, Patent Owner does not dispute Petitioner's proposed level of ordinary skill. Prelim. Resp. 7. Patent Owner clarifies, however, "that a POSA who does not have an advanced degree in the fields mentioned [by Petitioner] would have a bachelor's degree in a

field related to drug delivery." *Id.* (citing Ex. 2001 ¶¶ 26–28). We adopt Petitioner's definition, with Patent Owner's clarification, for purposes of this decision.

We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect the appropriate level of ordinary skill in art). Further, based on the information presented at this stage of the proceeding, we consider each parties' declarant—Dr. Brain and Dr. Williams—qualified to opine from the perspective of an ordinary artisan at the time of the invention. *See* Ex. 1002 ¶¶ 1–11 (Dr. Brain's qualifications); Ex. 1003 (Dr. Brain's curriculum vitae); Ex. 2001 ¶¶ 4–16 (Dr. Williams's qualifications); Ex. 2002 (Dr. Williams's curriculum vitae).

B. Claim Construction

The Board interprets claims in an unexpired patent using 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*, 136 S. Ct. 2131, 2144–46 (2016). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

Petitioner and Patent Owner propose interpretations of the claim terms "about," "coat weight," "flux," and "therapeutically effective amount." Pet. 23–28; Prelim. Resp. 25–30. For purposes of this decision, and in order to determine whether to institute an inter partes review, we need not explicitly interpret every claim term for which the parties propose a

construction. *See* 35 U.S.C. § 314(a); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy."). We determine that, to resolve whether Petitioner has demonstrated a reasonable likelihood of prevailing, we need only address the parties' respective proposed interpretations of "about" and "flux."

1. *"about"*

Claim 1 recites "a coat weight of greater than *about* 10 mg/cm^2," and "an estradiol flux of from *about* 0.0125 to *about* 0.05 mg/cm^2/day." Ex. 1001, 15:55–59 (emphases added). Both Petitioner and Patent Owner agree that, based on the written description of the '900 patent, the term "'about' will mean up to plus or minus 10% of a particular term." *See* Pet. 25 (citing Ex. 1001, 4:42–52); Prelim. Resp. 26 (accord). Because the written description of the '900 patent provides an express definition of that term, we agree with the parties and find that the broadest reasonable interpretation of "about" is "up to plus or minus 10% of a particular term." Ex. 1001, 4:42–52; *see also In re Bass*, 314 F.3d 575, 577 (Fed. Cir. 2002) ("[T]he PTO must apply the broadest reasonable meaning to the claim language, taking into account any definitions presented in the specification.").

2. *"flux"*

Claim 1 recites that the monolithic transdermal drug delivery system achieves "an estradiol *flux* of from about 0.0125 to about 0.05 mg/cm^2/day." Ex. 1001, 15:57–59 (emphasis added). The written description of the '900 patent refers to "flux" as both the "delivery rate" and the "permeation rate." *Id.* at 3:40–41, 3:67–4:1, 5:24. The written description explains that flux "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." *Id.* at 5:24–32.

Petitioner recites the definition of "flux" provided in the specification, but also alleges that the '900 patent is silent on how flux is measured and does not require the system to achieve the claimed estradiol flux "for any particular time [period]." Pet. 26 (citing Ex. 1002 ¶¶ 86–88). Thus, Petitioner alleges, "[u]nder the broadest reasonable interpretation, flux may include flux for any time period when the system is applied to the skin." *Id.* at 27.

Patent Owner also recites the same definition of "flux" provided in the written description, but disagrees with Petitioner that the '900 patent fails to provide a method for measuring flux. Prelim. Resp. 28. Specifically, Patent Owner argues that the '900 patent "illustrates in Example 1 how flux can be measured using human cadaver skin permeation studies, a methodology that was well-known and conventional." *Id.* (citing Ex. 2001 ¶ 124). Patent Owner also argues that the Declaration of Richard H. Guy, Ph.D.—submitted during prosecution of the application maturing into the '900 patent—"provides further information on flux and how flux can be measured." *Id.* (citing Ex. 1004, 580–581).

