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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte JUN LIAO, TAKITO SHIMA, PUCHUN LIU, and STEVEN DINH

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Appeal 2020-001376
Application[1] 14/208,348
Technology Center 1600

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Before RICHARD M. LEBOVITZ, RYAN H. FLAX, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to transdermal drug delivery systems for tertiary amine drugs, which have been rejected as obvious. Oral argument was held on September 14, 2020. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

STATEMENT OF THE CASE

Appellant's Specification acknowledges that "[t]he use of a transdermal drug delivery system, for example, a patch comprising a

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Noven Pharmaceuticals, Inc. (Appeal Br. 3.)

pressure-sensitive adhesive containing a drug, as a means of delivering drug through the skin is well known." (Spec. 1.) Appellant's Specification explains: "[h]owever, there remains a need for transdermal drug delivery systems designed for the delivery of specific classes of drugs, such as tertiary amine drugs, including rivastigmine, fentanyl and rotigotine . . . [and] over an extended period of time, such as over a period of time of 3 days, or 7 days, or longer." (*Id.*) Appellant's invention concerns such a drug delivery system.

Claims 1–19, 22–28, 31, and 32 are on appeal. Claims 1 and 22 are illustrative and read as follows:

> 1. A transdermal drug delivery system comprising:
>
> a polymer matrix formed by blending the free base form of a tertiary amine drug and at least one carboxyl group-containing compound, wherein the relative amounts of free base and carboxyl group-containing compound is such that greater than 50% of the free base is associated with a carboxylic acid group to form a salt, and
>
> a backing layer,
>
> wherein the transdermal drug delivery system releases drug upon application to skin, and is effective to deliver a therapeutically effective amount of the tertiary amine drug through skin for at least 3 days.
>
> 22. A transdermal drug delivery system comprising a polymer matrix comprising the free base form of a tertiary amine drug, a rate-controlling membrane, and a face adhesive comprising a carboxyl group-containing compound, wherein the rate controlling membrane is disposed between the polymer matrix and the face adhesive, and wherein the system is effective to deliver a therapeutically effective amount of the tertiary amine drug through skin for at least 3 days.

(Appeal Br. 27, 30.)

The prior art relied upon by the Examiner is:

Name	Reference	Date
Kochinke	US 5,613,958	Mar. 25, 1997
Breitenbach	WO 2013/072062 A1	May 23, 2003
Kanios	US 7,063,859 B1	June 20, 2006
Audett	US 2007/0098771 A1	May 3, 2007
Gargiulo	US 2007/0128263 A1	June 7, 2007
Yum	US 2009/0060986 A1	Mar. 5, 2009
Chan et al., *Transdermal Delivery of Treatment for Alzheimer's Disease*, 25(9) Drugs Aging ,761–775 (2008)		
Duro-Tak and Gelva Transdermal Pressure Sensitive Adhesives: Product Selection Guide, Henkel (Sept. 2013)		

The following grounds of rejection by the Examiner are before us on review:

Claims 1–14 and 16–19[2] under 35 U.S.C. § 103[3] as unpatentable over Gargiulo, Duro-Tak, Chan, Audett, and Kochinke.

Claims 1–19 and 31[4] under 35 U.S.C. § 103(a) as unpatentable over Gargiulo, Duro-Tak, Chan, Audett, Kochinke, and Breitenbach.

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[2] We conclude that the Examiner's recitation of claim 32 in this rejection is an inadvertent error because that claim depends from independent claim 22, which the Examiner did not indicate is obvious over only Gargiulo, Duro-Tak, Chan, Audett, and Kochinke.

[3] The AIA amendments to § 103 took effect on March 16, 2013. The Application on Appeal was filed on March 13, 2014, based on an Application filed March 15, 2013. Although we cite to the post-AIA version of § 103, the current law and respective pre-AIA law are, in all aspects relevant to this Decision, the same.

[4] We conclude that the Examiner's recitation of claim 32 in this rejection is an inadvertent error as well because that claim depends from independent claim 22, which the Examiner did not indicate is obvious over only Gargiulo, Duro-Tak, Chan, Audett, Kochinke, and Breitenbach.

Claims 1–14, 16–19, 22–28, 31, and 32 under 35 U.S.C. § 103(a) as unpatentable over Gargiulo, Duro-Tak, Chan, Audett, Kochinke, Kanios, and Yum.

