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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BERNHARD GÜNTHER, BASTIAN THEISINGER, SONJA THEISINGER, and DIETER SCHERER

Appeal 2018-005066
Application 14/427,927
Technology Center 1600

Before MICHAEL J. FITZPATRICK, ULRIKE W. JENKS, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

FITZPATRICK, *Administrative Patent Judge*.

DECISION ON APPEAL

Bernhard Günther, Bastian Theisinger, Sonja Theisinger, and Dieter Scherer ("Appellants")[1] appeal under 35 U.S.C. § 134(a) from the Examiner's final decision rejecting claims 16–18, 22, 24, 25, and 28–30. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] The real party in interest is identified as Novaliq GmbH. Appeal Br. 2.

STATEMENT OF THE CASE

The Specification

A human eye has on the surface of its cornea a tear film, which is a dynamic structure composed of an innermost mucous layer, an intermediate aqueous layer, and an outermost lipid layer. Spec. 1:22–2:15.

The outermost lipid layer is:

> formed from meibum (a complex mixture of polar and non-polar lipids including wax and cholesterol esters, phospholipids, di- and tri-glycerides and hydrocarbons) secreted by the [M]eibomian (tarsal) glands which are positioned at the tarsal plates of the eyelids, and to some degree also by the glands of Zeis which open into the eyelash follicles. . . . It is understood that the blinking action helps to promote the spreading and mixing of the lipids in the lipid layer. The major role of the lipid layer is primarily to reduce the rate of evaporation of the aqueous layer by evaporation, but its functions also include enhancing the spreading of the tear film, forming a barrier to prevent tear film contamination, and providing a clear optical surface. It has been proposed that increased tear film stability is associated with a thicker tear film lipid layer.

Spec. 2:15–28.

According to Appellants, their invention "is in the field of ophthalmic compositions, in particular topical ophthalmic compositions which are useful in the treatment keratoconjunctivitis sicca and/or [M]eibomian gland dysfunction and symptoms associated therewith." Spec. 1:1–4.

> Keratoconjunctivitis sicca is a complex, multifaceted disease or condition as described above. It is also known as dry eye syndrome, dry eye disease (DED), or dysfunctional tear syndrome. Aqueous-deficient DED, evaporative DED are within the scope of keratoconjunctivitis sicca and form specific subtypes thereof. Sjogren syndrome, lacrimal gland insufficiency, [M]eibomian gland disease and Meibomian gland

> dysfunction, and other conditions are also within the scope of keratoconjunctivitis sicca, being direct or indirect causes thereof.

Spec. 9:26–32. "Meibomian gland dysfunction can often be characterized by gland obstruction and clogging through hyperkeratinisation of the gland and increased viscosity of the meibum." *Id.* at 4:7–9.

The specification discloses topically administering to the surface of a patient's eyes semifluorinated alkanes, including $F(CF_2)_6(CH_2)_8H$ ("F6H8") which is the semifluorinated alkane recited in the independent claims. *See, e.g.*, Spec. 15:26–32, 16 (Table I). The semifluorinated alkane is administered for "solubilizing meibum lipids and for removing abnormal and obstructive meibum found in clogged [M]eibomian gland ducts." *Id.* at 15:31–32.

The Rejected Claims

All pending claims, namely claims 16–18, 22, 24, 25, and 28–30, stand rejected. Final Act. 1. Independent claim 16 is representative and reproduced below.

> 16. A method for solubilizing meibum and removing abnormal and obstructive meibum from obstructed meibomian gland ducts in a patient in need thereof, comprising
>
> topically administering the semifluorinated alkane $F(CF_2)_6(CH_2)_8H$ (F6H8) to the cornea or conjunctiva of the eye of the patient, wherein the semifluorinated alkane spreads over the corneal surface or conjunctiva; and
>
> wherein said semifluorinated alkane is administered in the absence of any therapeutically effective amount of a pharmaceutically active drug substance useful for the topical ophthalmic treatment of keratoconjunctivitis sicca; and

wherein the patient has keratoconjunctivitis sicca which is caused by meibomian gland dysfunction.

Appeal Br. 25.

