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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KARINE DEFFEZ and JEAN-PIERRE CASSIERE[1]

Appeal 2019-004972
Application 15/054,899
Technology Center 1600

Before ERIC B. GRIMES, ULRIKE W. JENKS, and
RACHEL H. TOWNSEND, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a dispersible tablet, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM but designate the affirmance a new ground of rejection.

STATEMENT OF THE CASE

The Specification describes Compound I (4-[3,5-bis(2-hydroxyphenyl)-[1,2,4]triazol-1-yl]benzoic acid). Spec. 1. "Compound I is

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[1] Appellant identifies the real party in interest as Novartis AG. Appeal Br. 3. We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

an orally active iron chelator that is indicated in the treatment of iron overload in transfusion dependent anemias." *Id.* Compound I is also known as deferasirox. Appeal Br. 14.

Claims 16 and 27–31 are on appeal. Claim 16, reproduced below, is illustrative:

> 16. A dispersible tablet comprising 125mg deferasirox or a pharmaceutically acceptable salt thereof; and, at least one disintegrant selected from the group consisting of cross-linked polyvinylpyrrolidone, starch, CMC-Ca, CMC-Na, microcrystalline cellulose, alginic acid, sodium alginate, and guar gum, in a total amount of about 5 to 40% by weight based on the total weight of the tablet.

Claims 27 and 28 are also independent, and are identical to claim 16 except for requiring 250 mg or 500 mg, respectively, of deferasirox.

OPINION

Claims 16 and 27–31 stand rejected under 35 U.S.C. § 103(a) as obvious based on Lattmann[2] and Patel.[3] Ans. 3. The Examiner finds that "Lattmann teaches a dispersible tablet formulation comprising deferasirox." *Id*. at 4. "The dosage form is administered to a patient in need thereof in a concentration from 20–80 mg/kg. . . . The compound is an iron chelator and can be used to treat iron overload." *Id.* The Examiner finds that Lattmann discloses that its tablets can include "excipients such as fillers like, lactose, sucrose and mannitol, disintegrants such as starches, binders such as polyvinylpyrrolidone," etc. *Id.*

[2] Lattmann et al., WO 97/49395, published Dec. 31, 1997.
[3] Patel et al., US 5,698,221, issued Dec. 16, 1997.

The Examiner finds that Lattmann "is silent to the specific concentrations of these compounds, however their presence and concentrations are well known in the art as seen in the Patel patent." *Id.* Specifically, "Patel discloses a dispersible tablet comprising" a different active agent. *Id.* The tablets comprise, among other things, "disintegrants up to 30%." *Id.*

The Examiner concludes that "[i]t would have been obvious to combine the specific formulation of [Patel] with the formulation of [Lattmann] since both patents disclose dispersible tablets comprising Alzheimer's medications." *Id.* The Examiner reasons that "the specific concentrations and ranges of the instant claims" are "result effective parameters" and "[e]ach of them can be manipulated and optimized in order to arrive at an optimal dispersible tablet . . . through routine experimentation." *Id.* at 5.

We agree with the Examiner that Lattmann and Patel support a prima facie case of obviousness for the claimed tablets. Lattman discloses compounds for treating iron overload caused by, for example, repeated blood transfusions. Lattmann 1. Lattmann describes deferasirox in a working example. *Id.* at 19, Example 5.

Lattmann states that "[p]harmaceutical preparations for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, dispersible tablets," etc. *Id.* at 7. "Pharmaceutical preparations for oral administration can thus be obtained by combining the active ingredient with solid carriers." *Id.* "Suitable carriers are, in particular, fillers . . . , furthermore binders . . . , and, if desired, disintegrants, such as . . .

starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate." *Id.*

"Dispersible tablets are tablets which rapidly disintegrate in a comparatively small amount of liquid. . . . They can advantageously be employed for the oral administration of large individual doses." *Id.* at 8. Lattmann discloses that

> [t]he doses to be administered daily in the case of oral administration are between 10 and approximately 120 mg/kg, in particular 20 and approximately 80 mg/kg, and for a warm-blooded animal having a body weight of approximately 40 kg, preferably between approximately 400 mg and approximately 4,800 mg, in particular approximately 800 mg to 3,200 mg, which is expediently divided into 2 to 12 individual doses.

Id. A dosage of 800 mg divided into 12 doses corresponds to about 67 mg/dose, and a dosage of 3200 mg divided into 2 doses corresponds to 1600 mg/dose. Lattmann thus suggests individual doses containing 67–1600 mg of active agent.

Patel discloses a water-dispersible tablet comprising an active agent ("AMTP"), a swellable clay disintegrating agent, and "a further pharmaceutically acceptable disintegrating agent." Patel 1:31–36. Patel suggests specific further disintegrating agents and ranges of amounts for them, including: "cross-linked povidone 0 to 10% w/w, preferably 2 to 6% w/w, alginic acid and alginates 0 to 10% w/w, 2 to 5% w/w, pregelatinised starch 0 to 10% w/w, preferably 0.5 to 5% w/w, . . . modified corn starch (e.g. starch 1500 R) 0 to 20% w/w, preferably 1 to 10% w/w, starch (e.g. potato/maize starch) 0 to 15% w/w, preferably 0.2 to 10% w/w." *Id.* at 5:56 to 6:4.

In view of the disclosures of Lattmann and Patel, the tablets of claims 16, 27, and 28 would have been prima facie obvious to a person of ordinary skill in the art. Lattmann discloses deferasirox as being useful in pharmaceutical compositions for treating iron overload, and suggests dispersible tablets for oral administration of large doses. Lattmann also suggests individual doses of 67–1600 mg, a range that encompasses the amounts of deferasirox recited in the instant claims.

Finally, Lattmann suggests including disintegrants that include several of those recited in the claims, and Patel discloses ranges for amounts of the same disintegrants, also in a dispersible tablet, that include amounts within the 5–40% range recited in the claims. It would have been obvious to a skilled artisan to use the specific disintegrants suggested by both Lattmann and Patel, in the amounts disclosed by Patel to be useful in dispersible tablets, for their recognized function of promoting disintegration, in the deferasirox dispersible tablets suggested by Lattmann.

Appellant argues that "no motivation to single out deferasirox from the primary reference Lattmann exists." Appeal Br. 10. Appellant argues that Lattmann's formula I encompasses hundreds of thousands of compounds, and "[e]ven if considering the teaching of Example 5, deferasirox is only one of 42 compounds exemplified." *Id.* at 10–11.

This argument is unpersuasive. Lattmann's specific description of deferasirox, among forty-two exemplified compounds, is sufficient reason for a skilled artisan to use deferasirox in Lattmann's pharmaceutical formulations. The forty-one other exemplified compounds do not make deferasirox any less obvious. *Cf. Merck & Co. v. Biocraft Labs., Inc.*, 874

F.2d 804, 807 (Fed. Cir. 1989) ("[D]isclos[ing] a multitude of effective combinations does not render any particular formulation less obvious.").

Appellant argues that "Lattmann provides no teaching or suggestion that among the range of formulation choices, dispersible tablets provide any benefits or advantages for any particular . . . compounds." Appeal Br. 11. This argument is unpersuasive, because Lattmann states that dispersible tablets "can advantageously be employed for the oral administration of large individual doses." Lattmann 8. Lattmann also suggests individual doses in the range of 67–1600 mg of active agent, a range which includes large amounts of an active agent. Thus, a dispersible tablet would have been among the obvious choices for a deferasirox dosage form, based on Lattmann's teachings.

Appellant argues that Patel's active agent has different properties than deferasirox. Appeal Br. 13–14. However, the Examiner cites Patel only for teaching the amount of excipients (e.g., disintegrants) used in dispersible tablets. Ans. 4. Appellant has not shown that the alleged properties of Patel's active agent would affect the amount of disintegrant(s) used in dispersible tablets comprising deferasirox. The argument is therefore unpersuasive.

Appellant argues that Patel requires a swellable clay disintegrant and "[n]owhere in Patel does it teach or suggest a non-sipatrigine water-dispersible tablet without a first swellable clay, as the current claims recite." Appeal Br. 15. *See also id.* at 16 ("The Markush group for disintegrant selection is closed and enumerated with the swellable clay excluded."); *id.* at 19 (with respect to claims 29–31, "[t]he presently claimed invention does not involve a swellable clay as a disintegrant.").

The instant claims, however, use the transition term "comprising." "In the patent claim context, the term 'comprising' is well understood to mean 'including but not limited to'." *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007). Thus, the instant claims encompass ingredients in addition to those recited, including a swellable clay disintegrant.

Appellant argues that "the Examiner has not articulated why a person of ordinary skill in the art at the time of the present invention would have had the motivation to select the specific amounts of deferasirox recited in claims 16, 27 and 28." Appeal Br. 17.

This argument is unpersuasive because Lattmann describes a range of individual doses for its compounds, including the exemplified compound deferasirox, and that range encompasses the claimed amounts. "A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). "Selecting a narrow range from *within* a somewhat broader range disclosed in a prior art reference is no less obvious than identifying a range that simply *overlaps* a disclosed range." *Id.* at 1329–30.

For the reasons discussed above, we conclude that Lattmann and Patel support a prima facie case of obviousness for the claims on appeal. "Once the examiner establishes a prima facie case of obviousness, the burden shifts to the applicant to rebut that case. . . . However, once the applicant has come forward with rebuttal evidence, the examiner must consider the totality of the evidence to determine whether the obviousness rejection should stand."

In re Huai-Hung Kao, 639 F.3d 1057, 1066 (Fed. Cir. 2011). *See also id.* at 1067 ("[W]hen secondary considerations are present, though they are not always dispositive, it is error not to consider them.").

Appellant argues that the evidence of record shows that the claimed invention solved a long-felt but previously unsolved need and has been a commercial success. Appeal Br. 21. Appellant also argues that, in the Final Action, "the Examiner made no mention of the evidence proffered by the Appellant at all." *Id. See also* Reply Br. 12 ("The Examiner neither responds to nor acknowledges the arguments in the Appeal Brief related to the second[ary] considerations.").

We agree with Appellant that the Examiner erred in not addressing the proffered evidence and re-considering the case for obviousness based on all of the evidence. We therefore address Appellant's evidence below and, although we ultimately affirm the rejection, we designate the affirmance a new ground of rejection to allow Appellant a fair opportunity to respond to our critique of the evidence.

Long-felt but Unsolved Need

Appellant argues that "[p]rior to the approval of EXJADE® (deferasirox) by the FDA, DESFERAL® (deferoxamine) was the principal treatment of chronic transfusional iron overload for over forty years." Appeal Br. 21, citing Danko Decl.[4] ¶¶ 8, 10. *See also id.* at 22 ("EXJADE®

[4] Appellant cites to Exhibit 5 of the Appeal Brief's Evidence Appendix, but Exhibit 5 is an unsigned declaration that refers to a different patent application. We understand Appellant's citations to "Ex. 5" to instead refer to the Declaration under 37 C.F.R. § 1.132 of Laszlo Danko submitted in the

(deferasirox) dispersible tablets are the commercial embodiment of the claimed subject matter."). Appellant argues that deferoxamine "is delivered by continuous subcutaneous infusion for 8–12 h/day, 5–7 days/week." *Id.* at 21–22, citing Danko Decl. ¶ 10, Porter[5] ¶ 2. Appellant argues that parenteral administration of deferoxamine "hinders adherence (compliance), with resultant premature deaths related to iron overload." *Id.* at 22, citing Danko Decl. ¶ 12.

Appellant cites the Danko Declaration and Cappellini[6] as evidence that EXJADE® provides "vastly improved patient compliance" or a "substantial improvement in patient compliance." *Id.* Appellant cites Jordan[7] and Vichinsky[8] as evidence that, among patients with sickle cell disease, "[c]ompliance is vastly improved with EXJADE@ (deferasirox) compared to DESFERAL® (deferoxamine) in this, mostly African American, population." *Id.* at 23.

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instant application on February 26, 2016. Our discussion pertains to that declaration, not to Exhibit 5 of the Evidence Appendix.

[5] Porter et al., Health-Related Quality of Life, Treatment Satisfaction, Adherence and Persistence in β-Thalassemia and Myelodysplastic Syndrome Patients with Iron Overload Receiving Deferasirox: Results from the EPIC Clinical Trial, *Anemia*, Article ID 297641, 10 pages (2012).

[6] Cappellini et al., Patient Satisfaction with Deferasirox (Exjade®, ICL670) an Oral Form of Chelation Therapy Versus Deferoxamine an Infused Chelation Therapy, *Blood* 106: Abstract 2704 (2005).

[7] Jordan et al., Persistence and compliance of deferoxamine versus deferasirox in Medicaid patients with sickle-cell disease, *Journal of Clinical Pharmacy and Therapeutics* 37:173–181 (2012).

[8] Vichinsky et al., Satisfaction and Convenience of Chelation Therapy in Patients with Sickle Cell Disease (SCD): Comparison between Deferasirox (Exjade®, ICL670) and Deferoxamine (DFO), *Blood* 106: Abstract 2334 (2005).

We find that the cited evidence supports Appellant's position that EXJADE® solved a long-felt need in the art for an iron chelation agent that, unlike deferoxamine, could be conveniently administered, thereby increasing patient compliance.

Commercial Success

Appellant also argues that "evidence of commercial success [was] detailed in the Danko Declaration." Appeal Br. 23. Appellant argues that EXJADE® "is now approved in about 100 countries, [and] had global sales exceed $870 and $893 million in 2012 and 2013, respectively." *Id.*, citing Danko Decl. ¶¶ 19–22. "This accounts for over 500% increase from the sales of DESFERAL® (deferoxamine), and proves that the market share gained by EXJADE® (deferasirox) is based on its superior effectiveness." *Id.*, citing Danko Decl. ¶ 18.

We agree with Appellant that the Danko Declaration provides evidence that EXJADE® is a commercially successful iron chelation treatment agent. Mr. Danko declares that "DESFERAL® (deferoxamine) . . . has been (was) the standard of care for transfusional iron overload for over forty (40) years." Danko Decl. ¶ 10. "FDA approved *dispersible tablet* EXJADE® (deferasirox) as the first oral drug for chronic iron overload November 9, 2005." *Id.* ¶ 15. "EXJADE® (deferasirox) . . . now accounts for over 500% (5x) the sales of DESFERAL® (deferoxamine)." *Id.* ¶ 18. Mr. Danko also declares that global sales of EXJADE® exceeded $870 million in 2012 and $893 million in 2013. *Id.* ¶¶ 19, 21.

The Danko Declaration therefore provides persuasive evidence that EXJADE® sales have increased substantially since its introduction, that at

least as of 2013 EXJADE® sales were much greater than those of deferoxamine, and that purchasers spent hundreds of millions of dollars to buy EXJADE® in 2012 and 2013. The evidence thus shows that EXJADE® is a commercially successful product.

Nexus

"[T]here is a . . . fundamental requirement that must be met before secondary considerations can carry the day. '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*.'" *In re Kao*, 639 F.3d at 1068, quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (emphasis added by the *Kao* court). With regard to commercial success, for example, "an applicant 'need not sell every conceivable embodiment of the claims in order to rely upon evidence of commercial success, so long as what was sold was within the scope of the claims.'" *Id.* at 1069, quoting *In re DBC*, 545 F.3d 1373, 1384 (Fed. Cir. 2008).

We find that Appellant's evidence falls short with respect to the required nexus between the evidence relating to EXJADE® and the claimed dispersible tablets. The Danko Declaration provides evidence that EXJADE® represents dispersible tablets comprising deferasirox, in dosages that include 125, 250, and 500 mg. Danko Decl. ¶¶ 15, 22. However, the instant claims are directed to *specific* formulations of deferasirox: dispersible tablets comprising at least one of eight specific disintegrants, in an amount of about 5 to 40% by weight based on the total weight of the tablet.

Appellant has not pointed to evidence showing that EXJADE® dispersible tablets comprise at least one of the disintegrants recited in the instant claims, in the required amount. Thus, the evidence does not show that EXJADE® is a deferasirox dispersible tablet formulation encompassed by the claims.

Although Appellant states that "EXJADE® (deferasirox) dispersible tablets are the commercial embodiment of the claimed subject matter," Appeal Br. 22, "[a]ttorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). Thus, Appellant has not shown that the evidence that has been submitted pertaining to EXJADE® is evidence of nonobviousness for the *claimed* invention.

CONCLUSION

A preponderance of the evidence of record supports a conclusion of obviousness and therefore we affirm the rejection of claims 16 and 27–31 under 35 U.S.C. § 103(a) based on Lattmann and Patel. Because the Examiner did not address Appellant's evidence of nonobviousness, however, we designate our affirmance a new ground of rejection.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed	New Ground
16, 27–31	103(a)	Lattmann, Patel	16, 27–31		16, 27–31

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). Section 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review." Section 41.50(b) also provides:

> When the Board enters such a non-final decision, the appellant, within two months from the date of the decision, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:
>
> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in the Manual of Patent Examining Procedure § 1214.01.

AFFIRMED; 37 C.F.R. § 41.50(b)