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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/133,071	08/31/2011	Valerie Masini-Eteve	088734-0163	1127

22428 7590 11/15/2018

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EXAMINER	
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ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
11/15/2018	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte VALERIE MASINI-ETEVE

Appeal 2017-003027
Application 13/133,071[1]
Technology Center 1600

Before DONALD E. ADAMS, ERIC B. GRIMES, and RYAN H. FLAX, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This Appeal under 35 U.S.C. § 134(a) involves claims 1, 11, 12, and 18–21 (Final Act.[2] 2).[3] Examiner entered a rejection under 35 U.S.C. § 103(a). We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] Appellant identifies "Besins Healthcare Luxembourg SARL" as the real party in interest (App. Br. 3).
[2] Final Office Action mailed January 4, 2016.
[3] Pending claims 13–17 stand withdrawn from consideration.

STATEMENT OF THE CASE

Appellant's disclosure "relates to SERM[4]-containing pharmaceutical compositions, such as gels, and to methods of making and using the same" (Spec. 1:12–13). Claims 1, 11, and 18 are representative and reproduced below:

> 1. A pharmaceutical composition for topical administration to a skin surface for percutaneous delivery of *endoxifen* comprising a mixture of:
>
> (i) 0.01 to 10 % (w/w) of *endoxifen* or a pharmaceutically acceptable salt thereof,
>
> (ii) 60 to 80 % (w/w) of at least one monoalcohol,
>
> (iii) 0.01 to 10 % (w/w) of at least one penetration enhancer selected from the group consisting of *oleic acid, propylene glycol, and a mixture thereof*,
>
> (iv) 0.01 to 5 % (w/w) of at least one gelling agent,
>
> (v) 0.01 to 30 % (w/w) of at least one moisturizer, and
>
> (vi) q.s. 100 % (w/w) water,
>
> wherein the *composition does not contain isopropyl myristate and does not contain sodium hydroxide*.
>
> 11. A dose packet, unit dose packet or multiple dose packet containing a pharmaceutical composition according to claim 1.
>
> 18. A pharmaceutical composition according to claim 1, comprising 2 to 5 % (w/w) of endoxifen or a pharmaceutically acceptable salt thereof.

(App. Br. 18 (emphasis added).)

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[4] "The Selective Estrogen Receptors Modulators (SERMs) are a class of pharmacological agents formerly referred to as anti-estrogens, which are generally understood to be compounds capable of blocking the effect of estradiol without displaying any estrogenic activity of their own" (Spec. 1:15–18).

Claims 1 and 19–21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ahmad,[5] Williams,[6] Excerpt,[7] and Hsu.[8]

Claims 11 and 12 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ahmad, Williams, Excerpt, Hsu, and Salin-Drouin.[9]

Claim 18 stands rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ahmad, Williams, Excerpt, Hsu, and Taravella.[10]

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness?

FACTUAL FINDINGS (FF)

FF 1. Ahmad "relates to the use of endoxifen[11] in the treatment of mammalian diseases" and "to liposomes and other formulations such as complexes, vesicles, emulsions, micelles and mixed micelles of endoxifen, methods of preparation, and uses" (Ahmad ¶ 1; *see also* ¶ 85 ("Complexes can be in the form, *e.g.*, of . . . emulsions")).

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[5] Ahmad et al., WO 2008/070463 A2, published June 12, 2008.
[6] Williams et al., *Penetration enhancers*, 56 ADVANCED DRUG DELIVERY REVIEWS 603–618 (2004).
[7] *Making Solutions*, 93–105, Ch. 4, Cold Spring Harbor Laboratory Press (2003).
[8] Hsu et al., US 6,582,724 B2, issued June 24, 2003.
[9] Salin-Drouin, EP 1 634 583 A1, published Mar. 15, 2006.
[10] Taravella et al., US 2004/0175416 A1, published Sept. 9, 2004.
[11] "4-hydroxy-N-desmethyl-Tamoxifen (endoxifen)" (Ahmad ¶ 3).

FF 2. Ahmad discloses compositions for topical administration (Ahmad ¶ 18; *see* Final Act. 6).