The Appealed Rejections

The following rejections are before us for review:

1. claims 16–18, 22, and 24 provisionally for nonstatutory double patenting over claims 18–29 of the '031 application[2] in view of Blackie,[3] Günther,[4] admitted prior art,[5] Troiano,[6] and Meinert (Final Act. 5);[7]

2. claims 25 and 28–30 provisionally for nonstatutory double patenting over claims 18–29 of the '031 application (Final Act. 8);

3. claims 16–18, 22, 24, 25, and 28–30 provisionally for nonstatutory double patenting over claims 1–19 of the '306 application[8] in view of Blackie, Günther, admitted prior art, Troiano, and Meinert (Final Act. 9);

4. claims 16–18, 22, and 24 under 35 U.S.C. § 103(a) over Blackie, Günther, admitted prior art, Troiano, and Meinert (Final Act. 17); and

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[2] US Application No. 15/428,031 ("the '031 application").
[3] Caroline A. Blackie and Donald R. Korb, *MGD: Getting to the Root Cause of Dry Eye*, Review of Optometry 1–12 (2012) ("Blackie").
[4] EP 2,335,735 A1, published June 22, 2011 ("Günther").
[5] Page 2 of the Specification.
[6] Pasquale Troiano and Gaspare Monaco, *Effect of Hypotonic 0.4% Hyaluronic Acid Drops in Dry Eye Patients: A Cross-Over Study*, 27(10) Cornea 1126–1130 (2008) ("Troiano").
[7] US 6,262,126 B1, issued July 17, 2001 ("Meinert").
[8] US Application No. 15/280,306 ("the '306 application").

5. claims 25 and 28–30 under 35 U.S.C. § 103(a) over Blackie, Günther, admitted prior art, Troiano, and Meinert (Final Act. 22).[9]

DISCUSSION

Rejection 1

The Examiner rejected claims 16–18, 22, and 24 provisionally for nonstatutory double patenting over claims 18–29 of the '031 application in view of Blackie, Günther, admitted prior art, Troiano, and Meinert. Final Act. 5. For this rejection, Appellants rely on the same arguments they present for Rejection 4 (*see* Appeal Br. 23), which rejection we affirm below. Thus, we also affirm this rejection.

Rejection 2

The Examiner rejected claims 25 and 28–30 provisionally for nonstatutory double patenting over claims 18–29 of the '031 application. Final Act. 8. For this rejection, Appellants do not present arguments. *See* Appeal Br. 23. Instead, they indicate that they "will amend the copending ['031] application and/or file a terminal disclaimer in the present application in order to address the Examiner's concerns." *Id.* Accordingly, we summarily affirm this rejection.

Rejection 3

The Examiner rejected claims 16–18, 22, 24, 25, and 28–30 provisionally for nonstatutory double patenting over claims 1–19 of the '306

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[9] The Final Action contains an objection to claim 16 as well as rejections under 35 U.S.C. § 112 ¶¶ 2 and 4. Final Act. 3, 14–16. However, that objection and those rejections were withdrawn in the Examiner's Answer. Ans. 4.

application in view of Blackie, Günther, admitted prior art, Troiano, and Meinert. Final Act. 9. For this rejection, Appellants rely on the same arguments they present for Rejection 4 (*see* Appeal Br. 23–24), which rejection we affirm below. Thus, we also affirm this rejection.

Rejection 4

The Examiner rejected claims 16–18, 22, and 24 under 35 U.S.C. § 103(a) over Blackie, Günther, admitted prior art, Troiano, and Meinert. Final Act. 17. Appellants argue all of these claims together. Appeal Br. 4–21. Accordingly, we select independent claim 16 as representative. *See* 37 C.F.R. § 41.37(c)(1)(iv).

The Examiner found that Blackie teaches that Meibomian gland dysfunction ("MGD") is the leading cause of dry eye and that obstructive MGD results in inadequate lipid production for the formation of the lipid layer of the tear film. Final Act. 17 (citing Blackie 2). The Examiner further found that, when obstructive MGD presents, the goal is to evacuate the obstruction and other Meibomian gland material from the gland thereby creating a new environment that offers the potential for normal gland secretion. *Id.* at 18 (citing Blackie 4). The Examiner conceded that Blackie "does not teach a method for solubilizing meibum and removing abnormal and obstructive meibum from obstructed meibomian gland ducts with specifically F6H8 wherein the semifluorinated alkane composition is in the absence of a drug substance." *Id.*

The Examiner found that Günther teaches a method of treating dry eye by applying to the cornea a composition comprising a semifluorinated alkane carrier, such as F6H8, and an active ingredient. *Id.* at 19 (citing Günther, [57], ¶44). The Examiner further found that Günther observed that

at least one tested semifluorinated alkane "exhibit[ed] a positive effect on the healing of damaged cornea similar to that of hyaluronic acid." Günther ¶75 (cited at Final Act. 19).[10]

The Examiner relies on the specification's admission that meibum is a "complex mixture of polar and nonpolar lipids including wax and cholesterol esters, phospholipids, di- and tri-glycerides and hydrocarbons." Final Act. 19.

