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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte LUIS FELIPE VEJARANO RESTREPO

Appeal 2017-011478[1]
Application 13/553,615
Technology Center 1600

Before RICHARD M. LEBOVITZ, MICHAEL J. FITZPATRICK, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims directed to an ophthalmic formulation. The Examiner rejected the claims under 35 U.S.C. § 103 as obvious. Appellant appeals the Examiner's determination that the claims are unpatentable. We have jurisdiction under 35 U.S.C. § 6(b). The § 103 rejections are affirmed.

STATEMENT OF THE CASE

Claims 1, 4–6, 9, 11, and 12 stand finally rejected by the Examiner as follows:

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[1] The Appeal Brief ("Br.") identifies Luis Felipe Vejarano Restrepo as the real-party-in-interest.

1. Claims 1 and 4–6 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Abad (U.S. Pat. Pub. 2014/0200211 A1, published July 17, 2014) and Kaufman (U.S. Pat. Pub. 2011/0152274 A1, published June 23, 2011). Ans. 2.

2. Claims 1 and 4–6 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Kaufman. Ans. 4.

3. Claim 1 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Lubkin (U.S. Pat. 5,041,434, issued Aug. 20, 1991). Ans. 5.

4. Claims 4 and 5 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Lubkin and Conway (U.S. Pat. 4,902,696, issued Feb. 20, 1990). Ans. 6.

5. Claim 6 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Lubkin and Boldrini (WO 00/64425, published Nov. 2, 2000). Ans. 7.

6. Claims 9, 11, and 12 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Lubkin and York (U.S. Pat. 5,192,780, issued Mar. 9, 1993). Ans. 7.

A declaration under 37 C.F.R. § 1.132 by the sole inventor, Luis Felipe Vejarano Restrepo ("Restrepo Decl."), M.D., dated September 25, 2015, was submitted with the Response to the Office Action dated September 28, 2015 and is relied upon in this Appeal by Appellant.

Claim 1, the only independent claim on appeal, is reproduced below:

> 1. An ophthalmic formulation comprising an effective amount of pilocarpine or a pharmaceutically acceptable salt thereof, phenylephrine or a pharmaceutically acceptable salt thereof, and naphazoline or a pharmaceutically acceptable salt thereof.

App. Br. 9 (Claims Appendix).

1. REJECTION BASED ON ABAD AND KAUFMAN

Findings of Fact ("FF")

The following findings of fact are pertinent to the rejection:

Abad

FF1. Abad teaches a composition for treating presbyopia, mild hyperopia, and irregular astigmatism. Abad, Abstract.

FF2. The composition includes 1) a cholinergic agent and 2) an alpha-stimulant agonist having an imidazoline group or a non-steroidal anti-inflammatory agent (NSAID) having COX-2 selectivity. Abad ¶ 11.

FF3. Among the list of cholinergic agents (muscarinic acetylcholine receptor M3 agonists) disclosed by Abad is pilocarpine. Abad ¶ 11.

FF4. Among the list of alpha-stimulant agonists having an imidazoline group disclosed by Abad is naphazoline. Abad ¶ 11.

FF5. Abad discloses a composition comprising pilocarpine and naphazoline. Abad ¶ 41.

Kaufman

FF6. Kaufman teaches a composition "to create optically beneficial miosis to, for example, temporarily treat presbyopia." Kaufman, Abstract.

FF7. The composition comprises 1) one or more parasympathomimetic drugs or cholinesterase inhibitors and 2) "one or more alpha agonists" or antagonists. Kaufman, Abstract.

FF8. Kaufman describes one embodiment in which the 1) parasympathomimetic is pilocarpine and the 2) alpha agonist is brimonidine. Kaufman ¶ 17.

FF9. Kaufman defines an alpha agonist as a compound that stimulates "both alpha1 and alpha2" adrenoceptors. Kaufman ¶ 24.

FF10. Among the list of alpha agonists disclosed by Kaufman is naphazoline and phenylephrine. Kaufman ¶ 24.

FF11. In claim 2 of Kaufman, the alpha agonist is brimonidine or naphazoline.

Discussion

The Examiner found Abad discloses a composition for treating presbyopia that comprises pilocarpine and naphazoline as required by claim 1. Final Act. 4; FF3–FF5. The Examiner found that Abad does not disclose that the composition comprises phenylephrine as required by claim 1. Final Act. 4. However, the Examiner found that Kaufman discloses a composition for treating presbyopia, the same indication described by Abad, in which the composition comprises the exemplified pilocarpine and one or more alpha agonists of which naphazoline and phenylephrine appear in a list. *Id.* at 4–5; FF1, FF6.

The Examiner determined it would have been obvious to one of ordinary skill in the art to have incorporated phenylephrine into Abad's composition because it was taught for the same purpose by Kaufman. Final Act. 5.

Appellant argues that phenylephrine is a well-known mydriatic – a compound that induces dilation of the pupil – which would have been expected "to cancel out miosis", the constriction of the pupil of the eye "produced by pilocarpine." Br. 5. Appellant contends that, for this reason, "a person of ordinary skill in the art would not have been motivated to add

phenylephrine to a formulation containing pilocarpine for temporarily treating, ameliorating, or reducing presbyopia." *Id.*

This argument does not persuade us that the Examiner erred. Despite Appellant's contention that phenylephrine would have the opposite effect of pilocarpine, phenylephrine is expressly disclosed as a useful alpha adrenergic receptor drug by Kaufman to treat the same indication as Abad (FF1, FF6), and in combination with a parasympathomimetic drug, such as the preferred pilocarpine.[2] FF8, FF9, FF10.

Appellant makes a similar argument for Abad, arguing that Abad teaches utilizing alpha-2 adrenergic agonists, such as brimonidine and naphazoline, which constrict the pupil, while phenylephrine is an alpha-1 agonist, which dilates it. Br. 5.

While it is true that Abad discloses these apparently opposing effects of alpha-1 and alpha-2 agonists (Abad ¶ 5), Kaufman contains an express teaching that phenylephrine is useful to treat presbyopia. FF10. The fact that it appears in a list of other alpha adrenergic agonists does not detract from this teaching. Rather, the list of compounds are expressly disclosed as suitable alpha agonists, indicating that Kaufman believed all such drugs in it are efficacious for treating the identified eye disorder. Appellant has not provided adequate objective scientific evidence that outweighs the explicit

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[2] Appellant did not address the issue of combining pilocarpine and phenylephrine in the declaration by inventor Luis Felipe Vejarano Restrepo, M.D. We note that Appellant discloses several publications which describe the application of pilocarpine and phenylephrine to the eye, including, Mapstone, *British J. of Opthalmol.*, 1977, 61:510–511; Tabandeh et al., *Eye*, 1995, 9:452-455.

disclosure in Kaufman of utilizing one or more alpha agonists to treat presbyopia, where the list of drugs includes phenylephrine. An argument made by counsel in a brief does not substitute for evidence lacking in the record. *Estee Lauder, Inc. v. L'Oréal, S.A.*, 129 F.3d 588, 595 (Fed. Cir. 1997). Thus, Appellant has not established a lack of a reasonable expectation of success by objective scientific evidence.

Appellant also argues that Kaufman teaches "that brimonidine potentiates the effect of pilocarpine on the pupil" and that, in view of this teaching, "a person of ordinary skill in the art would have only been motivated to try other alpha agonist[s] that may potentiate the effect of pilocarpine on the pupil." Br. 5.

This argument is not persuasive. Kaufman has explicit disclosure that the alpha agonist can be brimonidine or naphazoline (FF10, FF11), both of which are alpha-agonists having an imidazoline group. Because pilocarpine is preferred by Kaufman (FF8), one of ordinary skill in the art would have had reason to combine it with either brimonidine or naphazoline since both are described as suitable by Kaufman.

Moreover, with regard to Appellant's argument about the potentiation of pilocarpine by brimonidine (Br. 5), Abad contains a broader teaching that other alpha agonists could potentiate the action of pilocarpine:

> The compositions of the present invention were surprisingly and unexpectedly found <u>to potentiate the action of and decrease the side effects of a cholinergic agent such as pilocarpine</u>, such that a cholinergic agent can be effectively used in combination with an alpha-stimulant agonist having an imidazoline group or a non-steroidal anti-inflammatory agent (NSAID) having COX-2 selectivity to contract the ciliary and pupillary sphincter muscles for treating ocular conditions, such as presbyopia . . .

> without the patient experiencing the undesirable side effects normally associated with pilocarpine therapy.

Abad ¶ 12 (emphasis added).

In sum, we are persuaded by the evidence that the Examiner established that claim 1 is *prima facie* obvious in view of Abad and Kaufman.

Declaration

Appellant provided a declaration by inventor Luis Felipe Vejarano Restrepo, M.D. to establish the nonobviousness of the claimed subject matter. The declaration is said by Appellant to show surprising and unexpected results compared to other ophthalmic formulation containing pilocarpine, establishing the nonobviousness of the claimed invention. Br. 7.

A showing of "unexpected results" can be used to demonstrate the non-obviousness of the claimed invention. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' *i.e.,* to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.")

Dr. Restrepo states that "one drop of a formulation containing **0.26% pilocarpine, 0.50% phenylephrine, and 0.003% naphazoline** (Formulation A)" (emphasis added) was administered to patients to test its efficacy in treating presbyopia. Decl. ¶ 11. Dr. Restrepo states that near vision improved with Formulation A, while far vision was not adversely affected as might have been expected "due to miosis caused by pilocarpine."

Id. Furthermore, Dr. Restrepo stated "The fact that effectiveness of Formulation A remained after 1 month of administering only one drop was unexpected and surprising." *Id.*

Dr. Restrepo also compared Formulation A to:

1) one drop of a formulation containing **0.25% pilocarpine**, and one drop of a formulation containing **0.2% brimonidine** (which he referred to as the "Kaufman formulation"); and

2) one drop of a formulation that contains **1% pilocarpine** and **0.025% oxymetazoline** (which he referred to as the "Abad formulation").

Kaufman

With respect to the "Kaufman formulation," Dr. Restrepo stated that Figure 3 of his declaration showed that "Formulation A not only resulted in a greater improvement in the near vision compared to the Kaufman formulation; Formulation A also achieved a longer lasting efficacy." Restrepo Decl. § 12. Dr. Restrepo concluded: "Compare[d] to Kaufman formulation, which contains about the same amount of pilocarpine, Formulation A was able to achieve better near visual acuity. Furthermore, Formulation A retained a longer lasting effect on near visual acuity - for at least one month." *Id.* at ¶ 13.

Abad

With respect to the "Abad formulation," Dr. Restrepo states:

> The Abad formulation seems to have a very similar effect on the near vision compared to Formulation A. However, Abad formulation contains 1 % pilocarpine, while Formulation A contains only 0.26% pilocarpine, which is close to quarter of

> the amount of pilocarpine in Abad formulation. Figure 4 below shows the overlay plots of changes in far UCVA following administration of Formulation A and Abad formulation. The Abad formulation was unable to avoid the adverse effect of decreasing far vision.

Restrepo Decl. ¶ 12.

Dr. Restrepo concluded that "Compare[d] to Abad formulation, Formulation A was able to achieve similar results for the first 5 hours with about a quarter of the pilocarpine. In addition, Formulation A also improved the far visual acuity while Abad formulation decreased it." *Id.* at ¶ 13.

Analysis

We agree with the Examiner that Appellant's showing of unexpected results is not commensurate with the full scope of the claim. As discussed by the Examiner, claim 1 is unrestricted as to the amount of each of pilocarpine, phenylephrine, and naphazoline present in the ophthalmic formulation, but only one concentration of each drug was tested by Dr. Restrepo. Ans. 10. When unexpected results are proffered by an appellant to rebut a *prima facie* case of obviousness, the appellant must "provide[] an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner" in order to "establish that the evidence is commensurate with [the] scope of the claims." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). One data point is insufficient "to ascertain a trend in the exemplified data which would allow [one having ordinary skill in the art] to reasonably extend the probative value thereof." *In re Kollman*, 595 F.2d 48, 56 (CCPA 1979). Consequently, we find the

evidence inadequate to establish unexpected results for the claim's full scope.

To establish unexpected results, the claimed subject matter must be compared with 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"). Abad has an example of pilocarpine and naphazoline, the same two drugs recited in claim 1. FF5. However, the only comparison made in the declaration is with pilocarpine and oxymetazoline. Consequently, the comparison should have been between the claimed subject matter and Abad's example of pilocarpine and naphazoline.

Accordingly, for the reasons set forth above, we conclude that the showing provided by Appellant is insufficient, when the evidence is considered anew, to establish the non-obviousness of claim 1 based on Abad and Kaufman.

Conclusion

The obviousness rejection of claim 1 based on Abad and Kaufman is affirmed. Claims 4–6 were not separately argued and fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

2. OBVIOUSNESS BASED ON KAUFMAN

The Examiner rejected the composition of claim 1 comprising pilocarpine, phenylephrine, and naphazoline as obvious based on Kaufman. Final Act. 6; Ans. 4. The Examiner found that Kaufman discloses a composition for treating presbyopia in which the composition comprises the exemplified pilocarpine, a parasympathomimetic drug, and one or more

alpha agonists, which include the claimed naphazoline and phenylephrine in a list of compounds. Final Act. 6–7. The Examiner found that Kaufman teaches that the parasympathomimetic drug can be combined with "one or more alpha agonists," making it obvious to have selected naphazoline and phenylephrine from the list of drugs described as suitable for treating presbyopia. *Id.* at 7.

Appellant argues that there would have been a lack of a reasonable expectation of success "in view of the mydriatic effect [dilation of the pupil] of phenylephrine [alpha-1 agonist] and the Kaufman's emphasis on selecting alpha-2 agonist for the ophthalmic composition." Br. 6. While it is true that Kaufman exemplifies brimonidine, an alpha-2 agonist, Kaufman expressly discloses that "alpha1 and alpha2" adrenoceptor agonists are suitable for its composition and expressly lists phenylephrine as an example of one. FF9, FF10. Appellant did not provide adequate evidence or scientific reasoning as to why one of ordinary skill in the art would have not have selected these two alpha agonists for the purposes described in Kaufman. *See also* discussion above under Abad and Kaufman rejection,

Appellant also argues the claimed subject matter exhibits unexpected results over Kaufman. Br. 6–7. However, for the reasons already discussed, we find the results insufficient to establish nonobviousness of the full scope of claim 1. Consequently, the rejection of claim 1 as obvious in view of Kaufman is affirmed. Claims 4–6 were not separately argued and fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

3. OBVIOUSNESS BASED ON LUBKIN

The Examiner rejected the composition of claim 1 comprising pilocarpine, phenylephrine, and naphazoline as obvious based on Lubkin. Final Act. 9; Ans. 5. The Examiner cited the following disclosure from Lubkin:

> D. 17-beta Estradiol or its water soluble derivatives combined with one or more of the following active ingredients for the purpose of treating associated ophthalmologic conditions in conjunction with dry eye syndrome:
>
> 1. Anti-infectives: gentamicin sulfate, neomycin sulfate, sulfacetamide sodium, chloramphenicol
>
> 2. Anti-inflammatory: dexamethasone, dexamethasone phosphate, prednisolone, prednisolone phosphase
>
> 3. Antiviral: idoxuridine
>
> 4. Antihistamine: naphazoline HCl
>
> 5. Cycloplegic: tropicamide, atropine sulfate
>
> 6. Local anesthetics: proparacaine, lidocaine
>
> 7. Miotics: pilocarpine
>
> 8. Vasoconstrictors: phenylephrine HCl

Lubkin 4:33–49 (emphasis added).

As found by the Examiner, Lubkin discloses all three drugs recited in claim 1, making their selection obvious to one of ordinary skill in the art. Final Act. 10.

Appellant contends that Lubkin teaches that the composition is for treating dry eye, and not for ameliorating or treating presbyopia. Br. 7. Appellant states that "A person of ordinary skill in the art trying to develop an ophthalmic formulation for ameliorating presbyopia would not have been motivated to specifically combine these three active ingredients." *Id.* This argument is not persuasive because claim 1 is directed to a composition and the composition is not limited to treating a specific ophthalmic disorder.

Appellants also argue the claimed subject matter exhibits unexpected results over Lubkin. Br. 7. However, for the reasons already discussed, we find the results insufficient to establish nonobviousness of the full scope of claim 1. Appellant did not separately address Lubkin in Dr. Restrepo's declaration. Consequently, the rejection of claim 1 as obvious in view of Lubkin is affirmed.

4, 5, 6. OBVIOUSNESS REJECTIONS BASED ON LUBKIN AND CONWAY, BOLDRINI, OR YORK

Claims 4, 5, 6, 9, 11, and 12 are rejected by the Examiner as obvious in view of Lubkin combined with Conway, Boldrini, or York. Appellant states that neither Conway, Boldrini, nor York "cure the defect of Lubkin." Br. 8. As we find the arguments against Lubkin to be unavailing, we affirm Rejection 4, 5, and 6 for the same reasons as for Lubkin.

Appellant also argues the claimed subject matter exhibits unexpected results over Lubkin. Br. 7. However, for the reasons already discussed, we find the results insufficient to establish nonobviousness of the full scope of claim 1. As noted, Appellant did not address Lubkin in Dr. Restrepo's Declaration.

The rejections of claims 4, 5, 6, 9, 11, and 12 as obvious is affirmed.

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