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BUCHANAN, INGERSOLL & ROONEY PC
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte THOMAS C. DOWLING

Appeal 2018-007814
Application 14/507,391
Technology Center 1600

Before DEBORAH KATZ, JOHN G. NEW, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

SCHNEIDER, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 8–10, 12, and 13 as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.[2]

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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 the inventor, Thomas C. Dowling. Appeal Br. 2.

[2] We have considered and herein refer to the Specification of Oct. 6, 2014 ("Spec."); Final Office Action of July 11, 2017 ("Final Act."); Appeal Brief of Feb. 5, 2018 ("Appeal Br."); Examiner's Answer of May 24, 2018

STATEMENT OF THE CASE

The invention relates to a method for determining drug interactions to prevent or reduce renal failure. *See* Spec. 1–2.

Claims 8–10, 12, and 13 are on appeal.[3] Claim 8 is representative of the rejected claim and reads as follows:

> 8. A method of determining drug interactions of pharmaceutical combinations, said method comprising conducting a metabolite formation study in phase II enzymes in human HK-2 cells using Para-aminohippuric acid (PAH) and a first active pharmaceutical ingredient in a control group, measuring phase II enzyme metabolite formation in said pharmaceutical control group, exposing said cells to one or more active pharmaceutical ingredients pharmaceuticals in a treatment group, measuring phase II enzyme metabolite formation in said treatment group, comparing phase II enzyme metabolite formation in said control group and said treatment group, and determining the drug interactions of said pharmaceutical combinations.

("Ans."); and Reply Brief July 24, 2018 ("Reply Br."). Oral Arguments were heard on Sept. 17, 2019.

[3] Claims 1–7, 11, and 14–20 are pending in the application but have been withdrawn from consideration. Final Act. 2.

The claims have been rejected under 35 U.S.C. § 103(a) as unpatentable over Carpenter[4] in view of Naud[5] as evidenced by Colman[6] and Geisler.[7]

DISCUSSION

Issue

The issue before us is whether a preponderance of the evidence supports the Examiner's conclusion that the subject matter of claims 8–10, 12, and 13 would have been obvious to one of ordinary skill in the art at the time the invention was made over Carpenter combined with Naud.

The Examiner finds that claim 8 is directed to a method comprising the steps of

> A. Conducting a metabolite formation study in phase II enzymes in cells using PAH and a first active pharmaceutical ingredient in a control group
>
> B. Measuring phase II enzyme metabolite formation in said pharmaceutical control group
>
> C. Exposing cells to one or more active pharmaceutical ingredients in a treatment group

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[4] Carpenter, H.M. & Mudge, G.H. (1980). Uptake and Acetylation of *p*-Aminohippurate by Slices of Mouse Kidney Cortex. *J. Pharmacol. Exp. Ther.*, *213*(2), 350–354. ("Carpenter").

[5] Naud, J., Michaud, J., Beauchemin, S., Hébert, M.-J., Roger, M., Lefrancois, S., . . ., Pichette, V. (2011). Effects of Chronic Renal Failure on Kidney Drug Transporters and Cytochrome P450 in Rats. *Drug Metabolism and Disposition*, *39*(8), 1363–1369. ("Naud").

[6] Colman, E. (2007). Dinitrophenol and obesity: An early twentieth-century regulatory dilemma. *Regulatory Toxicology and Pharmacology*, *48*(2), 115–117. ("Colman").

[7] Geisler, J.G., Marosi, K., Halpern, J., & Mattson, M.P. (2017). DNP, mitochondrial uncoupling, and neuroprotection: A little dab'll do ya. *Alzheimer's and Dementia*, *13*(5), 582–591. ("Geisler").

> D. Measuring phase II enzyme metabolite formation in said treatment group
> E. Comparing metabolite formation in said control group and said treatment group
> F. Determining the drug interactions of said pharmaceutical combinations

Final Act. 3.

The Examiner finds that Carpenter teaches a study of metabolite formation in cells using PAH and a first pharmaceutical in a control group, thus teaching steps A and B of claim 8. *Id.* at 4. The Examiner finds that lactate, acetate, and succinate used with PAH in Carpenter meet the limitation calling for an "active pharmaceutical ingredient" as the term is used the present application. *Id.* at 5.