Finally, the Examiner relies on Meinert as teaching the use of semifluorinated alkanes in the eyes, including as a drug or washing solution, and further teaching that such alkanes are soluble in hydrocarbons and their derivatives and compounds with higher alkyl group contents such as liquid paraffins, silicone oils, fatty acid esters and thus in meibum. Final Act. 19–20 (citing Meinert 2:31–50, 3:54–60, 5:30–35).

The Examiner explains how and why the method of claim 16, for example, would have been obvious to a person of ordinary skill in the art in light of the cited prior art teachings. *See* Final Act. 20–22. To paraphrase, according to the Examiner, the person of ordinary skill in the art would be motivated to unclog solidified meibum in the Meibomian gland of a person suffering from obstructive MGD, would know that semifluorinated alkanes may be topically administered to the eyes safely to provide a therapeutic effect, would know what meibum is made of, would know that semi-fluorinated alkanes dissolve various known components that make up meibum, would reasonably believe that such dissolution would unclog the

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[10] The Examiner also cites Troiano as evidence that hyaluronic acid is used to treat dry eye patents by reducing the symptoms. Final Act. 19 (citing Troiano abstract).

Meibomian gland, and would be motivated to try F6H8 as the semifluorinated alkane because it is specifically identified in the prior art. *See id.*

Appellants present arguments in opposition, but they are not persuasive.

First, Appellants present a series of arguments that are not commensurate with the rejection. In that regard, Appellants argue that the claimed invention would not have been obvious because: (1) Günther, Troiano, and Meinert are directed to different mechanisms of dry eye diseases than obstructive MGD (Appeal Br. 5–9); (2) Günther and Troiano are "[i]rrelevant" to the treatment of MGD-caused dry eye diseases (Appeal Br. 10–12); and (3) none of the references teaches or suggests using a chemical solvent to dissolve meibum (Appeal Br. 13).

The Federal Circuit has held the following:

> Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.

In re Merck & Co., 800 F.2d 1091, 1097 (Fed. Cir. 1986). Under *Merck*, Appellants' entire series of arguments is unpersuasive because the Examiner's rejection is not premised or dependent on any of Günther, Troiano, and Meinert being directed to obstructive MGD. The rejection relies on those references as evidence that a person of ordinary skill in the art would know that topical administration of semifluorinated alkanes to the eyes is safe and provides therapeutic benefit to dry eye generally and that semifluorinated alkanes dissolve various known components that make up

meibum. *See* Final Act. 19–20. The rejection relies on Blackie for providing the motivation to apply these teachings as a solution to obstructive MGD. *Id.* at 18–22.

Next, Appellants present a series of arguments that there would not have been a reasonable expectation of success in dissolving solidified meibum and thereby unclogging the Meibomian gland using semi-fluorinated alkanes. Appeal Br. 14–19. These arguments are not persuasive in light of the Examiner's findings, which we adopt, that (1) "meibum [is] a complex mixture of polar and non-polar lipids including wax and cholesterol esters, phospholipids, di- and tri-glycerides and hydrocarbons" (Spec. 2:16–18 (cited at Final Act. 7, 12, 19, 21, 24, 25); and (2) Meinert explicitly teaches that "semifluorinated alkanes . . . are soluble . . . in hydrocarbons and their derivatives and compounds with higher alkyl group contents (e.g., liquid paraffins, silicone oils, fatty acid esters, etc.)." Meinert 2:31–42 (cited at Final Act. 20).

Appellants' arguments seek to cast doubt that a person of ordinary skill in the art at the time of the claimed invention would have been *certain* that semifluorinated alkanes would successfully unclog an obstructed Meibomian gland. *See, e.g.*, Appeal Br. 19 ("[T]he skilled artisan would recognize that meibum might not dissolve with sufficient speed to unblock the Meibomian gland during the fairly brief period of time before which the SFA would be too diluted by tears to be effective."). "Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988). The Examiner has shown as much.

Lastly, Appellants argue that the claimed invention is non-obvious as evidenced by unexpected results. Appeal Br. 19–21. "[I]t is well settled that unexpected results must be established by factual evidence. 'Mere argument or conclusory statements in the specification does not suffice.'" *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (quoting *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984)). The factual evidence must have a nexus with the claimed invention. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) ("For objective [evidence of secondary considerations] to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the *claimed invention*."). Additionally, such factual evidence must show results that are unexpected relative to the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

In a first variation of their unexpected results argument, Appellants state:

> As demonstrated in Appellant's Table 2 of the specification, pure F6H8 has an unexpected ability to spread out over the surface of the eye much more than other pure SFAs, for example, F4H5. The data demonstrates that SFAs generally are unexpectedly superior to hydrocarbons and perfluorocarbons in their ability to spread into a monolayer film, and that F6H8 in particular is unexpectedly superior in this capacity compared to F4H5.