FF 3. Ahmad discloses a "composition comprising endoxifen [] formulated in a hydroalcoholic[12] composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent" (Ahmad ¶ 21; *see id.* ¶ 20 ("the composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil"); *see also id.* ¶ 135 ("For percutaneous administration, the formulation or composition of [Ahmad's] invention containing endoxifen may be delivered in the form of . . . [a] gel"); *see* Final Act. 5–6).

FF 4. Ahmad's "composition or formulation . . . comprises an aqueous vehicle that permits solubilization of hydrophilic molecules, and promotes moisturization of skin" (Ahmad ¶ 140; *see id.* ("Aqueous vehicles include . . . purified water"); *see* Final Act. 6).

FF 5. Ahmad discloses that "[t]he amount of an aqueous vehicle preferably ranges between 0.1% to 65% by weight of the pharmaceutical composition, preferably between 15% to 50%, and more preferably between 25% to 40%" (Ahmad ¶ 140).

FF 6. Ahmad's compositions comprise "excipient additives, including . . . glycerine . . . [and] urea" (Ahmad ¶ 135; *cf.* Spec. 5: 25 ("The moisturizer may comprise glycerine"); Spec. 16: 1–27).

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[12] Ahmad discloses that "the term 'hydroalcoholic' as used in reference to a substance or composition indicates that [the] substance or composition comprises both water and alcohol" (Ahmad ¶ 66).

FF 7. Ahmad discloses that "the gelling agent is selected from the group consisting of polyacrylic acid, hydroxypropylcellulose and a cellulose derivative other than hydroxypropylcellulose" (Ahmad ¶ 26; *see also id.* ¶ 67; *cf.* Spec. 5: 22–23 ("The gelling agent may be selected from the group consisting of polyacrylic acids, cellulosics, and mixtures thereof"); Spec. 15: 1–17 ("examples of gelling agents")).

FF 8. Ahmad discloses that the gelling agent "may constitute between 0.1% to 20% by weight of [the] formulation depending on the nature of gelling agent, preferably between 0.5% to 10% and more preferably between 0.5% to 5%" (Ahmad ¶ 141; *see* Final Act. 6).

FF 9. Ahmad discloses that the "alcohol is ethanol or isopropanol, and constitutes in absolute form" (Ahmad ¶ 24; *see id.* ¶ 139 ("*ethanol may effectively contribute to the percutaneous absorption of endoxifen* by rapidly evaporating upon contact with skin" (emphasis added)); *see* Final Act. 6; *cf.* Spec. 5: 16–17 ("The monoalcohol may be selected from the group consisting of ethanol and isopropanol")).

FF 10. Ahmad discloses "[t]he amount of absolute nonaqueous vehicle in a gel formulation ranges from 35% to 99% by weight, preferably between 50% to 85% and more preferably between 60% to 75%" (Ahmad ¶ 139).

FF 11. Ahmad discloses that "[p]ercutaneous administration of the endoxifen composition . . . may be advantageous because this may reduce systemic drug exposure and the risks from non-specifically activating estrogen receptors throughout the body" (Ahmad ¶ 132).

FF 12. Ahmad discloses that "[t]he effectiveness of percutaneous drug administration depends on many factors, such as drug concentration, surface area of application, time and duration of application, skin temperature, skin

hydration, previous irradiation, physiochemical properties of the drug, and partitioning of the drug between the formulation and the skin" (Ahmad ¶ 134).

FF 13. Ahmad discloses that "to enhance percutaneous effectiveness, the compositions or complexes comprise penetration enhancers that improve percutaneous absorption," wherein such penetration "enhancers include but are not limited to . . . propoylene [sic] glycol,[13] fatty acids . . . and their derivatives . . . and mixture[s] thereof" (Ahmad ¶ 134; *see also id.* ¶ 138 ("In other embodiments, the composition . . . comprises one or more fatty acid esters as a penetration enhancer. One of the highly preferred examples of a fatty acid ester penetration enhancer is isopropyl myristate"); *see* Final Act. 6 (Ahmad discloses a "composition comprising penetration enhancers such as . . . fatty acids and fatty acid alcohol or mixtures thereof," wherein "isopropyl myristate is the preferred permeation enhancer" (emphasis omitted)); *cf.* Spec. 5: 19–20 ("The penetration enhancer may be selected

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[13] Appellant recognizes that, in discussing penetration enhancers, Ahmad misspelled propylene glycol, a penetration enhancer known to those of ordinary skill in this art prior to Appellant's filing date (App. Br. 11 (citing Ahmad ¶ 134); *see* FF 22). Nonetheless, Appellant contends "that when a prior art reference contains an obvious typographical error—as is the case here—'it cannot be said that one of ordinary skill in the art would do anything more than mentally disregard [the erroneous compound] as a misprint" (App. Br. 11 (alteration original) (citing *In re Yale*, 434 F.2d 666, 668–69 (CCPA 1970)); *see also* Reply Br. 3–5). In addition, Appellant contends that because Ahmad discusses "**poly**propylene glycol" in the context of additional excipients, a "skilled artisan would have interpreted [Ahmad's] typographical error[, made in the context of penetration enhancers, as] "'**poly**propylene glycol,'" an additional excipient in Ahmad, and not the known penetration enhancer, propylene glycol (App. Br. 11 (citing Ahmad ¶ 135); *see* Reply Br. 3–5).

from the group consisting of oleic acid, and propylene glycol"); *id.* 13:25–26 (Appellant's "composition . . . comprises a penetration enhancer with the proviso of isopropyl myristate"); *see also id.* 13:28–31 ("when the SERM is endoxifen . . . the composition of [Appellant's] invention preferably comprises a penetration enhancer with the proviso of isopropyl myristate").

FF 14. Ahmad discloses a

> hydroalcoholic composition compris[ing] endoxifen at about 0.01% to 0.20% by weight; isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight; alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight; aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight. In some embodiments, the wherein the percentage of components is weight to weight of the composition.

(Ahmad ¶ 23; *see also id.* ¶ 37 and 48: 4–15; *see* Final Act. 5–6.)

FF 15. Examiner finds that Ahmad does not disclose the meaning of "q.s 100% (w/w)" and relies on Excerpt to teach that "q.s. 100% (w/w) water[]" means add enough water to bring the total of amount of the formulation to 100% (Final Act. 7).

FF 16. Examiner finds that Ahmad does not disclose a composition comprising glycerine, a moisturizer, in the amount required by Appellant's claimed invention and relies on Hsu to make up for this deficiency in Ahmad (Final Act. 7; *see* FF 6).

FF 17. Hsu "relates generally to the topical and transdermal administration of pharmacologically active agents, and more particularly relates to permeation enhancer compositions for enhancing the permeability of skin or mucosal tissue to topically applied pharmacologically active agents" (Hsu 1: 16–20).

FF 18. Hsu discloses that an "enhancer composition may [] contain irritation-mitigating additives[, such as glycerin,] to minimize or eliminate the possibility of skin irritation or skin damage resulting from the enhancer, the drug to be administered, or other components of the composition," wherein "[t]he irritant-mitigating additive, if present, may be incorporated into the present enhancer compositions at a concentration effective to mitigate irritation or skin damage, typically representing not more than about 20 wt. %, more typically not more than about 5 wt. %, of the composition" (Hsu 11: 8–23).

FF 19. Examiner finds that, although Ahmad discloses that "permeation enhancers can include fatty acids and propylene glycol," Ahmad does not exemplify a "permeation enhancer [that] is a mixture of oleic acid and propylene glycol" (Final Act. 7).

FF 20. Williams discloses that "[p]ercutaneous drug absorption has been increased by a wide variety of long chain fatty acids, the most popular of which is oleic acid" (Williams 609: § 3.5).

FF 21. Williams discloses that "fatty acids have been used to improve transdermal delivery of, amongst others, estradiol" (Williams 610: § 3.5).

FF 22. Williams discloses that "[p]enetration enhancers tend to work well with co-solvents such as PG [(propylene glycol)] or ethanol. Synergistic effects are found between enhancers such as . . . oleic acid . . . with PG" (Williams 615: § 4; *see also id.* at 610: § 3.5; *see also id.* at Abstract ("propylene glycol, PG, [is] a common excipient in topically applied dosage forms")).