DISCUSSION

I. Claim 1 and dependent claims thereof

The Examiner interprets claim 1's "wherein" clause as not "impart[ing] to the actual matrix which is recited [in the other portions of the claim] any particular structure or physical requirements aside from the explicitly recited matrix components." (Final Action 3.) Consequently, the Examiner concludes that the wherein clause is "an intended use, rather than affirmative limitation of the matrix otherwise fully set forth by the claim[]." (*Id.*)

With the foregoing interpretation in mind, the Examiner finds that Gargiulo teaches a transdermal therapeutic system (TDS) having a silicone adhesive layer and a polymeric matrix containing the tertiary amine, rivastigmine, with a carboxylate-containing acrylate copolymer that has free carboxylate groups, such as DUROTAK 387-2353. (Final Action 4–5 (relying on DUROTAK for confirmation that this compound has free carboxylate groups).) The Examiner finds that a specific embodiment disclosed by Gargiulo "contains a substrate having a coat weight of 6mg/cm^2 of a composition containing (all percentages are by weight) 30% free base rivastigmine, 49.9% DUROTAK 387-2353, 20% PLASTOID B as a thickener, and 0.1 % Vitamin E as an antioxidant, as well as a silicone adhesive layer. [0092-101]." (*Id.* at 4.) The Examiner also finds that Gargiulo teaches that dosage amounts of the active ingredient, e.g., rivastigmine, as well as other patch components and patch dimensions can

be adjusted "to provide appropriate dosages and treatment durations, including once daily administration." (*Id.*; *see also id.* at 10 (citing Gargiulo ¶¶ 71–82).) According to the Examiner, such disclosure "would suggest modifying the relative amounts of each of the rivastigmine and carboxylate-containing acrylate copolymer," to achieve duration of treatment periods of time up to and including three and seven day periods, and doing so would be prima facie obvious to "reduce application intervals and improve patient compliance." (*Id.* at 5–6, 10.)

The Examiner finds that Chan, Audett, and Kochinke collectively teach that it was known that the amount of a drug incorporated into the TDS, as well as the coating weight, are result-effective variables as to the dosage amount to be delivered and duration of therapy. (*Id.* at 7–8.) The Examiner finds that Chan "specifically indicat[es] that the rate of release from a transdermal patch directly corresponds to the amount of drug included in the device, while also describing alternative transdermal delivery devices capable of delivering alternative agents useful in the treatment of Alzheimer's Disease as capable of delivering drug for seven days. (Pg. 770-71)." (*Id.* at 7.) In addition, the Examiner finds that Audett teaches including the active ingredient from about 1–20% by weight of the device and selection of additional components "provides transdermal drug delivery systems with the proper adhesive properties for effective transdermal delivery of agents contained therein for periods of 24 hours, 3, or even 7 days." (*Id.*) The Examiner finds that Kochinke teaches

> the duration of the delivery phase for transdermal drug delivery devices is determined by the total amount of drug included in the system, which depends on the thickness of and drug concentration within the reservoir as well as the delivery rate

> which depends on the drug itself, the composition of the remainder of the device, and the skin permeability of the drug itself.

(*Id.*) The Examiner concludes that it would have been obvious to optimize the amount of rivastigmine and the DUROTAK of Gargiulo to achieve at least 3 days drug delivery in order to increase patient compliance. (*Id.* at 10.) Regarding the claimed salification of the free base and carboxylic acid, the Examiner contends that "[s]ince modifications to the amounts of active and excipients included in transdermal drug delivery systems are explicitly taught by Gargiulo, the modification of these precise parameters [to achieve the recited salification minimum] claimed by applicants cannot be considered an non-obvious modification of the prior art." (*Id.*)

The Examiner further finds that Gargiulo teaches the TDS can have a polyethylene backing layer that is impermeable to the active agent. (*Id.* at 5.)

We do not agree with the Examiner's conclusion that the prior art relied upon by the Examiner renders the claimed TDS obvious.

It is true that Gargulio teaches that varying the nature and amount of excipients and active ingredients is a known way to adjust plasma profiles of the active agent. (Gargiulo ¶ 71.) Gargiulo further teaches that formulating a TDS should take into consideration the rate of release of an active agent as well as lag or delay time, improving patient compliance, and reducing application intervals. (*Id.* ¶¶ 75–81.) However, as Appellant notes, "Gargiulo is directed to providing 'once a day' products" (Appeal Br. 18; Gargiulo ¶¶ 70, 89), not a TDS that can be adhered for multiple days and provide a therapeutically effective amount of drug for multiple days.