Patent Owner disagrees with Petitioner that flux may relate to any time period. *Id.* at 29. Citing Dr. Williams's Declaration, Patent Owner alleges that an ordinarily skilled artisan would only consider "flux values for

a time period once steady state or pseudo steady state is reached." *Id.* (citing Ex. 2001 ¶ 124). Patent Owner also contends that there is an "essential need to account for variations in skin permeability . . . between different skin samples." *Id.* at 29 (citing Ex. 2001 ¶ 125). An ordinarily skilled artisan measuring flux, Patent Owner contends, "would be aware of the impact of skin permeation variability on flux measurements, and would implement one or more well-known 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." *Id.* at 29–30 (citing Ex. 2001 ¶¶ 126–127; Ex. 1004, 597–99).

For these reasons, Patent Owner states, the broadest reasonable interpretation of the term "flux" "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 that the flux achieved by a transdermal delivery system "would be reflected by flux values for a period when the flux is at steady state or pseudo steady-state." *Id.* at 30 (citing Ex. 2001 ¶ 126).

We agree with the parties that the '900 patent expressly defines "flux" as "the absorption of a drug through skin or mucosal tissue" as described by Fick's first law of diffusion. Ex. 1001, 5:24–32. The parties' disagreement centers on whether additional limitations to that definition are necessary. On this record, however, we discern no reason to deviate from the express definition set forth in the written description. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc) (stating that the specification is "the single best guide to the meaning of a disputed term" and "[u]sually, it is

dispositive" (citation omitted)). In particular, we determine that Patent Owner attempts to cabin the broadest reasonable interpretation of "flux" by adding restrictions on the testing methodology that are not found in the written description of the '900 patent. Thus, we determine that flux requires no further construction for purposes of this decision. *Vivid Techs.*, 200 F.3d at 803.

C. Asserted References

Before turning to Petitioner's asserted grounds of unpatentability, we provide a brief summary of the asserted references.

1. *Mueller*

Mueller relates to a "transdermal therapeutic system" (TTS) such as a patch, for the administration of estradiol. Ex. 1005 ¶¶ 1, 56–61. Mueller's patches comprise an "active substance-containing matrix," a backing layer, and a "releasable protective layer." *Id.* ¶¶ 25–26. In one embodiment, the "active substance-containing matrix" "has a single-layer structure and is self-adhesive." *Id.* ¶ 26. Mueller teaches increasing hydrophilic polymer content (e.g., polyacrylate adhesive and PVP) in the matrix layer improves the release of the active substance. *Id.* ¶ 21. "By improving the active substance release," Mueller continues, "the invention enables the manufacture of transdermal systems which can have a smaller surface area due to the high active substance release rates." *Id.* ¶ 22.

Mueller provides an example of a monolithic TTS comprising silicone adhesives with hydrophile additives. *Id.* ¶¶ 56–61 (Example 3). The patch comprises hydroxypropyl cellulose, polyacrylate adhesive, silicone adhesive, Kollidon 90F (PVP), and estradiol hemihydrate. *Id.* ¶ 56. The final film has a coat weight of 115 g/m^2. *Id.* ¶ 57. Mueller states that permeation studies

were conducted to compare "between samples without hydrophilic additives (2a) and samples with hydrophilic additives (3)." *Id.* ¶ 58. Mueller explains that these studies were performed "using Franz diffusion cells and human epidermis." *Id.* ¶ 60. According to Mueller, Figure 3 (below) shows a constant release rate for TSSs of the invention for a period of at least 72 hours, "whereas in the case of the comparison examples a marked flattening of the permeation profile can be seen already after 32 h[ours]." *Id.* ¶ 61.