FF 23. Williams discloses:

> It is difficult to select rationally a penetration enhancer for a given permeant. Penetration enhancer potencies appear to be drug specific, or at best may be predictive for a series of permeants with similar physico-chemical properties (such as similar partition coefficients, molecular weights and solubilities). Some broad generic trends are apparent, such as the use of hydrocarbon monoterpenes for lipophilic permeants, but the level of enhancement expected for these agents is unpredictable.

(Williams 615: § 4.)

FF 24. Ahmad discloses that "[i]n the complexes, the active agent can be bound to the lipid by covalent, hydrophobic, electrostatic, hydrogen, or other bonds, and is considered bound even where the drug is simply entrapped within the interior of lipid structures" (Ahmad ¶ 85).

FF 25. Ahmad's compositions include "complexes with free and/or salts or esters of fatty acid," wherein the fatty acid may be "oleic acid ($C_{18:1}$)" (Ahmad ¶ 89).

ANALYSIS

The combination of Ahmad, Williams, Excerpt, and Hsu:

Based on the combination of Ahmad, Williams, Excerpt, and Hsu, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious

> to modify the composition taught by Ahmad et al[.] by using the amount of glycerine i.e.[,] 5-20% (w/w) as an irritation-mitigating additive, taught by Hsu et al[.] in order to . . . minimize or eliminate the possibility of skin irritation or skin damage resulting from the enhancer and the drug to be administered, and further substitute the isopropyl myristate taught by [Ahmad]

> . . . with the mixture of penetration enhancers i.e.[,] the oleic acid and propylene glycol taught by Williams.

(Final Act. 8; *see* FF 1–23.) We find no error in Examiner's prima facie case.

Appellant contends, however, that the evidence relied upon by Examiner fails to provide a person of ordinary skill in this art with a reasonable expectation of success in formulating an endoxifen composition for topical administration, wherein "oleic acid (OA), propylene glycol (PG), [or] a mixture thereof" is substituted for Ahmad's preferred penetration enhancer, isopropyl myristate (IPM) (*see* App. Br. 9; *see also id.* at 10 ("Williams does not provide any reasonable expectation that OA would be an effective enhancer for endoxifen"); Reply Br. 3). In this regard, Appellant contends that Ahmad does not expressly disclose OA, PG, or a mixture thereof as a penetration enhancer for endoxifen and "Williams' explicitly discusses the high level of unpredictability in the art with regard to the selection of an effective penetration enhancer for a given drug, and expressly advises against generalizing penetration enhancers across drug classes as [] Examiner has done here" (App. Br. 10; Reply Br. 6–7; *see* FF 23). We are not persuaded.

Ahmad discloses an endoxifen composition comprising penetration enhancers, such as fatty acids, and discloses a preference for, and exemplifies the use of, the fatty acid ester, isopropyl myristate (FF 13). Given Ahmad's disclosure of a variety of penetration enhancers useful in Ahmad's compositions, we decline to limit Ahmad to its preferred and exemplified penetration enhancer, isopropyl myristate. *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976) (a reference disclosure is not limited only to its

preferred embodiments, but is available for all that it discloses and suggests to one of ordinary skill in the art).

Given Ahmad's disclosure of the use of fatty acid penetration enhancers, one of ordinary skill in this art would reasonably look to Williams' disclosure of "penetration enhancers," and, specifically, fatty acid penetration enhancers (FF 21). In this regard, Williams discloses that "oleic acid" is "the most popular" choice of a fatty acid penetration enhancer (FF 20).

Appellant recognizes that Ahmad expressly discloses the use of oleic acid to formulate endoxifen complexes for transdermal delivery (*see* App. Br. 9; Reply Br. 5–6; *see also* FF 24–25). Thus, the evidence of record supports the reasonable expectation of those of ordinary skill in this art that the presence of oleic acid in a transdermal endoxifen composition would *not* inhibit the transdermal delivery of endoxifen (*cf.* App. Br. 14; Reply Br. 7 (citing Piette Dec.[14] ¶¶ 7–8); *see also* Reply Br. 5 (citing Piette Declaration) ("Given such unpredictability, Ahmad's generic disclosure of a 'fatty acid' penetration enhancer cannot provide a reasonable expectation that oleic acid could be successfully used in endoxifen formulations as claimed"); Reply Br. 10 (Although "Williams teaches oleic acid is the most popular permeation enhancing fatty acid. . . . [Piette's] experiments show that IPM and OA are not *per se* interchangeable")).

