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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ERIC SCHENKEL, CLAIRE POULAIN, BERTRAND
DODELET, and DOMENICO FANARA¹

Appeal 2014-001930
Application 12/920,524
Technology Center 1600

Before DEMETRA J. MILLS, JOHN G. NEW, and RYAN H. FLAX,
Administrative Patent Judges.

FLAX, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims directed to an epimerically stable solution of a pharmaceutical compound. Claims 1, 2, and 4–7 are on appeal as rejected under 35 U.S.C. § 103(a). We have jurisdiction under 35 U.S.C. § 6(b).

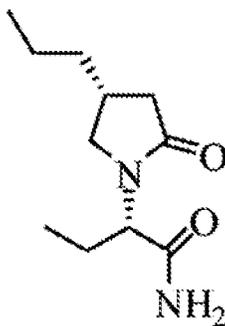
We affirm.

¹ We understand the Real Party in Interest to be UCB Pharma, S.A. App. Br. 3.

STATEMENT OF THE CASE

The appealed claims can be found in the Claims Appendix of the Appeal Brief. Claim 1 is representative and reads as follows:

1. An epimerically stable solution of a pharmaceutical compound of formula (I) comprising brivaracetam,



and water, wherein the solution has a pH value of between 4.5 and 6.5, wherein the brivaracetam of formula (I) is epimerically stable in said solution.

App. Br. 12 (Claims App'x).

The following rejection is on appeal:

Claims 1, 2, and 4–7 rejected under 35 U.S.C. § 103(a) over Verdru² and Theuer.³ Final Action 2.

Oral argument was presented at a hearing on October 14, 2016. The transcript thereof was mailed October 28, 2016, and is a part of the record (hereinafter “Hr’g Tr.”).

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

² European Patent Application Pub. No. EP 1 731 149 A1 (published Dec. 13, 2006) (hereinafter “Verdru”).

³ Hagen Theuer et al., *Stabilitätsuntersuchungen von Piracetam-Infusionslösungen*, 132 PHARMAZEUTISCHE ZEITUNG 1024–29 (1987) (English translation of record) (hereinafter “Theuer”).

Answer. The findings of fact set forth below are provided only to highlight certain evidence of record.

FINDINGS OF FACT

FF1. Verdrü disclosed:

The present invention relates to the use of brivaracetam for the preparation of drugs effective for the prevention or treatment of progressive myoclonic epilepsy. . . .

[one example is] the compound 2-pyrrolidineacetamide . . . also known as piracetam. . . .

2-oxo-1-pyrrolidine derivatives, such as brivaracetam, as well as their use as pharmaceuticals are described . . .

Verdrü ¶¶ 1–4; *see also* Ans. 3 (discussing Verdrü).

FF2. Verdrü disclosed, “[i]n addition to the active compound [brivaracetam], these solutions or suspensions can optionally also contain . . . buffers such as acetates, citrates or phosphates. Verdrü ¶¶ 21–22; *see also* Ans. 3, 14–15 (discussing Verdrü).

FF3. Theuer disclosed, “[p]iracetam is 2-oxo-pyrrolidine-1-acetamide” and has the chemical structure:



Theuer (translation) 1; *see also* Ans. 4, 10, 12–15 (discussing Theuer).

FF4. Theuer disclosed:

The most important degradation reaction affecting the stability of aqueous solutions is hydrolysis.



This is a pseudo-first order reaction. In the more stable *cis* conformation, the amidic NH₂ group points towards the pyrrolidine ring, which hinders the approach of the polar water molecules. Taking account also of the stabilizing effect of the intramolecular hydrogen bonding, piracetam might therefore be expected to show low sensitivity to hydrolysis.

Theuer (translation) 2; *see also* Ans. 4, 10, 12–15 (discussing Theuer).

FF5. Theuer disclosed:

pH profile

In order to define the optimal pH range for the stability of piracetam in aqueous solutions, we created a pH profile. This was done by adjusting the pH of a 20% solution to different values and determining the ammonium ion concentration after autoclave sterilization at 121°C for 20 min and storage. The results are shown in Table 1.

Table 1: Ammonium ion content of piracetam i.v. solution after storage for 6 months and log k values of the hydrolysis reaction at different pH values

pH	NH ₄ ⁺ [mg/l]	log k
3.75	217	-2.845
4.16	119	-3.572
5.08	22	-3.875
5.90	23	-3.828
6.44	35	-3.632
8.96	46	-3.523
11.58	465	-2.510

The rate-pH profile for the hydrolysis reaction of piracetam in aqueous solution is shown in Fig. 1. From the rate-pH profile for piracetam hydrolysis, it can be seen that the optimal pH range for the stability of the solution is between 5.5 and 6.0.