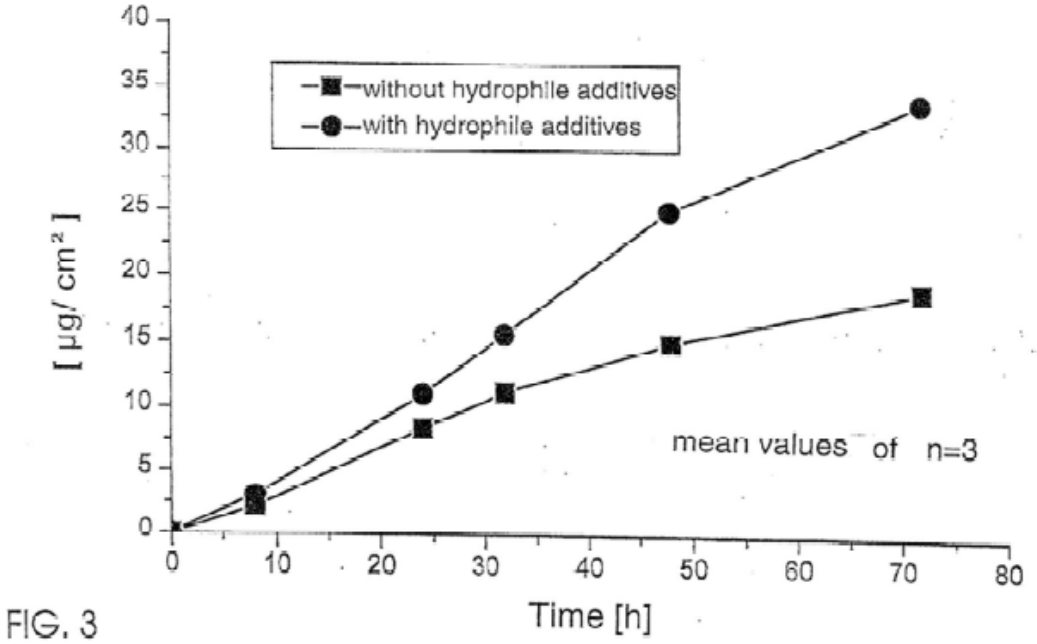

FIG. 3

Figure 3 provides the estradiol permeation of samples with hydrophilic additives (●) and without hydrophilic additives (■). Ex. 1005 ¶ 58.

2. *Vivelle-Dot Label*

The Vivelle-Dot Label describes an estradiol transdermal patch comprising a backing, an adhesive layer containing estradiol, and a protective layer. Ex. 1006, 12–13. According to the Vivelle-Dot Label, the patch "provide[s] nominal in vivo delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin" and has active surface

areas of "2.5, 3.75, 5.0, 7.5, or 10.0 cm^2," respectively. *Id.* at 12. The Vivelle-Dot Label describes the patch as a "revised formulation with smaller system sizes," which "was shown to be bioequivalent to the original formulation, Vivelle." *Id.* at 14.

3. *Kanios*

Kanios describes a transdermal delivery system "where 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." Ex. 1007, Abstract. "The drug carrier composition may be comprised of (a) one or more acrylic-based polymers having one or more different monomers selected from the group consisting of hard and soft monomers; (b) one or more silicone-based polymers; and (c) one or more active agents . . . ." *Id.*

Kanios provides examples of dermal compositions comprising, *inter alia*, acrylic-based polymer, silicone-based polymer, PVP, and estradiol. *Id.* ¶ 127 (Examples 1–3). In each example, the proportion of soft monomers to hard monomers in the acrylic-based polymer is varied. *Id.* Specifically, the dermal composition of Example 1 comprises 70% soft monomers and 30% hard monomers; the dermal composition of Example 2 comprises 50% soft monomers and 50% hard monomers; and the dermal composition of Example 3 comprises 20% soft monomers and 80% hard monomers. *Id.* The average flux profile of each Example is illustrated in Figure 1, below. *Id.* ¶ 128.

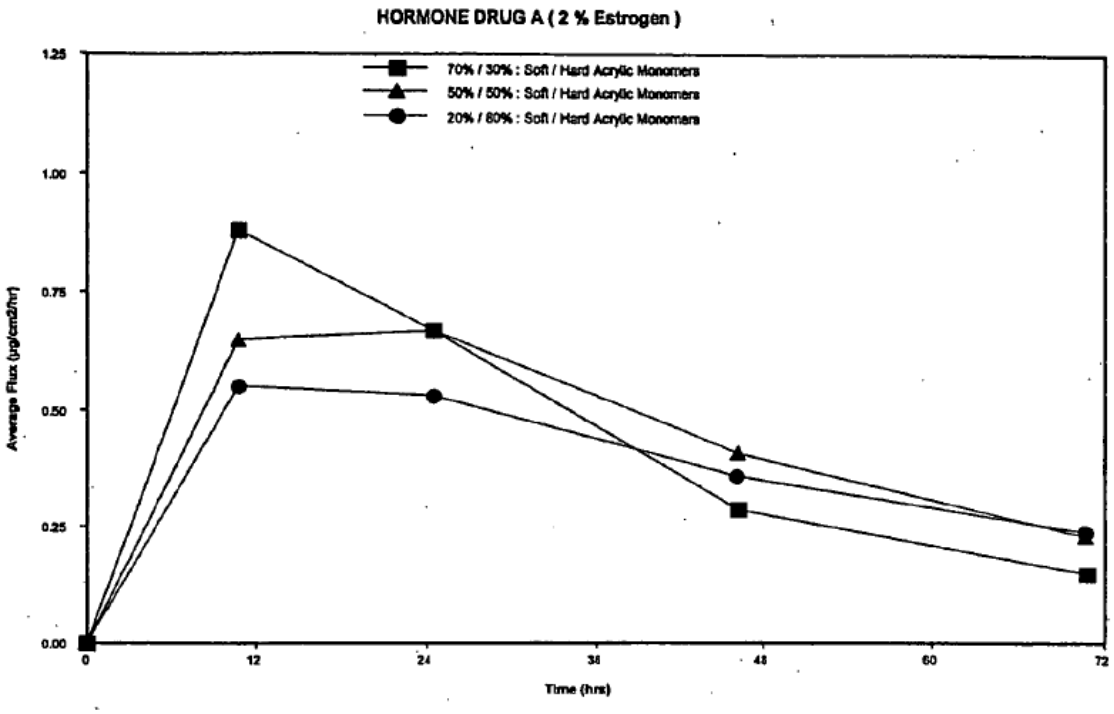

Figure 1 provides the average flux of dermal compositions comprising different proportions of soft and hard acrylic-based monomers. Ex. 1007 ¶ 20.

According to Kanios, "the in-vitro permeation rate for each transdermal drug matrix varied depending upon which acrylic polymer was utilized in the matrix." *Id.* ¶ 135. "These results indicate that drug delivery rate and profile can be manipulated by modifying the acrylic monomer composition of the acrylic pressure sensitive adhesive in the transdermal drug delivery device." *Id.*

4. *Chien*

Chien discloses "[t]ransdermal absorption dosage units . . . for treatment of postmenopausal syndrome." Ex. 1009, Abstract. The units "comprise a backing layer, [and] an adjoining adhesive polymer layer in which at least minimum effective daily doses of an estrogen is microdispersed." *Id.* The adhesive polymer layer also comprises "one or

more transdermal absorption enhancing agents." *Id.* at 2:59–62. In Example 2, Chien describes various dermal compositions comprising estradiol, n-decyl alcohol (a permeation enhancer), and polyacrylate adhesive polymer. *Id.* at 11:22–12:16. The dermal compositions were made into patches comprising, in addition to a backing layer and a release layer, an adhesive layer with a permeation enhancer, a separating layer, and an adhesive layer containing estradiol. *Id.* at 11:64–12:14. In Tables 1–5, Chien provides the permeation rates for estradiol from various samples that differ in the thickness of the separating layer (Table 1), the chain length of the fatty alcohol (Table 2), the estradiol loading dose (Table 3), the thickness of the enhancer-containing upper adhesive layer (Table 4), and the concentration of n-decyl alcohol in the upper adhesive layer (Table 5). *Id.* at 12:15–13:33.

D. Asserted Anticipation by Mueller

Petitioner contends that Mueller anticipates claims 1, 2, 8, 10–16, and 18–23 of the '900 patent because Mueller "describes as part of a single embodiment each element of the challenged claims." Pet. 28 (citing Ex. 1002 ¶ 149). A claim is anticipated and, therefore, unpatentable under 35 U.S.C. § 102, if all of its limitations are disclosed either explicitly or inherently in a single prior art reference. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). That single prior art reference must disclose all of the limitations of the claim "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008).

Taking claim 1 as illustrative, Petitioner argues that Mueller teaches the preamble ("[a] method for administering estradiol, comprising applying

to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system"), by disclosing a monolithic TTS that provides for the constant release of estradiol through the skin. Pet. 28–29 (citing Ex. 1005 ¶¶ 1–4, 56–61; Ex. 1002 ¶¶ 150–151, 158). As to claim 1's backing layer and single adhesive polymer matrix layer of adhesive polymer matrix and estradiol, Petitioner points out that the monolithic TTS described in Mueller's Example 3 comprises (1) a self-adhesive, single-layer active substance matrix that contains estradiol, and (2) a backing layer. *Id.* at 29 (citing Ex. 1005 ¶¶ 25, 26, 56, and 57; Ex. 1002 ¶¶ 151–156). Next, as to the "coat weight of greater than about 10 mg/cm^2" element of claim 1, Petitioner asserts that Mueller describes the dried film of Example 3 as "having a coating weight of 115 g/m^2," which converts to 11.5 mg/cm^2. *Id.* at 29–30 (citing Ex. 1005 ¶¶ 56–57; Ex. 1002 ¶ 153).

Petitioner contends that Mueller also discloses that the TTS "includes greater than 0.156 mg/cm^2 estradiol," as further recited in claim 1. Pet. 30–31. Specifically, Petitioner reproduces a table from Dr. Brain's Declaration that sets forth the initial mass (g), the mass in the dried product (g), and the percent total dried product (%) for each ingredient of Mueller's Example 3 composition. *Id.* (citing Ex. 1002 ¶¶ 154–157). Dr. Brain calculates the amount of estradiol per unit area by first calculating the percent total of estradiol in the final dried product (1.50 %), and then multiplying that percentage by the final coat weight (11.5 mg/cm^2) of Mueller's dried TTS. Ex. 1002 ¶¶ 156–157 (citing Ex. 1005 ¶¶ 56-57). According to Petitioner, "[c]oat 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," as claimed. *Id.* at 31 (citing Ex. 1005 ¶¶ 56-57; Ex. 1002 ¶¶ 156–57; Ex. 1004, 126).

Finally, as to claim limitation "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," Petitioner contends that "results [in Mueller] 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." *Id.* at 31–32. Both flux values, Petitioner asserts, are "well within the range recited in the claim." *Id.*

At this stage of the proceeding, Patent Owner only challenges Petitioner's assertion that Mueller discloses claim 1's estradiol flux range. Patent Owner argues that institution should be denied because Petitioner fails to show that Mueller discloses a TTS that achieves the claimed estradiol flux of from about 0.0125 to about 0.05 mg/cm^2/day. Prelim. Resp. 41–48. Having reviewed the evidence and arguments, we agree with Patent Owner that Petitioner has not shown on this record a reasonable likelihood of prevailing in its assertion that claims 1, 2, 8, 10–16, and 18–23 of the '900 patent are anticipated by Mueller. Specifically, we agree with Patent Owner that Petitioner fails to show sufficiently for institution that Mueller teaches a TTS having the claimed estradiol flux range.

As explained above, Mueller teaches that a permeation study was conducted to compare TTS samples without hydrophilic additives to TTS samples with hydrophilic additives. Ex. 1005 ¶ 58. Relying on Figure 3 and Dr. Brain's Declaration, Petitioner asserts that the results of that study "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." Pet. 31. Petitioner provides a table summarizing "[t]he 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." *Id.* at 32–33. We reproduce that table here for ease of reference:

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

Pet. 33 (citing Ex. 1005, Fig. 3; Ex. 1002 ¶¶ 159–62, Ex. 1001, Fig. 1; Ex. 1004, 543–44).

We note that Petitioner does not provide the calculations necessary to calculate flux, but instead directs us to Dr. Brain's Declaration. *Id.* at 32–33 (citing Ex. 1002 ¶¶ 158–62). Dr. Brain states that flux may be calculated by first determining the slope at each data point, and then converting the slope from units of $\mu g/cm^2$/hour to units of mg/cm^2/day. Ex. 1002 ¶ 159. But Dr. Brain does not actually step us through those calculations. Nevertheless, both Petitioner and Dr. Brain represent that Mueller's TTS sample with hydrophilic additives has a flux of 0.015 mg/cm^2/day at 32 hours and 0.014 mg/cm^2/day flux at 48 hours. Pet. 33; Ex. 1002 ¶ 159.*

* Although Petitioner and Dr. Brain do not provide the calculations, we are able to obtain Petitioner's asserted flux value at 32 hours by first subtracting the estradiol permeation at 32 hours from that at 24 hours (16–11 = 5), and then dividing that number by the change in time (32–24 = 8). We then convert the resulting slope, 0.625 $\mu g/cm^2$/hour (5/8 = 0.625) to the claimed

Even putting aside Petitioner's and Dr. Brain's failure to fully explain their calculations, we agree with Patent Owner that Petitioner's reliance on Mueller's Figure 3 for teaching flux values fails to satisfy the reasonable likelihood standard.

Mueller does not disclose any numerical data for the comparative permeation studies in the written description, but instead states that the results of those permeation studies "are represented in FIG. 3." Ex. 1005 ¶ 58. Thus, Petitioner must rely on the estradiol permeation values shown graphically in Figure 3 to calculate flux values. Pet. 32–33 (citing Ex. 1005, FIG. 3). But, as Patent Owner points out and we agree, those estradiol permeation values cannot be reasonably ascertained from Figure 3. *See* Prelim. Resp. 42–48.

First, Petitioner does not establish at this stage of the proceeding that Figure 3 provides an accurate scale for estradiol permeation because the x-axis and y-axis of that figure are not perpendicular to each another. The deficiencies of Figure 3 are readily observable to the naked eye and when superimposed onto a grid, as provided in Dr. Williams's Declaration and reproduced below. As shown below, the intersection of the y-axis and the x-axis is greater than a 90 degree angle.

units of mg/cm^2/day by dividing 0.625 by 1000 and multiplying the resulting number by 24 (0.625/1000 x 24). This results in the alleged flux of 0.015 mg/cm^2/day flux at 32 hours.

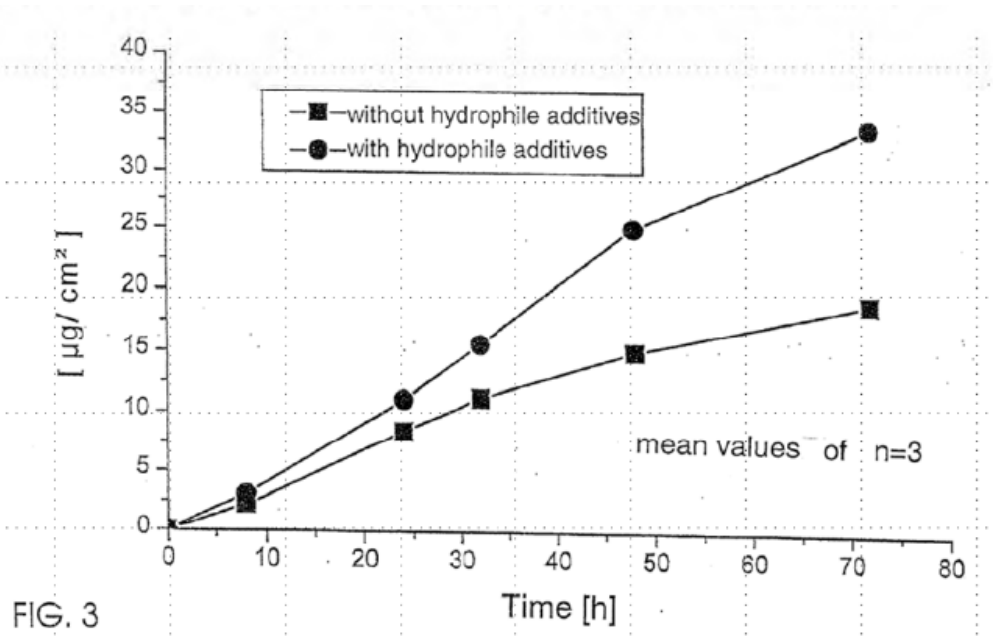

FIG. 3

Ex. 2001 ¶ 158.

Neither Petitioner nor Dr. Brain address how an ordinarily skilled artisan would interpret Figure 3, given these deficiencies of the graph. Instead, Petitioner and Dr. Brain set forth estradiol permeation values in a table, without explaining why or how an ordinarily skilled artisan would ignore or adjust for the imprecisions of Figure 3. *See* Pet. 33 (setting forth flux at 32 hours and 48 hours), 34 (setting forth average flux from 0 to 48 hours, 8 to 32 hours, and 24–48 hours); Ex. 1002 ¶¶ 127, 129.

Second, because of the greater than 90 degree angle between the x- and y-axes in Figure 3, it is not clear to us on this record that an ordinarily skilled artisan would have selected the same estradiol-permeation values as Petitioner for each time point provided in the graph. For example, Petitioner and Dr. Brain select an estradiol permeation of 16 µg/cm^2 at 32 hours. Pet. 33; Ex. 1002 ¶¶ 158–59. It is unclear to us, however, whether this value would change if only the y-axis is rotated to be perpendicular to the x-axis, or if only the x-axis is rotated, or if both axes are rotated to create a graph

with an accurate 90 degree angle. In addition, Petitioner and Dr. Brain do not address the impact on flux calculations if the estradiol permeation at 32 hours is slightly higher or slightly lower than 16 μg/cm^2.

For these reasons, we cannot say with any certainty on this record that Mueller's disclosure sufficiently supports Petitioner's flux calculations. We agree with Patent Owner, therefore, that Petitioner fails to show sufficiently for purposes of institution that Mueller teaches a TTS having an estradiol flux within the range recited in claim 1. Further, because claims 2, 8, 10–16, and 18–23 also require an estradiol flux within the range of about 0.0125 to about 0.05 mg/cm^2/day (either by their dependence on claim 1 or claim 16), Petitioner also fails to show sufficiently for purposes of institution that it would prevail in its assertion that Mueller anticipates those claims.

E. Asserted Obviousness Grounds

Petitioner contends that claims 1, 2, and 8–23 are unpatentable as obvious over Mueller in view of the Vivelle-Dot Label, Pet. 44–52, that claims 3–7 are unpatentable as obvious over Mueller, Vivelle-Dot Label, and Kanios, *id.* at 52–59, and that claims 1–23 are unpatentable as obvious over Mueller, Vivelle-Dot Label, Kanios, and Chien, *id.* at 59–63. It appears that each of these grounds of unpatentability, however, relies on Mueller for an alleged express teaching of an estradiol flux from about 0.0125 to about 0.05 mg/cm^2/day. *See* Pet. 44, 52, 59; Ex. 1002 ¶¶ 209–11 (for the ground of unpatentability based on Mueller and Vivelle-Dot Label, repeating tables of flux calculations based on Figure 3 of Mueller, and stating, "for the reasons discussed above, claims 1, 2, and 16 of the '900 patent are obvious in view of the teachings of Mueller"), *id.* ¶ 233 (as to the ground of unpatentability based on the teachings of Mueller, Vivelle-Dot Label, and

Kanios, stating that "Mueller Example 3 discloses each and every element of [the] independent claims 1 and 16"), *id.* ¶ 257 (as to the ground of unpatentability based on the teachings of Mueller, Vivelle-Dot Label, Kanios, and Chien, stating that "[a]s can be seen in Figure 3 of Mueller, the delivery system of Example 3 achieves an estradiol flux of about 0.0125 to about 0.05 mg/cm^2/day").

Accordingly, for the reasons set forth above, we are not persuaded that Petitioner establishes a reasonable likelihood that the subject matter of claims 1–23 would have been obvious over Mueller in combination with Vivelle-Dot Label, Vivelle-Dot Label and Kanios, or Vivelle-Dot Label, Kanios, and Chien.

To the extent that Petitioner's obviousness challenge to claims 1–23 based on Mueller, Vivelle-Dot Label, Kanios, and Chien does not rely on Mueller's Figure 3 for expressly teaching the claimed estradiol flux range, *see* Pet. 59–63, we nevertheless agree with Patent Owner that the record does not establish a reasonable likelihood that Petitioner would prevail on this ground. Specifically, Petitioner relies on Figure 5 of Chien for "expressly teach[ing] that increasing the coating thickness (or coat weight) of the adhesive polymer matrix increases estradiol flux." Pet. 60 (citing Ex. 1009, 5:20–28, FIG. 5; Ex. 1002 ¶ 265).

But as Patent Owner points out, Chien describes a multi-layer transdermal dosage form, but fails to identify the layer to which the "coating" data in Figure 5 refers. *See* Ex. 1009, 2:45–3:40; Prelim. Resp. 58–59. Chien states only that "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." Ex. 1009, 5:26–28.

The ambiguity in Chien's written description is particularly troubling because Chien describes each layer of the multi-layer dosage form as having a "coating," and explains that "[t]he respective coatings can be combined to make the final multi-layer dosage form by application of lamination technique under a constant pressure or sequential solvent casting technique." Ex. 1009, 9:30–33. Because it is unclear whether the coating thickness data of Figure 5 corresponds to the "coating thickness . . . of the adhesive polymer matrix," as recited in challenged claim 1, we agree with Patent Owner that Petitioner fails to show sufficiently for purposes of institution that claims 1–23 would have been obvious over the Mueller, Vivelle-Dot, Kanios, and Chien.

IV. CONCLUSION

Taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner fails to demonstrate a reasonable likelihood of prevailing at trial as to any challenged claim. Accordingly, the Petition is *denied*, and no trial is instituted.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*, and no trial is instituted.

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