The Examiner finds that Carpenter teaches steps C and D as Carpenter teaches exposing a set of cells to active pharmaceutical agent such as p-aminobenzoate, sulfadiazine, sulfanilamide, and dapsone. *Id.* The Examiner finds that Carpenter teaches measuring acetylation or metabolite formation of the recited compounds. *Id.*

The Examiner finds that Carpenter teaches steps E and F in that Carpenter compares the metabolite formation by cells exposed to PAH and an active pharmaceutical ingredient with the second set of cells exposed to as p-aminobenzoate, sulfadiazine, sulfanilamide, and dapsone. *Id.* at 6.

The Examiner finds that while Carpenter does not teach the use of human HK-2 cells, this element is taught by Naud. *Id.* at 7.

The Examiner concludes

> It would be obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to

> modify Carpenter's method by conducting the method of determining drug interactions of pharmaceutical combinations as taught by Carpenter within the HK-2 cells taught by Naud. One would be motivated to do so to determine drug interaction in a human model. One would expect a reasonable amount of success due to the similarities Naud demonstrated between a rodent model and the HK-2 along with the conclusion that para-aminohippuric acid is a known modulator of drug transporters responsible for alteration in renal transporters in vivo.

Id. at 8.

Principles of Law

> [T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant.
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

In re Oetiker, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

Analysis

We adopt the Examiner's findings of fact, reasoning on scope and content of the prior art, and conclusions set out in the Final Action and Answer regarding this rejection. We find the Examiner has established that the subject matter of the claims would have been obvious to one of ordinary skill in the art, at the time the invention was made, over Carpenter combined with Naud. Appellant has not produced evidence showing, or persuasively argued, that the Examiner's determinations on obviousness are incorrect. Only those arguments made by Appellant in the Briefs have been considered in this Decision. Arguments not presented in the Briefs are waived. *See* 37

C.F.R. § 41.37(c)(1)(iv) (2015). We have identified claim 8 as representative; therefore, all claims fall with claim 8.[8] We address Appellant's arguments below.

Appellant contends that the Examiner has improperly concluded that acetate, lactate, succinate, and 2,4-DNP are active pharmaceutical agents as the term is used in the claims and the Specification. Appeal Br. 4. Appellant contends that the evidence of record, including the inventor's declaration demonstrate that lactate, succinate, and acetate are inert ingredients are not used in the medical diagnosis, cure, treatment, or prevention of disease. *Id.* at 9–10. With respect to 2,4-DNP, Appellant contends that one skilled in the art would understand that the compound is toxic and would not be used as an active pharmaceutical agent. *Id.* at 11–12.

We have considered Appellant's argument, and we are not persuaded that the Examiner erred in finding that the recited compounds are active pharmaceutical agents. "[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000).

The Specification defines the term pharmaceutical or drug to mean "a pharmaceutical drug or medicinal product or any chemical substance formulated or compounded as a single active ingredient product intended for internal, or external or for use in the medical diagnosis, cure, treatment, or

[8] In its Reply Brief, Appellant for the first time presents separate arguments for dependent claims 9, 10, 12, and 13. Reply Br. 14–15. Since Appellant has not shown good cause why these arguments were not presented in its Appeal Brief, we decline to consider those arguments. 37 C.F.R. § 41.41(b)(2).

prevention of disease." Spec. 11. We agree with the Examiner that acetate, lactate, succinate, and 2,4-DNP are active pharmaceutical agents as the term is used in the claims. The Specification specifically teaches that sodium lactate is a pharmaceutical. Spec. 18. The Specification teaches that PAH "is a diagnostic agent used to measure renal plasma blood flow," which is an indicator of kidney disease. Spec. 2 and 5. Carpenter teaches that lactate, acetate, succinate, and 2,4-DNP affect the uptake and accumulation of PAH, which in turn affect the production of PAAH. Carpenter, 352. Thus, the recited compounds act with PAH as a diagnostic and fall within the definition of a pharmaceutical.

Appellant points to the declaration[9] of the inventor, Dr. Dowling as evidence that acetate, lactate, and succinate are not active pharmaceutical ingredients but are inactive ingredients. Appeal Br. 9–10, citing Dowling Decl. 2. Dr. Dowling, citing to Berge,[10] testifies that components such as acetate, lactate, and succinate are anions used to create salts but have no other active qualities. Dowling Decl. 2 ¶ 18.

We have considered Dr. Dowling's Declaration and are not persuaded that acetate, lactate, and succinate are inactive pharmaceutical ingredients. As noted above, the Specification teaches that sodium lactate is a pharmaceutical. In addition, Carpenter teaches that acetate, lactate, and succinate have an effect on the uptake of PAH indicating that the compounds are active.

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[9] Second Supplemental Declaration of Thomas C. Dowling, Pharm. D, Ph.D. Under 37 C.F.R. § 1.132, filed Apr. 6, 2017 Dowling Decl. 2").
[10] Berge S., Bighley, L.D., & Monkhouse, D.C. (1977). Pharmaceutical Salts. *J. Pharm. Sci.*, *66*(1), 1–19. ("Berge").

Appellant next argues that acetate, lactate, and succinate are not active pharmaceutical ingredients as the claims call for the active pharmaceutical ingredient to produce a phase II enzyme metabolite and there is no evidence of record that any of the recited compounds produce such a metabolite. Appeal Br. 11.

We are not persuaded by Appellant's argument. Claim 8, as written, merely calls for measuring phase II enzyme metabolite formation, it does not call for the metabolite to arise from the first active pharmaceutical ingredient. Appeal Br. Claims App. 1.

Appellant next argues that one skilled in the art would not use 2,4-DNP as the active pharmaceutical ingredient as it has been found to be toxic and has not been used in the US since 1938. Appeal Br. 11–12. Again we are not persuaded by Appellant's argument.

As the Examiner has pointed out, Geisler teaches that at low doses, 2,4-DNP is useful in treating certain neurological disorders such as Alzheimer's and Parkinson's disease. Ans. 14–15. Moreover, 2,4-DNP is but one compound taught by Carpenter that effects uptake and use of PAH. *See* Carpenter 352. As discussed above, the other compounds, acetate, lactate and succinate are used in pharmaceuticals and exhibit activity when combined with PAH. Thus Carpenter teaches that combination of PAH and an active pharmaceutical ingredient in that it teaches PAH in combination with acetate, lactate or succinate.

Appellant contends that the Examiner is improperly combining the teachings of Tables II and III of Carpenter. Appeal Br. 13. Appellant contends that the tables represent divergent data under differing study conditions. *Id.*

Once again, we are not persuaded by Appellant's argument. The Examiner's rejection is based on not only the data in Tables II and III of Carpenter, but the discussion of those experiments reflected on page 352 of Carpenter. Ans. 16. We agree with the Examiner that one skilled in the art would be led by the teachings of Carpenter to the claimed method. *Id.* As the Examiner points out, the active pharmaceutical ingredient used with the control group does not need to be the same as the one or more active pharmaceutical ingredients in the treatment group. *Id.* Additionally, claim 8 does not call for the administration of PAH to the control group.

Appellant also contends that the Examiner did not fully consider the evidence presented in the declarations by Dr. Dowling. Appeal Br. 14. Appellant contends that the Examiner failed to present any evidence to contradict Dr. Dowling's testimony. *Id.*

We are not persuaded that the Examiner failed to give Dr. Dowling's declarations careful consideration. The first declaration[11] of Dr. Dowling focused almost exclusively on the fact that Naud did not teach a method with the steps recited in the present claims. Dowling Decl. 1, ¶¶ 21–30. The Examiner, however, did not rely on Naud for teaching the steps of the claimed method but only for the teaching of human HK-2 cells. Final Act. 7. Dr. Dowling's opinion regarding Naud's failure to teach the steps of the method did not address the Examiner's rejection based on Carpenter and Naud.

[11] Declaration of Thomas C. Dowling, Pharm. D., Ph.D. Under 37 C.F.R. § 1.132, filed Oct. 5, 2016 ("Dowling Decl. 1").

With respect to the second Dowling declaration, the Examiner explained in detail why the Examiner found the declaration unpersuasive. Final Act. 11–17. For example, the Examiner discusses how Carpenter supports the Examiner's contention that acetate, lactate, and succinate fit the definition of active pharmaceutical ingredient and that Geisler teaches that 2,4-DNP can be used to treat various neurological conditions. *Id.* at 13–14.

We conclude that a preponderance of the evidence supports the Examiner's conclusion that the subject matter of the claim 8 would have been obvious over Carpenter combined with Naud. Claims 9, 10, 12, and 13 have not been separately argued and therefore fall with claim 8. 37 C.F.R. § 41.37(c)(iv).

CONCLUSION

In summary:

Claims Rejected	Basis	Affirmed	Reversed
8–10, 12, and 13	35 U.S.C. § 103(a) Carpenter and Naud	8–10, 12, and 13	

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