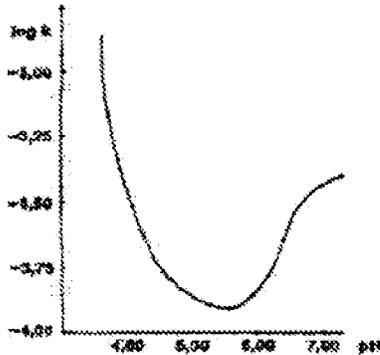


Fig. 1: Rate-pH profile for the hydrolysis of piracetam

Theuer (translation) 3–4; *see also* Ans. 4, 10, 12–15 (discussing Theuer).

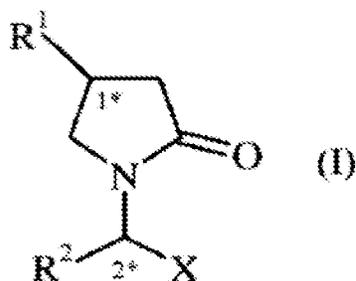
Figure 1, reproduced above, shows a graph comparing log K value to pH value, showing the lowest log k values between 5 and 6 pH.

FF6. The Specification states:

However, stability storage tests have shown that aqueous solutions of 2-oxo-1-pyrrolidine derivatives were partially unstable. During these tests, degradation products in solution are formed by basic or acid hydrolysis, in fact an epimerisation and/or amide hydrolysis occurred, but also oxidation, with detection of hydroxyamide and hydroxyacid impurities.

It has now surprisingly been found that these degradation products are not formed at pH values between 4.5 and 6.5. In fact kinetics of degradation is the slowest in normal conditions (room temperature) when the drug solution has a pH value of between 4.5 and 6.5.

The invention relates to a stable solution of a pharmaceutical compound, the solution having a pH value of between 4.5 and 6.5, and the pharmaceutical compound being an 2-oxo-1-pyrrolidine derivative of formula (I),



Spec. 2:15–29; *see also* Ans. 7, 10–11, 13–14 (discussing Spec.).

FF7. The Specification states, “[b]y ‘stable’ we mean optimum of stability in normal condition of storage (room temperature).” Spec. 3:5–6.

FF8. The Specification states:

Substances for adjusting the pH value are physiological buffers. The pH of the compositions is maintained by a buffer system. . . Ideally, the buffer has sufficient capacity to remain in the intended pH range upon dilution with a neutral, a slightly acidic or a slightly basic beverage.

Examples of buffers are acetic acid, phosphate and citric acid. The best results are obtained with acetic acid and citric acid.

Spec. 5:20–29; *see also* Ans. 6–7 (discussing motivation to optimize pH in view of Verdru and Theuer).

FF9. The claim term “epimerically stable” is not defined in the Specification and its meaning is not readily discernable from the context of the claims, but the Examiner determined the term is generally known to those of ordinary skill in the art as a compound that does not change chemical bond orientation. *See generally* Spec.; *see also* Ans. 6–7 (interpreting the claim terms) and Hr’g Tr. 8:3–11 (counsel conceding the Specification does not define the term “epimerically stable solution”).

FF10. The Schenkel Decl. states, we understand in relation to brivaracetam, “the chiral instability is a phenomenon totally independent of the hydrolytic instability.” Schenkel Decl. ¶ 2;⁴ *cf.* FF6, *supra*.

FF11. The Schenkel Decl. states, “the hydrolytic stability of Brivaracetam and Piracetam does not teach or suggest to one of skill in the art anything about the chiral stability of Brivaracetam. Schenkel Decl. ¶ 2; *cf.* FF6, *supra* (explaining hydrolysis as the/a cause of epimerization).

FF12. The Schenkel Decl. confirms a relationship between brivaracetam’s epimeric and hydrolytic stabilities exists, stating, “[r]esults show Brivaracetam stability to epimerization at position 2 into ucb-100230-1 between pH 4.5 and 6.0, i.e.[,] within the range of maximum stability with regards to hydrolysis reaction.” Schenkel Decl. ¶ 4.

DISCUSSION

The Examiner has made a prima facie case that the claims are obvious over Verdru and Theuer, which Appellants have not provided sufficient persuasive evidence to overcome. We address Appellants’ arguments below.⁵

⁴ Declaration of Eric Schenkel Under 37 C.F.R. § 1.132, dated July 20, 2012 (hereinafter “Schenkel Decl.”).

⁵ Appellants’ arguments in the Reply Brief regarding the Examiner’s alleged failure to consider the level of ordinary skill in the art, failure in the art to recognize the problem to be solved, obvious to try, lack of reasonable expectation of success, and the Examiner’s alleged application of the law of anticipation are not considered. *See* Reply Br. 2–11.

Any argument raised in the reply brief which was not raised in the appeal brief, or is not responsive to an argument raised in the examiner’s answer, including any designated new ground of rejection, will not be considered by the Board for purposes of the present appeal, unless good cause is shown.

Appellants argument for nonobviousness hinges on two contentions: (1) prior to their invention, those of ordinary skill in the art had not recognized the epimeric stability problem allegedly solved by the invention, which is unrelated to hydrolytic stability; and (2) evidence of unexpected “good epimeric stability” for brivaracetam is evidence of nonobviousness sufficient to overcome the Examiner’s prima facie case. App. Br. 5–8; Reply Br. 3–4 and 8–9; *see also* Hr’g Tr. 2:17–24 and 5:16–18. Appellants present other, related arguments, but these are central to their nonobviousness contentions.⁶ We are not persuaded by these arguments.

We first address Appellants’ contention that the person of ordinary skill in the art, in relation to the recited therapeutic compound brivaracetam, would not look to Theuer’s disclosure of optimizing pH to hydrolytically stabilize piracetam because piracetam is allegedly too chemically different from brivaracetam because it lacks brivaracetam’s potential for epimerization and because hydrolytic stability and epimeric stability are not closely related enough to make the combination of Theuer and Verdrum reasonable. App. Br. 4–7. As evidence, Appellants cite to the Schenkel Decl., which identifies the epimeric instability of brivaracetam, confirms that it is acceptably stabilized at pH 4.5–6.0, and states, “even if Brivaracetam instability due to hydrolysis reactions can be deduced from Piracetam behavior in hydrolysis reactions, one skilled in the art would not

37 CFR § 41.41(b)(2). Appellants have not shown good cause why these arguments, raised for the first time in the Reply Brief, should be considered.

⁶ Appellants contend there was an “Unmet Need in the Industry for Stable Liquid Brivaracetam Formulations,” App. Br. 9, but provide no direct evidence of such a need or that it was long felt, as required. “Attorneys’ argument is no substitute for evidence.” *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989).

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apply the same reasoning to the issue of chiral stability as no chiral center exists in Piracetam.” *See* App. Br. 5–7 and Schenkel Decl. ¶¶ 2–4.

We are not persuaded. The cited prior art combination disclosed that brivaracetam and piracetam are related compounds within the class of 2-oxo-1-pyrrolidine derivatives, which are useful to treat epilepsy. FF1 and FF3. The Specification explains, as a matter of science, that compounds within this class of “2-oxo-1-pyrrolidine derivatives” are partially unstable in that “basic or acid hydrolysis” produces degradation products in solution, including via “epimerization and/or amide hydrolysis [and] oxidation,” resulting in “hydroxyamide and hydroxyacid impurities.” FF6; *see also* Hr’g Tr. 4:5–6 (Appellants’ counsel confirms the statement in the Specification is correct).

The Specification describes the invention as preventing these hydrolysis-caused “degradation products,” including epimerisation, and explains that it is accomplished by adjusting pH using buffers. FF6–FF8. The Specification does not go into further detail regarding epimeric stability. FF9. “[T]here [is no] unfairness in holding the inventors to the consequences of their admissions.” *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007) (holding admissions in specification as to prior art are binding on inventors). The consequence here is that we understand there is a relationship between hydrolysis and epimeric stability in 2-oxo-1-pyrrolidine derivatives, such as brivaracetam, and that adjusting the pH of a brivaracetam solution to make the compound hydrolytically stable will also make it epimerically stable.

The claims are directed to a pharmaceutical solution with brivaracetam. *See* claim 1, *supra*. “From the standpoint of patent law, a compound [or a formulation] and all of its properties are inseparable; they

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are one and the same thing.” *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963).

[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer. . . . This same reasoning holds true when it is not a property, but an ingredient, which is inherently contained in the prior art.

Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999).

“The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, cannot impart patentability to the known composition.” *Tyco Healthcare Group LP v. Mutual Pharam Co., Inc.*, 642 F.3d 1370 (Fed. Cir. 2011) (quoting *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990)).

The Specification, the Schenkel Decl., and statements at oral argument confirm that the skilled artisan would share concerns regarding hydrolysis when dealing with brivaracetam, just as Theuer discloses would be the case when dealing with piracetam. FF6; FF12; Hr’g Tr. 8:19–21. Thus, it would be entirely reasonable for such a skilled artisan to combine the disclosures of Theuer and Verdru in formulating a brivaracetam solution, regardless of whether its epimeric stability was recognized or an objective. In so doing, the skilled artisan would be led to adjust the pH of the solution of Verdru to hydrolytically stabilize the 2-oxo-1-pyrrolidine derivative brivaracetam using a buffer, and Theuer teaches the optimum pH range to be between 5.0–6.0, most specifically 5.5–6.0. FF1–FF5. As Appellants point out, “[i]n this case, the epimeric stability of the claimed compositions is inseparable from the composition itself.” App. Br. 8. Where, as here, the

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formulation or composition is obvious, identifying an unappreciated property of that formulation or composition does not impart patentability.

Turning to Appellants' contention that unexpected results have been shown that overcome the Examiner's prima facie case for obviousness, we are also not persuaded. Appellants argue the epimeric stability of brivaracetam was unexpected because brivaracetam is different from piracetam in that it has an ethyl ligand at "2" and an isopropyl ligand at "4," which create "chiral centers" at these positions not present in piracetam – it is therefore capable of forming four epimers that piracetam is not and only one of these 4 epimers is the active ingredient. App. Br. 5–8; *see also* Schenkel Decl. ¶ 3.

As discussed above, "it is [] clear that the discovery that a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a prima facie case." *In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990) (en banc). Moreover,

[u]nexpected properties, however, do not necessarily guarantee that a new compound is nonobvious. While a "marked superiority" in an expected property may be enough in some circumstances to render a compound patentable, a "mere difference in degree" is insufficient. *In re Papesch*, 50 CCPA 1084, 315 F.2d 381, 392 (CCPA 1963); *In re Hoch*, 57 CCPA 1292, 428 F.2d 1341, 1344 n.5 (CCPA 1970) (explaining that unexpected "differences in properties" can mean "significant difference in degree of the same property" amounting to a "marked superiority" for purposes of evaluating unexpected results) (quotation omitted).

Bristol Myers Squibb Co. v. Teva Pharma USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014).

Here, we are presented with evidence not of marked superiority, but merely of greater detail about why a pH of 5.5–6.0 stabilizes a 2-oxo-1-

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pyrrolidine derivative. The brivaracetam solution stability would be expected based on the prior art's disclosure of hydrolytic stability of piracetam in the same pH range and the scientific fact that hydrolytic stability and epimeric stability are related in 2-oxo-1-pyrrolidine derivatives. *See* FF5 and FF6. Furthermore, pH is an optimizable variable in brivaracetam solutions, as evidenced by the fact that, in the prior art, as in the Specification, buffers were taught as added to control pH. FF2 and FF8.

Verdru does not indicate to what pH its otherwise disclosed brivaracetam solution should be adjusted with buffer, so the skilled artisan would reasonably consider other 2-oxo-1-pyrrolidine-derivative-disclosing references, such as Theuer, for this information and would learn that by adjusting pH to 5.5–6.0, one would obtain a stable 2-oxo-1-pyrrolidine derivative. FF5. The brivaracetam solution recited by the appealed claims would possess no properties different from those of the brivaracetam solution of Verdru having a buffer content adjusting its pH to that suggested by Theuer. *See In re Dillon*, 919 F.2d at 694; *see also* Hr'g Tr. 8:3–11 (Appellants suggesting epimeric stability properties would be inherent). “[B]y definition, any superior property must be *unexpected* to be considered evidence of non-obviousness.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Here, improved stability by optimizing pH was not unexpected.

Appellants argue that method claims 8–13 (not elected in restriction requirement) should be rejoined and allowed. We do not reach this issue as not before us for decision on appeal. *See In re Hengehold*, 440 F.2d 1395, 1404 (CCPA 1971).

For the above reasons, we find that the preponderance of evidence supports the Examiner's determination that the claims would have been

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obvious over Verdru and Theuer and that Appellants' evidence of secondary indicia of nonobviousness has not overcome this prima facie case. We affirm the rejection.

SUMMARY

The rejection of claims 1, 2, and 4–7 under 35 U.S.C. § 103(a) over Verdru and Theuer is affirmed. Claims 2 and 4–7 fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

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