In particular, Gargiulo teaches a goal of achieving a plasma concentration of 1 to 30 ng/ml of rivastigmine between two to sixteen hours after application of the TDS with a variation of the drug concentration in blood plasma over 24 hours ("AUC_{24h}") between about 25 to 450 ng h/ml with a TDS in the range of 2 to 50 cm^2 (Gargiulo ¶¶ 21, 53, 69–70) and provides an example of a TDS to achieve that result (*Id.* ¶¶ 92–97). Although varying the nature and amounts of excipients and the amount of active ingredient are known parameters that can be modified in ways that might change the time course of drug absorption, or its bioavailability, i.e., pharmacokinetic properties, Gargiulo does not provide a reasonable expectation of success as to a modification of amounts of any particular ingredient that would provide for delivery of a therapeutically effective amount of a tertiary amine drug through the skin to achieve the one day goal, much less the at least three days required by claim 1. Indeed, Gargiulo indicates that determining a TDS that could achieve the described results was only after "extensive testing." (*Id.* ¶ 84.) The only guidance in Gargiulo concerning ranges that might accommodate the once a day goal is the thickness of reservoir layer to adhesive layer (*id.* ¶ 50), an adhesive force of the TDS (*id.* ¶ 51), the size range of the TDS (*id.* ¶ 52), and the saturation solubility of active ingredient in the silicone adhesive (*id.* ¶¶ 43–45). Thus, we agree with Appellant, that "Gargiulo does not indicate which modifications of which parameters will achieve an intended impact on a specific pharmacokinetic property." (Appeal Br. 18.) In other words, Gargiulo does not indicate, with a reasonable expectation of success, to what extent the active ingredient or adhesive should be varied to achieve even the 24 hour goal. Thus, we agree with Appellant that "Gargiulo provides no

guidance whatsoever or expectation of success regarding TDSs that are effective over longer periods of time, such as at least 3 days, as recited in the instant claims." (Appeal Br. 18.) And, Gargiulo provides no indication that the relative amounts of free base and carboxyl group-containing compounds has any effect on drug delivery of the TDS.

We note that Appellant argues, relying on evidence in the Specification (Example 1), that "[i]n the cited example of Gargiulo, the ratio [of the free base amine drug and carboxyl group-containing compound] results in less than 50% salification." (Appeal Br. 16.) Appellant indicates that the Exelon patch in Example 1 (*see* Spec. 28) includes the same DUROTAK composition that is in Gargiulo's TTS#1. (*Id.* (citing Gargiulo ¶¶ 94–95).) Appellant notes, however, that in the Specification Example, the weight percentage of DUROTAK (70%) is higher than in Gargiulo's example (49.9%). (*Id.*) The amount of rivastigmine is the same in both (30%). (*Id.*) Appellant explains that the Example in the Specification shows that at a higher weight percentage of DUROTAK than in Gargiulo, the salt percentage formed is less than 49%. (*Id.*) Thus, Appellant indicates that "the cited example of Gargiulo does not even accidentally read on the claims." (*Id.* at 17.)

Furthermore, we do not find Chan, Audett, or Kochinke individually or together, provide a reason to modify the TDS of Gargiulo so that "the relative amounts of free base and carboxyl group-containing compound is such that greater than 50% of the free base is associated with a carboxylic acid group to form a salt," much less to arrive at a TDS with such relative amounts that is effective to deliver a therapeutically effective amount of the tertiary amine drug through skin for at least 3 days. The Examiner did not

point to a teaching in any of these references to suggest that it was known to adjust the association of the free base of a tertiary amine with a carboxyl group containing compound in order to achieve delivery of the amine in a therapeutically effective amount for at least three days. Consequently, the Examiner did not establish that this relationship was a known result effective variable such that optimization thereof would have been obvious as a matter of routine experimentation.

Moreover, we agree with Appellant that the paragraph of Audett the Examiner relies on in the rejection (Audett ¶ 51) does not, as the Examiner indicates, teach a TDS that is capable of delivering a therapeutically effective amount of a drug for at least three days. (Appeal Br. 19.) Rather, this paragraph of Audett teaches "proper selection of drug and other ingredients (such as permeation enhancers" can be made to achieve a TDS "with the *right adhesive properties* . . . such as 24 hours, 3 day, or even 7 day application." (Audett ¶ 51 (emphasis added).) That description does not provide one of ordinary skill in the art with sufficient information regarding the parameters of Gargiulo's TDS to modify to achieve a TDS "effective to deliver a therapeutically effective amount of the tertiary amine drug through skin for at least 3 day" with a reasonable expectation of success, much less to arrive at a TDS with 50% of the free base of the drug being associated with a carboxylic acid group to form a salt.

In addition, we disagree with the Examiner that Chan describes a device that is capable of delivering alternative agents useful in the treatment of Alzheimer's Disease *for seven days*. Chan indicates that a phase III clinical trial "is evaluating advanced adhesive polymer matrix technology to provide 7-day transdermal delivery of phenserine." (Chan 771.) However,

as Appellant correctly observes, Chan "does not discuss any specific components" of that TDS other than to mention it includes a different drug than what is claimed. (*Id.* at 20.) Thus, we also do not see how Chan's description would provide one of ordinary skill in the art with sufficient information regarding the parameters of Gargiulo's TDS to modify to achieve a TDS "effective to deliver a therapeutically effective amount of the tertiary amine drug through skin for at least 3 day" with a reasonable expectation of success, much less to arrive at a TDS with 50% of the free base of the drug being associated with a carboxylic acid group to form a salt.

Finally, the portion of Kochinke relied on by the Examiner, indicates, in pertinent part:

> The duration of the delivery phase is determined by the total amount of drug in the system which is in turn determined by the reservoir thickness and drug concentration in the reservoir; and the delivery rate, which is a function of the drug to be delivered, the composition of the drug delivery device, and the skin permeability of the drug.

(Kochinke 16:26–37). Such a general reference to drug delivery rate being a function of the drug to be delivered, the composition of the drug delivery device, and the skin permeability of the drug would not provide one of ordinary skill in the art with sufficient information regarding the parameters of Gargiulo's TDS to modify to achieve a TDS "effective to deliver a therapeutically effective amount of the tertiary amine drug through skin for at least 3 day" with a reasonable expectation of success, much less to arrive at a TDS with 50% of the free base of the drug being associated with a carboxylic acid group to form a salt.

At best, the references suggest a number of possible parameters, albeit those parameters do not include the relative amounts of free base and

carboxyl group-containing compound, that might be modified in an effort to try to achieve a TDS that is effective to deliver a therapeutically effective amount of the tertiary amine drug through skin for at least 3 days, without indicating which of the various parameters were critical and no direction as to which of many possible choices is likely to be successful. Thus, we conclude the references provide an invitation to experiment that does not equate with obviousness under § 103. *See In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

Consequently, we do not affirm the Examiner's rejection of claims 1–14 and 16–19 as obvious over Gargiulo, Duro-Tak, Chan, Audett, and Kochinke.

The Examiner relies on Breitenbach in rejecting claims 1–19 and 31 only as teaching that it was "well-known at the time of the instant application to include plasticizers in transdermal PSA matrices containing rivastigmine." (Final Action 11.) That finding, even if true, does not cure the deficiencies just discussed. Consequently we also do not affirm the Examiner's rejection of claims 1–19 and 31 as obvious over Gargiulo, Duro-Tak, Chan, Audett, Kochinke, and Breitenbach.

II. Claim 22 and dependent claims thereof

Claim 22 requires a TDS to include a rate-controlling membrane, and a face adhesive including a carboxyl group-containing compound, and a separate polymer matrix that includes the free base from of a tertiary amine drug. An additional structural requirement of the TDS required by claim 22 is that the rate-controlling membrane be disposed between the polymer matrix and the face adhesive layer. Unlike claim 1, claim 22 does not have a

salification limitation. Claim 22, like claim 1 however, does require that the TDS structure with the claimed elements "is effective to deliver a therapeutically effective amount of the tertiary amine drug through skin for at least 3 days."

The Examiner finds that the claim does not provide for any "particularly limiting definition or configuration of 'rate controlling membrane'." (Final Action 4.) The Examiner concludes that "any membrane which is described as contributing to the effective delivery of active agent from a polymeric matrix will be considered a 'rate controlling membrane.'" (*Id.*)

The Examiner finds that Kanios teaches

> that rate controlling membranes and drug permeable adhesive layers are known to be usefully employed in reservoir-type transdermal drug delivery devices, where the active agent is isolated from the adhesive used to affix the device to the user such as those disclosed by Gargiulo, as means to effectively control the delivery rate of the active agent and attachment of the device to the user. (Col.1, L.37-65).

(Final Action 13.)

The Examiner finds that Yum teaches a TDS where the polymeric matrix is separated from the face adhesive by a rate controlling membrane. (*Id.*)

We again disagree with the Examiner's conclusion of obviousness. Our conclusion rests on the fact that, contrary to the Examiner's position (Ans. 18), Gargiulo describes a TDS that is not designed to include a rate controlling membrane.

As indicated in Chan "there are two types of transdermal delivery systems: a drug reservoir-in-adhesive system and a drug matrix-in-adhesive

system. (Chan 770; *see also* Kanios 1:38–39.) Each of the structures are illustrated in the figures below.

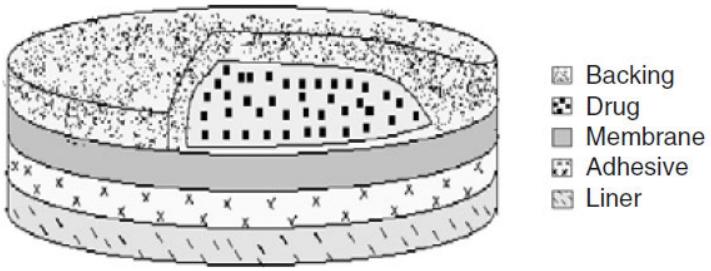

Fig. 1. Drug reservoir-in-adhesive.

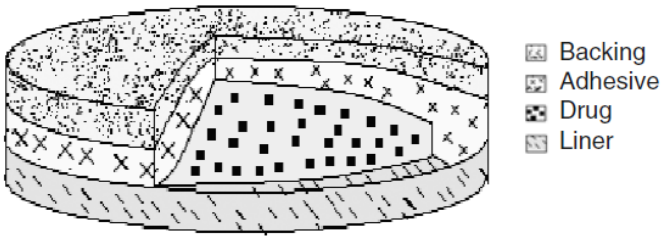

Fig. 2. Drug matrix-in-adhesive.

Figures 1 and 2 above, reproduced from Chan (Chan 770), depict the two structurally different transdermal patches. Chan explains that in the drug matrix-in-adhesive TDS, the drug is dissolved in a semisolid matrix, whereas in the drug reservoir-in-adhesive TDS, there is a liquid compartment containing a drug solution or suspension, that is separate from the adhesive layer, where the liquid compartment is separated from the adhesive layer by a semi-permeable membrane. (*Id.*; *see also* Kanios 1:50–2:5; Yum ¶ 76.)

The TDS described in Gargiulo is the structure described in Figure 2, where the drug is not separated from the adhesive layer with a rate-controlling membrane, but is rather part of the adhesive reservoir matrix. (Gargiulo ¶ 17 (noting that the adhesive properties of a "poorly adhesive reservoir matrix" was increased by the addition of a line of silicone

adhesive, but "without reducing the release of active ingredient from the matrix and its permeation through the skin."); *see generally id.* ¶¶ 12–16, 18.) Consequently, we disagree with the Examiner's finding that Gargiulo teaches a "reservoir-type transdermal drug delivery devices, where the active agent is isolated from the adhesive used to affix the device to the user" (Final Action 13).

We do not find the Examiner has established on this record that a person of ordinary skill in the art would have included a rate controlling membrane such as described in Kanios or Yum for use in a drug reservoir-in-adhesive TDS in the drug matrix-in-adhesive TDS described in Gargiulo. Indeed, Yum describes inclusion of a separate rate controlling membrane in the devices set forth in Figure 1, "where the reservoir is either a liquid or gel reservoir, or a non-adhesive matrix." (Yum ¶ 76.) Yum further explains that an adhesive layer in such reservoir systems itself may be a rate-controlling layer, but that in some such systems, "a further rate controlling membrane" is included. (*Id.* ¶ 96.) On the other hand, Yum does not ever describe including a rate controlling membrane in devices where the reservoir that includes the drug is "a matrix-type reservoir" where the matrix is an adhesive. (*See, e.g.*, *id.* ¶¶ 81–85, 88.)

Consequently, we do not affirm the Examiner's rejection of claim 22–28, and 32 as being obvious from Gargiulo, Duro-Tak, Chan, Audett, Kochinke, Kanios, and Yum.

Furthermore, the Examiner does not rely on Kanios or Yum to address the deficiency of the rejection of claim 1 as being obvious over Gargiulo, Duro-Tak, Chan, Audett, and Kochinke. Consequently, we do not affirm the

Examiner's rejection of claims 1–14, 16–19, and 31 as being obvious from Gargiulo, Duro-Tak, Chan, Audett, Kochinke, Kanios, and Yum.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–14, 16–19	103	Gargiulo, Duro-Tak, Chan, Audett, Kochinke		1–14, 16–19
1–19, 31	103	Gargiulo, Duro-Tak, Chan, Audett, Kochinke, Breitenbach		1–19, 31
1–14, 16–19, 22–28, 31, 32	103	Gargiulo, Duro-Tak, Chan, Audett, Kochinke, Kanios, Yum		1–14, 16–19, 22–28, 31, 32
Overall Outcome				1–19, 22–28, 31, 32

REVERSED