In addition, Ahmad discloses that ethanol facilitates transdermal delivery of endoxifen (FF 9). In this regard, we note that Williams discloses that "[p]enetration enhancers[, such as oleic acid,] tend to work well with co-solvents such as PG [(propylene glycol)] or ethanol" and "[s]ynergistic

[14] Declaration of Paul Piette, PharmD., signed Sept. 1, 2015.

effects are found between enhancers such as . . . oleic acid . . . with PG" (FF 22).

Therefore, we find no error in Examiner's conclusion that a person of ordinary skill in this art would have found it prima facie obvious to substitute oleic acid, the most popular choice of fatty acid penetration enhancer, and propylene glycol, a known co-solvent that acts synergistically with oleic acid, for the isopropyl myristate in Ahmad's preferred composition. Thus, we agree with Examiner's conclusion that the combination of Ahmad, Williams, Excerpt, and Hsu provides a person of ordinary skill in this art with a reasonable expectation of successfully formulating an endoxifen composition for topical administration within the scope of Appellant's claimed invention (*see* FF 1–25). For the foregoing reasons, we are not persuaded by Appellant's contention that the combination of Ahmad, Williams, Excerpt, and Hsu fails to provide a person of ordinary skill in this art with a reasonable expectation of success in formulating a composition within the scope of Appellant's claimed invention (*see* App. Br. 9; *see also id.* at 9–16). *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) ("Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success").

There is no doubt that Ahmad is the closest prior art on this record (*see* Ans. 17). Piette does not provide a comparison against the closest prior art, Ahmad (*see id.*; *see also id.* at 18; *cf.* Piette Dec. ¶¶ 7–8; Reply Br. 9 ("Appellant does not rely on the results with OA/4-OHT[15] formulations as predictive of OA/endoxifen formulations; to the contrary, Appellant relies

[15] "4-OH tamoxifen" (Spec. 30:32). *Cf.* footnote 11, *supra* ("4-hydroxy-N-desmethyl-Tamoxifen (endoxifen)" (Ahmad ¶ 3).)

on the data to demonstrate a general ***unpredictability*** in the field"). *See In re Fenn*, 639 F.2d 762, 765 (CCPA 1981) ("comparative testing must be between the claimed invention and the closest prior art").

Piette does not provide data based on endoxifen compositions, but instead tests 4-OHT compositions[16] (Piette Dec. ¶ 7; *cf.* Ans. 18; *see also* Ans. 23 ("4-OHT and endoxifen have different physico-chemical properties")). Further, Piette's study uses two different concentrations of *ethanol, a known facilitator of permeation* (FF 9): (a) 37.38% of 96% ethanol in "4-OHT Formulations with OA" and (b) 72% of absolute[17] ethanol in "4-OHT Formulations with IPM" (Piette Dec. ¶ 7; *cf.* Ans. 18). In addition, Piette's "4-OHT Formulations with OA" comprise "Alpha-tocopherol," whereas this ingredient is excluded from Piette's "4-OHT Formulations with IPM" (Piette Dec. ¶ 7; *cf.* Ans. 18). As Examiner explains, "[a]lpha-tocopherol is not present in the formulations of Ahmad" and "is not disclosed in . . . [Appellant's] [S]pecification as well" (Ans. 18). Thus, Piette's Declaration is "not commensurate in scope with [Appellant's] claimed invention" (Ans. 18). *In re Dill*, 604 F.2d 1356, 1361 (CCPA 1979) ("[E]vidence presented to rebut a prima facie case of obviousness must be commensurate in scope with the claims to which it pertains").

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[16] Endoxifen and 4-OH tamoxifen (4-OHT) are metabolites of Tamoxifen (App. Br. 13).

[17] Because Piette does not identify a lower percent alcohol in this formulation, a person of ordinary skill in this art would consider this ethanol to be absolute (*see* FF 9).