Appeal Br. 19.

Appellants have not shown a nexus between this evidence, which shows that 50 µL F6H8 spreads out over 12.89 cm^2 of glass surface whereas

the same amount of F4H5 spreads out over only 7.54 cm^2 of the same glass surface (Spec. 19 (Table 2)), and the claimed invention, which does not require any particular degree or amount of spreading out. Claim 16 recites "topically administering the semifluorinated alkane $F(CF_2)_6(CH_2)_8H$ (F6H8) to the cornea or conjunctiva of the eye of the patient, wherein the semifluorinated alkane spreads over the corneal surface or conjunctiva." Claim 16 does not require the topically-administered F6H8 to spread out over the entire corneal surface to any particular degree such as by any specified amount of surface area or within any specified amount of time.

Further, if Appellants recognized any unexpected results from using F6H8 in particular, it is not specifically evidenced in their application as filed. In that regard, the conclusion made by Appellants, based on the data of Table 2, was not that F6H8 in particular demonstrated unexpectedly good results. Rather, what the application describes, contrary to what is now claimed in claim 1, is that using two SFAs is better than any one SFA. Spec. 18:27–30 ("It has now been found by the inventors that compositions comprising at least two SFAs . . . can exhibit surprisingly enhanced spreading behavior compared to SFAs alone or SFAs in combination with non-fluorinated or fluorinated organic solvents."), 19:9–14 ("[C]ompositions comprising at least [two different SFAs per formulas provided] have moreover increased stability than compared to those formed by a single SFA alone.").

In another variation of their unexpected results argument, Appellants state:

> Appellant's clinical trial results demonstrate the unique ability of a liquid eye drop treatment consisting only of SFA F6H8 to effectively improve the functioning of Meibomian glands in

> patients with MGD (See Messmer, et al., *Semifluorierte Alkane als Therapie bei Meibomdrusen-Dysfunktion Ergebnisse einer prospektiven, multizentrischen Beobachtungsstudie* [Semifluorinated Alkanes as a Therapy for Meibomian Gland Dysfunction Result of a prospective, multi-centered observational study]) (submitted in a previous IDS along with an English translation [on January 16, 2017]). This data demonstrated that for the 61 patients tested (122 eyes), there was a significant improvement in both meibum quality and in meibum quantity resulting from treatment with F6H8 eye drops. Nothing in the cited prior art would have suggested such efficacy for administration of an eye drop comprising only the SFA F6H8, in the absence of any other treatment agent.

Appeal Br. 20. Through this argument, Appellants have shown neither that the observed positive results would have been unexpected at the time of the claimed invention nor a proper frame of reference for doing so, i.e., the efficacy of the closest prior art.

Appellants' unexpected results arguments are not probative of non-obviousness. Further, even if the use of F6H8 did exhibit a significant improvement relative to other treatments in the art, the evidence of obviousness here is strong and outweighs Appellants' rebuttal evidence. *See, e.g.*, *Pfizer Inc. v. Apotex Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("[E]ven if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion."). This is so because the prior art of record specifically identifies F6H8 as one of only three "most preferred" SFAs for compositions for the treatment of dry eye. *See* Günther, [57] ("The invention provides novel pharmaceutical compositions for the treatment of keratoconjunctivitis

sicca based on semifluorinated alkanes which are useful as carriers for a broad range of active ingredients."), ¶44 ("Preferred SFA's include in particular the compounds F4H5, F4H6, F6H4, F6Hb, F6H8, and F6H10. Presently *most preferred* for carrying out the invention are F4H5, F6H6 and *F6H8*." (emphasis added)).

For the foregoing reasons, we affirm the rejection of claims 16–18, 22, and 24 under 35 U.S.C. § 103(a) over Blackie, Günther, admitted prior art, Troiano, and Meinert.

Rejection 5

The Examiner rejected claims 25 and 28–30 under 35 U.S.C. § 103(a) over Blackie, Günther, admitted prior art, Troiano, and Meinert. Final Act. 22. For this rejection, Appellants rely on the same arguments they present for Rejection 4 (*see* Appeal Br. 23–24), which rejection we affirm above. Thus, we also affirm this rejection.

CONCLUSION

For the reasons discussed, we affirm all of the Examiner's rejections.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED