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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ROBERT SABIN

Appeal 2019-002986
Application 12/661,964
Technology Center 1600

Before ULRIKE W. JENKS, TIMOTHY G. MAJORS, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant submits this appeal under 35 U.S.C. § 134(a) involving claims to methods for treating Alzheimer's Disease and related conditions.[1] Examiner rejected claims 6, 21–23, and 28–37 as obvious and for obviousness-type double patenting ("ODP"). We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] Herein we refer to the Non-Final Office Action mailed February 21, 2018 ("Non-Final Act."); Appeal Brief filed June 11, 2018 ("App. Br."); Examiner's Answer mailed Jan. 8, 2019 ("Ans."); and Reply Brief filed March 7, 2019 ("Reply Br.").

STATEMENT OF THE CASE

Claims 6, 21–23, and 28–37 are on appeal and can be found in the Claims Appendix of the Appeal Brief. App. Br. 18–19. Claim 6 is representative of the claims on appeal. It reads as follows:

> 6. A method for the treatment of Alzheimer's disease and related amyloid plaque development and reduction of amyloid plaque, protein aggregation and amyloidosis consisting essentially of the steps of orally administering to a patient afflicted with Alzheimer's disease an effective amount of a compound selected from the group consisting of phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid or a phytate salt, or a mixture of any combination thereof, being administered in an amount from about 0.5 grams to about 18.75 grams per day to effectively treat Alzheimer's disease and related amyloid plaque development and reduction of amyloid plaque, protein aggregation and amyloidosis.

App. Br. 36 (Claims Appendix). Claims 23, 31, and 32 are also independent and similarly recite administration of a compound from the same Markush group within the same dosage range. Dependent claims 30 and 36 additionally recite that the compound "is administered to a patient on an empty stomach. *Id.* at 38–39.

Appellant seeks review of the following rejections:

I. Claims 6, 21–23, and 28–37 under 35 U.S.C. § 103 as obvious over Sabin[2] and Frey[3] ("Rejection I").

II. Claims 6, 21–23, and 28–37 under 35 U.S.C. § 103 as obvious over Sabin, Frey, and Grases[4] ("Rejection II").

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[2] US 4,847,082, issued July 11, 1989 ("Sabin").
[3] US 2006/0014716 A1, published Jan. 19, 2006 ("Frey").
[4] F. Grases et al., *Intracellular and Extracellular myo-Inositol Hexakisphosphate ($InsP_6$), from Rats to Humans*, Anticancer Research, Vol.

III. Claims 6, 21–23, and 28–37 for ODP over claims 1–7 of Sabin in view of Frey and Grases ("Rejection III).

IV. Claims 6, 21–23, and 28–37 for ODP over claims 1–3 of Sabin II[5] in view of Frey and Grases ("Rejection IV").

The issue for each of these rejections is whether Examiner's conclusion of obviousness is supported by the preponderance of the evidence. Appellant does not argue claims 21–23, and 28, 29, 31–35, and 37 separately from claim 6 for any of the above rejections so those claims stand or fall with claim 6. 37 C.F.R. § 41.37 (c)(1)(iv). Appellant offers some additional arguments regarding Grases and the "empty stomach" limitation of claims 30 and 36 (*see* App. Br. 26–29) that we address separately in our analysis below.

Findings of Fact

FF1. Sabin teaches the administration of "an effective symptom-alleviating amount of a compound selected from the group consisting of phytic acid, phytate salt, an isomer or hydrolysate of phytic acid or phytate salt, or a mixture of any combination thereof" to treat Alzheimer's Disease. Sabin, Abstr. Sabin teaches the "preferred method of administration is by oral dosages of about ½ to 3 grams/kilogram bodyweight per day." *Id.* According to Sabin, such a dosage "will usually be effective," but that the "dosage to be administered will vary with the severity of the diseased condition" and is left to the discretion of the attending physician. *Id.* at 4:4–12.

25, 2593-98 (2005) ("Grases").

[5] US 4,758,430, issued July 19, 1988 ("Sabin II").

FF2. Frey teaches the administration of "pyrophosphate analogs," including phytic acid, to treat or prevent, *inter alia*, Alzheimer's Disease. Frey ¶¶ 10, 12, 119. According to Frey, "[d]oses for humans and other mammals can range from about 0.001 mg/kg to about 100 mg/kg" and can be orally administered. *Id.* ¶¶ 80, 82. Frey teaches an embodiment in which the pyrophosphate analog is administered alone to protect a muscarinic acetylcholine receptor (mAChR) as well as embodiments in which it is administered to increase the efficacy of another agent. *Id.* ¶ 5.

FF3. Grases reports results from a "study of different stomach conditions before $InsP_6$ [i.e., phytic acid] administration (empty stomach, empty with an alkalinizing agent and full stomach)" in humans that "demonstrated that no differences in the excretion profiles between the three different conditions were produced at 8 hours." Grases 2595. According to Grases, this data suggests "that the overall $InsP_6$ absorption took place independently of the stomach state, full or fasted stomach." *Id.* Thus, Grases teaches that to "maintain optimum $InsP_6$ levels" phytic acid supplements "can be taken either during or between meals with the same efficacy." *Id.*

Analysis

Obviousness

We analyze Rejection I and Rejection II together because they are premised on the same references and present common issues.

Examiner found that "Sabin teaches a method of treating Alzheimer's disease . . . consisting essentially of orally administering phytic acid," albeit at a somewhat higher dosage range than that recited in Appellant's claims. Non-Final Act. 4. Examiner determined Frey teaches administering phytic acid at an oral dosage of about 100 mg/kg, "which would correspond to 7g

for an average 70kg adult." *Id*. (citing Frey ¶¶ 80, 82). According to Examiner, "it would have been prima facie obvious . . . to administer the therapy of Sabin at the dosages[in Frey] since Sabin teaches that the frequency and dosage . . . varies with the severity of the disease as needed and discretionarily determined by the attending physician . . . and the instantly claimed dosage ranges were known to be appropriate for Alzheimer's therapy." *Id.* at 3–4.

We agree that Examiner's obviousness rejections are supported by the preponderance of the evidence. Sabin teaches all of the limitations of claim 6 other than the dosage range. FF1. Frey teaches the administration of the same compound (i.e., phytic acid) to treat the same disease at a dosage range that substantially overlaps[6] with the "about 0.5 grams to about 18.75 grams per day" range recited in claim 6. FF2. That overlap is sufficient to establish a prima facie case of obviousness. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("[W]e and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness."). Such a prima facie case may be rebutted "by establishing that the claimed range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *Id.* at 1330 (citations omitted). But, as explained further below, Appellant has not shown that the claimed range achieves unexpected results as compared to the dosages taught in Frey or Sabin or otherwise established

[6] Examiner found that a 100 mg/kg dose (i.e., the upper end of Frey's range) in a 70 kg person overlaps with the claimed range. *See* Non-Final Act. 4. We note that the overlap extends down from 100 mg/kg to at least 10 mg/kg, which would equate to a dose of about 0.7 grams in the same person.

that the claimed range is critical. Accordingly, the record supports Examiner's obviousness determination and, as explained below, we are not persuaded by Appellant's arguments to the contrary.

Appellant argues that Frey fails to teach a dose within the claimed range because it discloses "an infinite/endless number of **combinations**" of pyrophosphate compounds with an "infinite/endless number of doses, with thousands of diseases, with different genders, with different ages." *See* App. Br. 8–14. We disagree. Frey teaches that the pyrophosphate analog "employed in the appropriate embodiment of the method of the invention" may be "an inositol hexaphosphate," i.e., phytic acid. Frey ¶¶ 7–10. And it teaches that "according to the method of the invention" such compounds are administered in a dosage range "from about 0.001 mg/kg to about 100 mg/kg." *Id.* ¶¶ 80, 82. Moreover, Frey teaches that "[p]referably, the method of the invention . . . can treat or prevent Alzheimer's Disease." *Id.* ¶ 12. Therefore, Frey ties these disclosures to the same "method of the invention" and Examiner is not merely "picking and choosing" from different embodiments, as Appellant contends. *See* App. Br. 11–12. The mere fact that Frey discloses a multitude of combinations "does not render any particular" combination less obvious. *See Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (explaining that a reference's disclosure of "a multitude of effective combinations does not render any particular formulation less obvious"). Moreover, the teachings in Sabin further demonstrate that it would be obvious to select this particular combination, i.e., to administer phytic acid orally for the treatment of and alleviation of symptoms associated with Alzheimer's Disease. *See* FF1.

We are also not persuaded by Appellant's argument that Frey's disclosure is so broad that it is not enabled. *See* App. Br. 12–14. "[A] prior art reference need not enable its full disclosure." *In re Antor Media Corp.*, 689 F.3d 1282, 1290 (Fed. Cir. 2012). Rather, "[e]nablement of prior art requires that the reference teach a skilled artisan to make or carry out what it discloses *in relation to the claimed invention*." *Id.* (emphasis added). Appellant does not argue, nor is there evidence in the record to suggest, that undue experimentation would be required to orally administer phytic acid to treat Alzheimer's Disease at the dosage taught in Frey. Accordingly, Appellant has not overcome the presumption that "both the claimed and unclaimed disclosures in [Frey] . . . are enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003).

Nonetheless, Appellant urges that Frey "admitted during prosecution that their disclosure was overly broad and non-enabled." App. Br. 15. We disagree. First, the fact that claims that ultimately issued from Frey, a published patent application, are limited to intranasal administration to treat meningitis does not constitute "a disavowing of other forms of administration for other diseases," as Appellant contends. *Id.* at 15–16. As our reviewing court has explained, "[t]he scope of a patent's claims determines what infringes the patent; it is no measure of what it discloses." *In re Benno*, 768 F.2d 1340, 1346 (Fed. Cir. 1985). Indeed, as a printed publication, Frey would be prior art for the teachings in that publication even if no patent had ultimately issued from that application. *See* 35 U.S.C. § 102.

Second, and contrary to Appellant's assertions, there are no "admissions in the [Frey] file history" that Frey's teachings as they relate to

the Appellant's claims are not enabled. App. Br. 17 (citing 132 Declaration of Robert Sabin dated March 29, 2017 ("Sabin Decl.")). The Sabin Declaration quotes passages from the prosecution of an application related to Frey, describing the "primary advantages of the present invention, as it is claimed," i.e., intranasal delivery as opposed to other routes, to try to distinguish those claims over the cited prior art. Sabin Decl. 2. At most this passage, and the others cited in the Sabin Declaration, suggest that the Frey inventors preferred intranasal delivery. *See* Sabin Decl. 2–6. None of the statements Appellant relies upon suggest that undue experimentation is required to practice Frey's other teachings, much less do they evidence that a skilled artisan would somehow be dissuaded from administering phytic acid orally, as expressly taught by both Frey and Sabin. *See* FF1–FF2.

Appellant also argues that Sabin "teaches away from using the lower dosages claimed" in Appellant's present claims. App. Br. 20 (emphasis omitted). Again, we disagree. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Appellant here points to Sabin's teaching that "oral administration of from ½ to 3 grams of phytic acid . . . per kilogram of body weight in the diet per day will usually be effective." App. Br. 20 (quoting Sabin 4:4–10). But the statement that a somewhat higher dose "will usually be effective" does not discourage a skilled artisan, nor does it lead away, from pursuing a lower dose. This is particularly so given that Sabin acknowledges that the dosage will "vary with the severity

of the diseased condition" and is left to discretion of the attending physician. FF1.

Finally, Appellant has not shown that the claimed dosage range of "about 0.5 grams to about 18.75 grams per day" is critical, or otherwise provides unexpected benefits, compared to the ranges taught in Sabin and Frey. The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. *See*, *e.g.*, *In re Peterson*, 315 F.3d at 1329 (citing cases). These cases have consistently held that the Appellant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range. *Id.* The burden rests with Appellant to establish that (1) the comparisons are to the disclosure of the closest prior art, (2) the evidentiary showing is commensurate in scope with the claimed subject matter, and (3) the alleged unexpected results are, in fact, unexpected over the prior art. *See In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972). All three of those requirements are lacking here.

First, Appellant has not provided evidence comparing the claimed dosage range to the ranges taught in Sabin and Frey. The data in the Specification purports to show "a reduction in Abeta plaque [in mice] after treatment with 2% phytic acid, compared to the control vehicle *without phytic acid*." Spec. 11 (emphasis added). Appellant further relies on data in an article on which he is a co-author, Anekonda.[7] That data similarly involves mice treated with 2% phytic acid in their drinking water. *See* App.

[7] Thimmappa S. Anekonda et al., *Phytic Acid as a Potential Treatment for Alzheimer's Pathology: Evidence from Animal and in vitro Models*, J. of Alzheimer's Disease, vol. 23, 21–35 (2011).

Br. 24–25, 31–32; Anekonda 24.[8] According to Appellant, the 2% phytic acid solution in these tests would equate to a daily dose in humans that falls within the claimed range. *Id.* at 31–32. But even then, these data merely compare the claimed dose to a "control vehicle without phytic acid." Spec. 11. They do not purport to compare the results achieved at the claimed dose to either the somewhat higher dose reported in Sabin or the 100 mg/kg dose taught in Frey. Thus, the data and statements in the Specification and in Anekonda[9] do not show that the claimed invention, i.e., administration of phytic acid within the claimed range, achieves unexpected results as compared to the closest prior art, i.e., administration of the same compound at the somewhat higher dosage in Sabin or at the dosage range in Frey. *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."). Indeed, Anekonda evidences that the opposite is true. It states that "the administered PA dose (2%) was likely too mild" and postulates that "a much higher dose of PA starting as early as 2–3 months of animal age is expected to provide preventative effect on the accumulation of Aβ plaques." Anekonda 30.

[8] Both the Specification and Anekonda report data from in vitro tests in MC65 cells. *See* Spec. 9; Anekonda 26–28. There is, however, no evidence demonstrating how the concentration of phytic acid applied to the cells in those tests relates to the claimed dosage range. Accordingly, this data does not evidence that Appellant's present claims are non-obvious over the prior art.

[9] Appellant additionally cites a July 29, 2011 email from Thimmappa Anekonda with the subject line "Re: Novel findings of our PA study in AD." *See* App. Br. 24–25 and 31. This email does not appear to present any additional information beyond the Anekonda article itself.

Second, there is no evidence that the results Appellant relies upon are reasonably commensurate with the full breadth of the claimed dosage range. According to Appellant's calculations, giving mice water containing 2% phytic acid equates to a daily dose in humans near, or slightly exceeding, the upper end of the claimed range (18.75 grams per day). App. Br. 31–32. But the lower end of the range in claim 6 is only 0.5 grams per day. There is no evidence suggesting that a dose at or near 0.5 grams per day, i.e., more than 35 times less than the 18.75 gram upper end of the range, would achieve results similar to the studies Appellant relies upon involving 2% phytic acid. Indeed, as noted above, Anekonda affirmatively evidences the contrary by stating that the 2% dose in those studies "was likely too mild." Anekonda 30.

Third, Appellant has not shown that the relied-upon results were unexpected over the prior art. Sabin teaches that phytic acid is useful to treat and alleviates symptom of Alzheimer's Disease. *See* Sabin 2:23–44. Appellant's mouse data supports Sabin's conclusion. What Appellant has not shown is how that data and the literature cited in the Appeal Brief (*see* App. Br. 24–26) demonstrate a result that is unexpectedly different in kind from the prior art, which already taught that phytic acid was effective to alleviate symptoms of Alzheimer's Disease. At most, Appellant's evidence elucidates the mechanisms by which phytic acid may be effective in alleviating symptoms of Alzheimer's Disease, e.g., by providing "protection against APP-C99-mediated toxicity," "[e]nhanc[ing] cytochrome oxidase (mitochondrial function)," or "[s]uppress[ing] malondialdehyde or Lipid peroxidation." *See id.* at 24–25. The question before us is not whether such findings are scientifically significant, but whether they are probative of non-

obviousness because they show unexpected results that are "'different in kind and not merely in degree from the results of the prior art.'" *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)). As our reviewing court has explained, even when unexpected if "in efficacy is measured by a small percentage . . . and the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind." *Id.* Here, there is no evidence that the claimed dosage increases efficacy or reduces toxicity as compared to the prior art dosages taught in Sabin and Frey, much less the percentage of any such change.

For all these reasons, Appellant has not persuasively demonstrated that the claimed dosage range is critical or that it otherwise exhibits unexpected results over the dosages taught in Sabin and Frey. Thus, when weighing the record as a whole in light of Examiner's comparatively strong prima facie case, we determine that the preponderance of the evidence supports Examiner's rejections as to claims 6, 21–23, and 28, 29, 31–35, and 37.

Regarding the "empty stomach" limitation of claims 30 and 36, Appellant additionally argues that Grases "teaching of administration on an empty stomach is lacking sufficient evidentiary support" to show obviousness because it involved healthy subjects and did not include the number of subjects required for a Phase 1 or Phase 0 clinical study. *See* App. Br. 27–28. We disagree. "Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d

1326, 1331 (Fed. Cir. 2014). Grases teaches that there were "no differences in the [phytic acid] excretion profiles" when administered on an empty versus a full stomach and concludes that optimum phytic acid levels can be achieved by taking supplements "either during or between meals with the same efficacy." FF3. That teaching is sufficient to support a reasonable expectation that phytic acid could be successfully administered to a patient on an empty stomach, as recited in claims 30 and 36. While additional data may be required for FDA approval, "absolute certainty for success" is not required to show obviousness. *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) (citation omitted). Accordingly, the preponderance of the evidence also supports Examiner's rejections of claims 30 and 36. We therefore affirm Rejection I and Rejection II.

ODP Rejections

With respect to Rejection III and Rejection IV, Appellant incorporates the same arguments it presents for the obviousness rejections. *See* App. Br. 34. As explained above, we are unpersuaded by those arguments. Since Appellant does not present any additional argument as to why the claims of Sabin and Sabin II, in view of Frey and Grases, do not render his present claims obvious, we affirm. *See* 37 C.F.R. § 41.37(c)(1)(iv) ("any arguments or authorities not included in the appeal brief will be refused consideration by the Board for purposes of the present appeal").

SUMMARY

We affirm the rejection of claims 6, 21–23, and 28–37 under 35 U.S.C. § 103 as obvious over Sabin and Frey.

We affirm the rejection of claims 6, 21–23, and 28–37 under 35 U.S.C. § 103 as obvious over Sabin, Frey, and Grases.

We affirm the rejection of claims 6, 21–23, and 28–37 for ODP over claims 1–7 of Sabin in view of Frey and Grases.

We affirm the rejection of claims 6, 21–23, and 28–37 for ODP over claims 1–3 of Sabin II in view of Frey and Grases.

TIME PERIOD FOR RESPONSE

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

AFFIRMED