In addition, we recognize Piette's reference to Lee[18] who "evaluated the relative efficiency of skin permeation of 4-OHT and [endoxifen] in vitro, and tested oleic acid (OA) as a permeation-enhancer" (Lee 61). As Piette acknowledges, Lee does not demonstrate Appellant's and Piette's asserted *inhibitory* effect of OA on permeation of 4-OHT (*see* Piette Dec. ¶ 9; *cf.* App. Br. 14; Reply Br. 7–8; Piette Dec. ¶ 7). To the contrary, Lee discloses that the addition of 1%–5% *OA* to compositions comprising 4-OHT or endoxifen *increased* both the *absorption and total penetration of both 4-OHT and endoxifen* (Lee 64 (emphasis added)).

In view of the foregoing, we note that Piette confirms that formulations and experimental conditions are important in assessing the effectiveness of penetration enhancers for any particular reagent (Piette Dec. 5: n. * ("The difference in the reported effect of [Lee's] OA on 4-OHT permeation is believed to stem from the different formulations tested and different experimental conditions"); *cf.* Reply Br. 8 (citing Ans. 21 and 30) (Examiner's "assertion [relating to the 'different components and different amounts' in the formulations set forth in Piette's Declaration] is inaccurate, because the effects of OA and IPM can be compared in these experiments")). Piette and Appellant both compare the results of Piette's Experiments 1 and 2 asserting that IPM and OA are not interchangeable and

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[18] Lee et al., *In vitro human skin permeation of endoxifen: potential for local transdermal therapy for primary prevention and carcinoma in situ of the breast*, 3 Breast Cancer: Targets and Therapy 61–70 (2011). Appellant contends that Lee, which published after the priority date of Appellant's application "is based on scientific facts that were in existence at the time the application was filed . . . and that did not change between the time the application was filed and the time Lee was published" (App. Br. 13, n. 1; *see also* Reply Br. 11).

that one formulation inhibits transdermal penetration and the other does not (*see* Reply Br. 9 ("Even though the experiments used 4-OHT, the data still show that for a given drug IPM and OA are not interchangeable"); *id.* at 9 ("Appellant does not rely on the results with OA/4-OHT formulations as predictive of OA/endoxifen formulations; to the contrary, Appellant relies on the data to demonstrate a general ***unpredictability*** in the field"); *see generally* Piette Dec. ¶ 7; App. Br. 14; Reply Br. 7–8). Therefore, we are not persuaded by Appellant's contention that "[a]s discussed in the Piette Declaration, such a comparison is possible because 'OA is the only tested variable in [Experiment 1]' and 'IPM is the only tested variable in [Experiment 2]'" (Reply Br. 8). For the foregoing reasons, we are not persuaded by Appellant's assertion that Examiner's "concerns are unfounded" (*id.*). Instead, we find that the evidence on this record supports Examiner's assertion that "[i]n order for the data in the Declaration to compare OA vs IPM, [as Appellant and Piette have done,] the components and their amounts have to be the same [in] each formulation" (Ans. 22; *cf.* Piette Dec. 5: n. *).

Notwithstanding Appellant's assertion to the contrary, we find no evidence on this record supporting Appellant's intimation that the experiments set forth in the Piette Declaration represent a "direct ***or indirect*** comparison" (*see* Reply Br. 8–9 (citing MPEP § 716.02(b)), that is sufficient to outweigh the preponderance of evidence on this record supporting Examiner's conclusion of obviousness. *See Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991) (The weight of the secondary considerations, as here, may be of insufficient weight to override a determination of obviousness based on primary considerations). Thus, for

the reasons set forth above, we are not persuaded by the comparative evidence set forth in Piette's Declaration or Appellant's reliance thereon.

Lee, which Appellant concedes "is based on scientific facts that were in existence at the time the application was filed . . . and did not change between the time the application was filed and the time Lee was published" (App. Br. 13, n. 1), further explains that, although

> [i]t is not clear why [endoxifen] benefited more from the addition of OA than 4-OHT, [] this [benefit] may be related to a difference in their structure. [*Endoxifen*] *is smaller and more polar than 4-OHT because one methyl group at a tertiary amine is replaced with a hydrogen, resulting in a secondary amine that is more hydrophilic than the tertiary amine of 4-OHT.* Because OA appears to make the stratum corneum fluidic and ethanol gives a continuous driving force, [Endoxifen] may move faster through the skin than 4-OHT. The amine group of [Endoxifen] may have a favorable balance of hydrophilic and hydrophobic properties to deal with the stratum corneum, which would allow [Endoxifen] to transverse the stratum corneum more easily. *The results here agree with previous findings using hairless rat skin, which showed that the co-solvent system of OA-ethanol-water efficiently increased skin permeation of both lipophilic and hydrophilic drugs.*

(Lee 66–67 (emphasis added); *see also* Williams 610 § 3.5 ("fatty acids . . . can be used to promote delivery of both lipophilic and hydrophilic permeants").)

Although Lee discloses that endoxifen benefited more from the addition of OA than 4-OHT (Lee 66–67), Lee established that the addition of 1%–5% *OA* to compositions comprising 4-OHT or endoxifen *increased* both the *absorption and total penetration of both 4-OHT and endoxifen* (Lee 64 (emphasis added)). We find no requirement in Appellant's claimed invention of a particular "benefit" from the choice of OA as the penetration

enhancer. In addition, as discussed above, Lee explains that the differences in the hydrophilic and hydrophobic properties, as well as, the structure of endoxifen relative to 4-OHT contribute to the different benefits, which is supported by Williams and the "previous findings" discussed in Lee (*see* Lee 66–67 (emphasis added); *see also* Williams 610 § 3.5 ("fatty acids . . . can be used to promote delivery of both lipophilic and hydrophilic permeants"). Therefore, we are not persuaded by Appellant's contention that "Lee's conclusion on page 66 that '[i]t is ***not clear*** why [endoxifen] benefited more from the addition of OA than 4-OHT' (emphasis added) demonstrates an unpredictability in the field of transdermal drug delivery" (Reply Br. 11 (emphasis and alteration original)).

For the foregoing reasons, we find the evidence relied upon by Examiner supports a conclusion of obviousness and that Appellant's Declaratory evidence fails to overcome Examiner's prima facie case. *Ryko Mfg.*, 950 F.2d at 719. For the reasons set forth above, we are not persuaded Appellant's contentions based on the Piette Declaration.

The combination of Ahmad, Williams, Excerpt, Hsu, and Salin-Drouin:

Examiner finds that the combination of Ahmad, Williams, Excerpt, and Hsu "do not teach a dose packet, unit dose packet or multiple dose packet and dispenser, and optionally with hand pump" and relies on Salin-Drouin to make up for this deficiency (Final Act. 9–10).

Based on the combination of Ahmad, Williams, Excerpt, Hsu, and Salin-Drouin, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to modify the composition suggested by the combination of Examiner finds that the

combination of Ahmad, Williams, Excerpt, and Hsu "to provide the composition in a dispenser or a unit dose packet or multiple dose packets . . . to make the application easier for the patient who is taking said composition" (Final Act. 10).

Having found no error in Examiner's combination of Ahmad, Williams, Excerpt, and Hsu, we are not persuaded by Appellant's contention that Salin-Drouin "does not cure [Appellant's asserted] deficiencies of the cited primary references" (App. Br. 16).

The combination of Ahmad, Williams, Excerpt, Hsu, and Taravella:

Examiner finds that the combination of Ahmad, Williams, Excerpt, and Hsu "do not teach the amount . . . of endoxifen recited in [Appellant's] claim 18" and relies on Taravella to make up for this deficiency (Final Act. 10–11).

Based on the combination of Ahmad, Williams, Excerpt, Hsu, and Taravella, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious, in view of Taravella, to adjust, through routine optimization, the amounts taught by the combination of Ahmad, Williams, Excerpt, and Hsu (Final Act. 11–12). Having found no error in Examiner's combination of Ahmad, Williams, Excerpt, and Hsu, we are not persuaded by Appellant's contention that Taravella "does not cure [Appellant's asserted] deficiencies of the other cited references" (App. Br. 16).

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness.

The rejection of claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ahmad, Williams, Excerpt, and Hsu is affirmed. Claims 19–21 are not separately argued and fall with claim 1.

The rejection of claim 11 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ahmad, Williams, Excerpt, Hsu, and Salin-Drouin is affirmed. Claim 12 is not separately argued and falls with claim 11.

The rejection of claim 18 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ahmad, Williams, Excerpt, Hsu, and Taravella is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED