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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARKUS KRUMME and KEITH JENSEN

Appeal 2019-000400
Application 13/354,714
Technology Center 1600

Before JOHN G. NEW, ELIZABETH A. LAVIER, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims to a transmucosal administration system comprising idebenone and certain analogs thereof in a film. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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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 Lohmann Therapie Systeme GmbH and Santhera Pharmaceuticals (Switzerland) Ltd. as the real parties in interest. Appeal Br. 3.

STATEMENT OF THE CASE

"Idebenone is a synthetic analogue of coenzyme Q10 (CoQ10), a vital cell membrane antioxidant and essential constituent of the adenosine-triphosphate (ATP) producing mitochondrial electron transport chain (ETC)." Spec. 1. It has previously "been used in a variety of medical applications" including those relating to treatment of Alzheimer's and other neurodegenerative diseases. *Id.*

The Specification explains that idebenone is "well absorbed in the gastrointestinal tract after conventional oral administration," but subject to "high liver metabolism [that] greatly reduces the potentially high plasma levels of the pharmacologically active idebenone." *Id.* at 1-2. "Because of this strong first pass metabolism, oral administration of idebenone requires high doses" that can cause side effects. *Id.* at 2. Moreover, "the requirement for oral formulations of idebenone to be swallowed inflicts difficulties in the practical administration to patients with swallowing problems, e.g., a patient with a serious neuromuscular disease." *Id.* at 2.

According to the Specification,

> A solution to this problem is presented in this invention which is based on data obtained with a specific type of transmucosal administration system consisting of especially a thin polymer-based film that when attached to the oral mucosa releases the active ingredient directly to the mucosa or partly into the saliva in the oral cavity, es[o]phagus and stomach. The active ingredient is absorbed through the mucosa primarily in the oral cavity, es[o]phagus and stomach, thus avoiding the first-pass metabolism observed after conventional oral administration and gastrointestinal absorption. This dosage form is also described as oral wafer.

Id. at 2. The Specification additionally states that "plasma levels of idebenone after oromucosal administration" of such a wafer are "significantly higher compared to oral administration" as a micro-emulsion. *Id.* at 3.

Claims 1, 6, 7, 10–21, 23–25, 27, 28, 30, 34, 44, and 46–48 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Appeal Br. 5. Claims 1 and 10 are the only independent claims and are representative of the claims on appeal. They read as follows:

> 1. A transmuccosal [sic] administration system comprising pharmaceutical ingredient consisting of active ingredient selected from the group consisting of of [sic] idebenone, idebenone analouges, decylubiquinone, ubiquinone and ubiquinone analouges and 80 to 97% by weight of a carrier material and optional second or further therapeutic agents,
>
> wherein said administration system is a film having a weight per unit area of between 50 and 250 g/m^2 and said pharmaceutical ingredient is present in an amount ranging from 3 to 20 % by weight,
>
> said pharmaceutical ingredient is molecularly dispersed within said carrier material,
>
> said system either has a gel consistency or forms a gel consistency upon swelling in saliva,
>
> and the system exhibits an AUC of the active ingredient concentration in the blood that is at least 100-fold greater than that exhibited through administering the active ingredient through the oral route on a dose-normalized basis.
>
> 10. A transmuccosal [sic] administration system comprising pharmaceutical ingredient consisting of active ingredient selected from the group consisting of idebenone, idebenone analouges, decylubiquinone, ubiquinone and ubiquinone analouges and 40 to 70 % by weight of a carrier material and optional second or further therapeutic agents,
>
> wherein said administration system is a film having a weight per unit area of between 50 and 250 g/m^2 and said

> pharmaceutical ingredient is present as a suspension after micronization in an amount ranging from 30 to 60 % by weight; and
>
> the system is a mucoadhesive film which dissolves in the mouth, the active ingredient is micronized into particles of less than 100 microns and absorbed through the mucosa primarily in the oral cavity, esophagus and stomach; and
>
> the system results in a higher plasma level of active ingredient than imparted by oral administration dosage forms absorbed in the gastrointestinal tract and the system exhibits an AUC of the active ingredient concentration in the blood that is at least 26 fold greater than that exhibited through administering the active ingredient through the oral route on a dose-normalized basis.

Id. at 28, 30–31.

Appellant seeks review of Examiner's rejection of claims 1, 6, 7, 10–21, 23–25, 27, 28, 30, 34, 44, and 46–48 under 35 U.S.C. § 103 as obvious over Rademacher[2] in view of Chen,[3] Dubach-Powell,[4] Krumme,[5] and Joshi.[6] *See* Appeal Br. 10–27.[7]

The issue before us is whether the preponderance of the evidence supports Examiner's conclusion that Appellant's claims are obvious over the cited prior art.

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[2] US 2006/0182786 A1, published Aug. 17, 2006 ("Rademacher").
[3] US 2002/0147201 A1, published Oct. 10, 2002 ("Chen").
[4] US 2009/0208425 A1, published Aug. 20, 2009 ("Dubach-Powell").
[5] US 2006/0222708 A1, published Oct. 5, 2006 ("Krumme").
[6] Jalay T. Joshi, *A Review on Micronization Techniques*, J. Pharma. Sci. & Tech., Vol. 3, 651–681 (2011) ("Joshi").
[7] Although Appellant lists claim 22 in the Claims Appendix (Appeal Br. 33) as an apparently pending claim, and refers to claim 22 in a heading in its arguments (*see id.* at 10), Appellant previously cancelled claim 22 (*see* Amendment filed Apr. 18, 2017 at 6, 10; *see also* Final Act. 2).

Analysis

Examiner finds that Rademacher teaches a mucoadhesive film dosage form comprising ranges of active ingredient and carrier material that overlap with those in claims 1 and 10. Final Act. 3–5. Examiner determines "Rademacher teaches that the active ingredient of the film may be a nootropic compound," but does not specify that the compound is idebenone and does not disclose "the area and weight per unit area of the system." *Id.* at 5. However, Examiner finds Chen teaches mucoadhesive films that "comprise nootropics such as idebenone for transmucosal delivery" and determines Krumme discloses films with an overlapping "weight per unit area." *Id.* at 6–8. Examiner finds Dubach-Powell teaches transmucosal administration of idebenone is "advantageous because it avoids the strong first pass metabolism observed after conventional oral administration" and "showed an improvement in bioavailability [when administered in a micro-emulsion] compared to oral administration." *Id.* at 7 (citing Dubach-Powell ¶¶ 3, 6, 48, 51, 54, Figs. 1 and 2).

Based on these teachings, Examiner determines it would have been obvious to substitute "the anti-Parkinson active ingredient of Rademacher with the anti-Parkinson idebenone active taught by Dubach Powell" and Chen, resulting in a film containing molecularly dispersed idebenone (claim 1) or micronized particles of idebenone (claim 10). *Id.* at 8–10. Examiner finds the recited concentrations and weight per unit area limitations are result-effective variables that may be optimized through routine experimentation. *Id.* According to Examiner, since the "system of the above prior art combination and the claims appear to be the same (i.e., the same dosage form, components, concentrations, and dimensions), the [prior

art] system would also be expected to exhibit" the recited degree of AUC increase over administration of idebenone orally on a dose-normalized basis. *Id.* at 10–11.

We agree that Examiner has established a prima face case of obviousness for claims 1 and 10. We are not persuaded by Appellant's arguments that a skilled artisan would not have had a motivation and reasonable expectation of success of combining the references as articulated by Examiner. *See* Appeal Br. 10–18. In particular, Dubach-Powell teaches that oramucosal delivery of idebenone in a micro-emulsion substantially increases its AUC as compared to conventional oral administration. *See* Dubach-Powell ¶¶ 50–51 (Table 7) (showing that AUC_{0-480} was 11.1 times higher on a dose normalized basis for the micro-emulsion). Accordingly, the record supports the Examiner's determination that a skilled artisan would have be motivated to administer idebenone in a mucoadhesive film, as taught in Rademacher, and would reasonably expect that doing so would increase bioavailability, at least to some degree, as compared to conventional oral dosage forms.

What distinguishes Appellant's claims, however, is the evidence of unexpected results set forth in the Specification and the Declaration of Rudolf Hausmann, dated November 10, 2015 (the "Hausmann Declaration"), demonstrating the extent to which the recited films increased AUC over the prior art. The Specification discloses pharmacokinetic data showing C_{max} and AUC_{0-360} parameters for three dosage forms: (1) 30 mg wafer A (micronized suspension), (2) 15 mg wafer B (solid solution), and (3) 300 mg oral gavage (micro-emulsion). *See* Spec. 12–16 (Tables 2–4). Wafer A and wafer B correspond to the film dosage forms in claims 10 and

1 respectively. According to Appellant, the third form, the 300 mg oral gavage, is "a liquid micro[-]emulsion, such as the liquid micro-emulsion provided in Dubach-Powell's Example 1, which Appellant[] consider[s] to be the closest prior art." Appeal Br. 19. The data show that both of the film dosage forms exhibited a higher absolute, and much higher dose-normalized, C_{max} and AUC_{0-360} than the oral gavage. *See* Spec. 14–15 (Tables 2 and 3). Table 4 of the Specification compares these values for wafer A and wafer B to those for the oral gavage. *Id.* at 16 (Table 4). The data there show that C_{max}/mg and AUC_{0-360}/mg values for wafer A were 33 and 26-fold greater than those values for the oral gavage, whereas those values for wafer B were 144 and 121-fold greater than the oral gavage. *Id.* The Hausmann Declaration, relying on data in the Specification and Dubach-Powell, likewise evidences that the recited mucoadhesive films exhibit "bioavailability/AUC values [that are] unexpectedly much higher than that taught by [Dubach-Powell]." Hausmann Decl. ¶ 9.

We agree with Appellant that these results represent an unexpected and substantial improvement over the prior art. *See In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) ("[W]hen an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results are *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary.") Examiner has not identified any evidence suggesting a skilled artisan would expect the recited film dosage forms to provide dose-normalized AUC values orders of magnitude greater than the micro-emulsion form that Dubach-Powell teaches is itself a substantial improvement over conventional oral dosage forms.

Instead, Examiner determines "Rademacher is the closest single prior art reference" and, therefore, Appellant's evidence "improperly compares the claimed invention with a reference that is not the closest prior art (i.e., Dubach-Powell et al)." Ans. 21. We disagree. Rademacher does not describe any dosage form containing idebenone. In contrast, Dubach-Powell describes an oromucosal dosage form of idebenone with a dose-normalized AUC more than 10 times higher than conventional oral forms. *See* Dubach-Powell ¶¶ 48–55 (Table 6). Thus, on this record, the idebenone micro-emulsion in Dubach-Powell is the closest prior art to the transmucosal administration systems recited in claims 1 and 10. For this reason, we agree with Appellant that the direct comparison of Dubach-Powell's micro-emulsion to embodiments of those claims (i.e., wafer A and B) in the Specification is "particularly probative" evidence of unexpected results. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention.").

We further determine that Appellant's evidence is reasonably commensurate with the scope of its claims. The data in the Specification demonstrate unexpected results for an embodiment of each of the two independent claims with concentrations of active ingredient and carrier material near the midpoint of the ranges recited in those claims. *See* Spec. 12. According to Examiner, these results are not reasonably commensurate because Appellant did not test every "type of film" and "the entire claimed range" of idebenone encompassed by claims 1 and 10. *See* Ans. 22.

However, an applicant is not "required to test every embodiment within the scope of his or her claims" to demonstrate unexpected results. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). In addition, the extent to which wafer A and wafer B exhibited increased C_{max} and AUC relative to Dubach-Powell's micro-emulsion provides "an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner," relative to that prior art. *See Kao*, 639 F.3d at 1068.

For these reasons and on this record, we agree with Appellant that the results evidenced by the Specification and Hausmann Declaration are unexpected and probative of non-obviousness. Considering "the entire merits of the matter" in light of this evidence, we determine that the preponderance of the evidence does not support the rejection. *See In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986). Accordingly, we reverse.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 6, 7, 10–21, 23–25, 27, 28, 30, 34, 44, 46–48	103	Rademacher, Chen, Dubach-Powell, Krumme, Joshi		1, 6, 7, 10–21, 23–25, 27, 28, 30, 34, 44, 46–48

REVERSED