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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MAURICE SYDNEY NEWTON,
NIGEL PETER RHODES, and ALEXIS JOHN TOFT

Appeal 2018-004205
Application 11/815,845
Technology Center 1600

Before RYAN H. FLAX, RACHEL H. TOWNSEND, and
CYNTHIA M. HARDMAN, *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 a medicament for binding phosphate in an animal, a pharmaceutical formulation, and a unit dosage form. Appellant appeals the rejection of claims 1, 3, 5, 6, 26, 28, 32, 34, 35, and 37–42 under 35 U.S.C. §§ 102(b) and 103(a).¹ We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

¹ “Appellant” herein refers to the “applicant” as defined by 37 C.F.R. § 1.42. Appellant identifies “OPKO Ireland Global Holdings, Ltd.,” as the real party in interest. Appeal Br. 3.

RELATED MATTERS

Appellant states, “[a]n appeal is pending in U.S. Patent Application No. 13,270,358, which is a divisional application of the present application. The ’358 application is also owned by OPKO Ireland Global Holdings, Ltd.” Appeal Br. 3. The aforementioned appeal was Appeal No. 2018-004161, wherein the Board rendered a decision on June 20, 2019.

STATEMENT OF THE CASE

The Specification states, “[p]lasma phosphate levels may be reduced by oral intake of inorganic and organic phosphate binders.” Spec. 1:14–15. “Other aluminium compounds such as microcrystalline aluminium oxide hydroxide (boehmite) and certain hydrotalcites have been proposed for this use.” *Id.* at 1:20–22. Issues with aluminum toxicity and efficiency were observed. *Id.* at 1–2. “To overcome the drawbacks associated with aluminium and also problems of efficacy over a limited pH range,” the Specification states, “WO-A-99/15189 [Roberts, *see infra*] discloses use of mixed metal compounds which are free from aluminium and which have a phosphate binding capacity of at least 30% by weight of the total weight of phosphate present, over a pH range of from 2-8.” *Id.* at 2:13–17. The Specification calls such materials “Layered Double Hydroxide” (also called LDHs) or “hydrotalcite-like compounds” (also called HTlcs). *Id.* at 4.

Even these improved compounds presented drawbacks. As stated in the Specification, “we have found that the mixed metal compounds of WO-A-99/15189 release some of their divalent metal content in soluble form during use.” *Id.* at 2:22–3:2. The Specification further states, “[w]e have now found that the release of the divalent metal, e.g. magnesium,

associated with the pharmaceutical use of compounds of WO-A-99/15189 can be significantly reduced by heat treatment.” *Id.* at 4:5–7.

Furthermore, the Specification describes that such heat treatment, also called calcination, is a delicate procedure because “[e]xcessive calcination also may lead to the formation of a Spinel crystalline structure, hence it is preferred that the substances of the invention do not exhibit a Spinel structure by x-ray diffraction.” *Id.* at 9:9–12. To address this spinel-formation drawback, promote phosphate absorption, and limit magnesium release, the Specification explains that, according to the invention, the heat treatment is most preferably kept to a range of 250°C to 500°C, and the duration is kept to no more than 3 hours. *See id.* at 7–9, 11, 13–14, 24–25, 29, 32, 37 (examples, method 1), 43 (Table 1), 55 (Table 4).

Claim 1 is representative and is reproduced below:

1. A substance for use as a medicament for binding phosphate in an animal, comprising greater than 30% and up to 95% by weight of a phosphate binding, pharmaceutically acceptable solid mixed metal compound of formula (I):



wherein M^{II} is at least one bivalent metal;

M^{III} is Fe^{3+} ;

A^{n-} is at least one n-valent anion;

$2+a = 2b+\sum cn$ and $\sum cn < 0.9a$, and

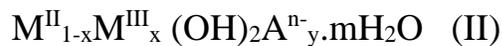
z is 2 or less;

wherein the compound of formula (I) is obtained by heating a starting material comprising a layered double hydroxide structure at a temperature in a range of 250 °C to 500 °C for 3 hours or less,

wherein the substance is free of a Spinel structure as determined by x-ray diffraction, and

upon administration, the compound releases into solution at least 50% by weight less of the at least one bivalent metal as compared to a release into solution of the at least one bivalent metal from the starting material, and

wherein the starting material comprises a compound of formula (II):



wherein M^{II} is at least one bivalent metal;

M^{III} is at least one trivalent metal;

A^{n-} is at least one n-valent anion;

$x = \sum ny$; and

$0 < x \leq 0.5$, $0 \leq m \leq 10$.

Appeal Br. 21 (Claims Appendix) (formatting added). The Examiner has identified that

[i]n the response to the Requirement for Restriction/Election dated 12/31/2009 applicants have elected Group I drawn to pharmaceutical compositions comprising a mixed metal compound and have elected the mixed metal compound species in which M^{II} is magnesium; M^{III} is iron; a is 0.21; b is 1.08; c is 0.22; z is 0.15 and A is carbonate.

Non-Final Act. 2. Pursuant to this election and using the indicated values for the recited variables, we understand the elected species covers $Mg_{0.79}Fe_{0.21}O_{1.08}(CO_3^{2-})_{0.22} \cdot 0.15H_2O$ as formula (I), i.e., the *post-heat-treatment* composition, and $Mg_{0.79}Fe_{0.21}(OH)_2(CO_3^{2-})_{0.14} \cdot 1.85H_2O$, as formula (II), i.e., the *pre-heat-treatment* starting material. We limit our analysis to the elected species. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461

(BPAI 1987) (appropriate to limit discussion on *ex parte* appeal to elected species).

Independent claim 26 is substantially the same as claim 1 except its preamble recites “[a] pharmaceutical formulation comprising a phosphate binding solid mixed metal,” and it recites that the formulation has “non-chemically bound water” and “a solid pharmaceutically acceptable carrier.” Appeal Br. 22 (Claims App’x.). Independent claim 38 is substantially the same as claim 1, except its preamble states, “[a] unit dosage form comprising greater than 30% by weight of a phosphate binding, pharmaceutically acceptable solid mixed metal compound of formula (I)” and, although reciting the same starting and resulting materials and the same heat treatment as claim 1, does not expressly recite that the resultant substance is “free of a Spinel structure.” *Id.* at 24.

The following rejections are appealed:

Claims 38 and 39 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hibino,² as evidenced by Forano,³ and Fernández,⁴ or in the alternative, under § 103(a) over this same prior art. Non-Final Act. 5–8.

² T. Hibino et al., *Calcination and rehydration behavior of Mg-Fe-CO₃ hydrotalcite-like compounds*, 19 J. MAT. SCI. LETT. 1403–05 (2000) (“Hibino”).

³ Claude Forano, *Environmental Remediation Involving Layered Double Hydroxides*, in CLAY SURFACES: FUNDAMENTALS AND APPLICATIONS, 426–58 (F. Wypych & K.G. Satayanarayana eds., 2004) (“Forano”).

⁴ José Maria Fernández et al., *The effect of iron on the crystalline phases formed upon thermal decomposition of Mg-Al-Fe hydrotalcites*, J. MATER. CHEM. 2507–14 (1998) (“Fernández”).

Claims 1, 3, 5, 6, 26, 28, 32, 34, 35, and 37–42 stand rejected under 35 U.S.C. § 103(a) over Hibino, Zhu,⁵ Forano, Châtelet,⁶ Roberts,⁷ Miyata,⁸ and Ansel.⁹ Non-Final Act. 8–20.

DISCUSSION

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

I. ANTICIPATION

“Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference.” *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). To anticipate “it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008); *see also Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d

⁵ H. Zhu et al., *Different Mg to Fe Ratios in the Mixed Metal MgFe Hydroxy-Carbonate Compounds and the Effect on Phosphate Binding Compared With Established Phosphate Binders*, 91 J. PHARMA. SCI. 53–66 (2001) (“Zhu”).

⁶ L. Châtelet et al., *Competition between monovalent and divalent anions for calcined and uncalcined hydrotalcite: anion exchange and adsorption sites*, 111 COLLOIDS & SURFACES A: PHYSIOCHEM. & ENGINEERING ASPECTS 167–75 (1996) (“Châtelet”).

⁷ WO 99/15189 (published Apr. 1, 1999) (“Roberts”).

⁸ US 4,629,626 (issued Dec. 16, 1986) (“Miyata”).

⁹ HOWARD C. ANSEL ET AL., PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS (Donna Balado ed., 7th ed. 1999) (“Ansel”).

1052, 1068 (Fed. Cir. 2017) (“In order to anticipate the claimed invention, a prior art reference must ‘disclose all elements of the claim within the four corners of the document,’ and it must ‘disclose those elements ‘arranged as in the claim.’”).

With these standards of law in mind, we analyze the Examiner’s rejection and Appellant’s arguments regarding anticipation below.

The Examiner determined that independent claim 38 and dependent claim 39, which depends therefrom, are anticipated by Hibino because the reference discloses a mixed metal compound (a hydrotalcite-like compound, or HTlc) having Mg and Fe in a 4:1 ratio, as well as the calcination of such a material at temperatures of 400°C, 450°C, and 500°C. Non-Final Act. 5. The Examiner took the position that the product disclosed by Hibino is “structurally identical or substantially identical to applicants [sic] elected species because it includes the same ingredient amounts made by the same method.” *Id.* Acknowledging that claim 38 recites “a unit dosage form,” the Examiner determined that Hibino’s “examples were rehydrated in Na₂CO₃ aqueous solution,” and that this was an aqueous suspension and, therefore, a unit dosage form. *Id.* at 6. The Examiner acknowledged that Hibino did not express that its compositions were free of spinel or functioned to reduce bivalent metal release into solution upon administration as compared to the claimed starting material. *Id.*

Appellant argues that Hibino fails to disclose a unit dosage form because such a form is not taught by mere rehydration, which may not result in an aqueous solution containing greater than 30% by weight of the calcined compound. Appeal Br. 7–8. Appellant argues that Hibino does not

indicate a spinel-free structure, but indicated the presence of spinel. *Id.* at 7–10 (Appellant’s Specification and other independent claims, as discussed above, indicate the claimed material would be essentially free of spinel). Appellant argues that Hibino does not actually disclose *any* calcination durations and the reference’s mere citation to Fernández, which does disclose 2 hour calcinations, is not sufficient for anticipation because it does not indicate that such a duration was actually used in Hibino, particularly because Fernández is directed to a different material (Mg-Al-Fe) than Hibino (Mg-Fe). Reply Br. 2.

We find Appellant’s arguments persuasive and conclude that Hibino does not anticipate the claims. Appellant is correct that Hibino does not disclose the recited heating parameters. *See, e.g.*, Hibino 1403–05; *see also* Fernández 2507 (Abstract) (reference is directed to LDHs containing Mg, FE, *and* Al, which is different from Hibino’s composition). Appellant’s Specification explains that using the claimed heating parameters for the claimed starting material results in a composition free of spinel, but Hibino discloses finding spinel over the entire range of its heating temperatures and suggests that the substance appears at even lower temperatures. *See* Hibino 1404–05. Hibino is silent as to providing its composition in a unit dosage form, as claimed; it is only directed to an investigation into the properties of the underlying composition. For at least these reasons, we reverse the anticipation rejection.

II. OBVIOUSNESS

“The combination of familiar elements [or steps] according to known methods is likely to be obvious when it does no more than yield predictable

results.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). “One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of ‘unexpected results,’ i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.” *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). “Evidence that a compound is unexpectedly superior in one of a spectrum of common properties [] can be enough to rebut a *prima facie* case of obviousness.” *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987) (evidence showed unexpectedly superior properties of an herbicide when used on corn and soybeans, which overcame a *prima facie* case of obviousness even though claims were not limited to use on those plants).

With these standards of law in mind, we analyze the Examiner’s rejection and Appellant’s arguments regarding obviousness below.

As noted above, the appealed (independent) claims are substantially similar. The same findings of fact and arguments are presented for the Board’s consideration and are determinative for both obviousness rejections. Therefore, we address both rejections together.

The Examiner determined that independent claims 1, 26, and 38, and all dependent claims, would have been obvious over the prior art combination of Hibino, Zhu, Forano, Châtelet, Roberts, Miyata, and Ansel (in the case of claims 38 and 39, the Examiner also cited Fernández, along with Hibino and Forano). Non-Final Act. 5–20. The Examiner’s position is that Zhu and Roberts each teach the usefulness of mixed metal compounds as pharmaceutical anion (phosphate) absorbers, such as the starting material

recited by each independent claim, which, when heat treated (calcinated), as taught or suggested by *other* cited references, becomes the final compound of the claims. The Examiner determined that Hibino, Châtelet, and Forano (Fernández in the rejection specific to claims 38 and 39) teach or suggest how to calcinate and the advantages of calcinating such materials, which enhances their anion exchange capabilities, which relatedly enhances their phosphate absorption. The Examiner determined that these references teach or suggest the claimed temperature range for such calcination and suggest the heating duration, e.g., Hibino teaches calcination at 400°C, 450°C, and 500°C, and Hibino references Fernández, which discloses calcinating at 450°C or 750°C for 2 hours. Finally, regarding the use of the compound in a pharmaceutical composition, e.g., a medicament, a pharmaceutical formulation, or a unit dosage form, the Examiner points to Miyata and Ansel as teaching this.

We agree with the Examiner that it may be possible to arrive at the claimed invention by piecing together the cited prior art. For example, Roberts and Zhu teach the starting material and identify its usefulness similarly to how the Specification describes it. But, while Hibino teaches calcination of hydrotalcite-like compounds at temperatures falling within the ranges claimed, it also discloses that its process causes spinel formation; spinel formation is something that both the Examiner and Appellants agree is undesirable in the claimed invention. *See* Hibino 1403–05. Châtelet may teach increasing anionic exchange capacity of hydrotalcite compounds by thermal treatment and the advantage of not exceeding 500–600°C, but it also suggests that the thermal treatment should occur for 18 hours, which is 15

hours longer than allowed by the appealed claims. *See* Châtelet 167–68. Forano likewise teaches that calcinated hydrotalcite materials display higher adsorption properties, such as for adsorbing phosphates, and describes a range of temperatures between 200–500°C for calcination, where such enhancement can occur before spinel formation, but Forano is not explicit about heating duration. *See* Forano 430, 431, and 442. Fernández, a reference cited by Hibino, and upon which the Examiner relies for the presumed duration of Hibino’s heat treatment (*see, e.g.,* Answer 15), teaches thermal decomposition of hydrotalcites for a 2 hour duration at temperatures of 450 °C and 750 °C; however Fernández also indicates that thermal decomposition in air at 450°C and also at 750°C leads to spinel formation. *See* Fernández 2507, 2510, and 2513. Furthermore, as pointed out by Appellant, Fernández is directed to a different material than Hibino.

Given the ambiguities of the prior art, we conclude the ordinary skilled artisan would not have recognized the significance of and relationships between the teachings of the cited prior art so as to achieve the claimed subject matter without knowledge of the claimed invention. Moreover, Appellant argues the Specification evidences that the claimed invention produces the unexpected result of “a reduced release of bivalent metal in solution, while improving phosphate binding capacity” (in addition to lack of spinel formation). Appeal Br. 17–20, Table 1 (citing Spec. 4:5–10, 43), 55 (Table 4) (citing Newton Declaration ¶¶ 20–25)). While the skilled artisan may have expected the exemplified improvements in phosphate binding capacity based on the disclosures of, e.g., Châtelet and Forano, the Examiner has not cited persuasive support in the record that the

exemplified reduction in Mg^{II} release would have also been expected. The Specification describes that when starting materials (which the Specification identifies as Batches A and B — *see* Spec. 37) were calcinated at the claimed temperature and duration, reductions in Mg^{II} release were observed compared to uncalcinated materials or materials calcinated outside the claimed time/temperature ranges. Significantly, in view of the claimed 3-hours-or-less claim limitation, the Specification's Table 4 shows that 5 minute and 3 hour heat treatments at 500°C provided respective Mg releases of, e.g., 0.15 and 0.1 mmol/L, while a heat treatment at the same temperature, but for 16 hours resulted in an Mg release of 1.05 mmol/L, or about 10 times greater. Uncalcinated material had an Mg release of, e.g., 5.9 mmol/L, or about 60 times greater.

The Newton Declaration, submitted by Appellant, states that such results were significant and unexpected. *See* Newton Declaration ¶¶ 21–24. The Newton Declaration states that “the inventive methods and compounds” produced the discussed results and “a mixed metal compound as we claim demonstrates a significant reduction in the release of the bivalent metal as compared to the uncalcinated starting material,” and that the “unexpected results” illustrated by the Specification's Table 1 and Table 4 are “of our invention.” *See* Newton Declaration ¶¶ 9, 21, 23, and 24. Appellant avers “the demonstration of unexpected results is commensurate in scope with the claims, particularly in view of the elected species.”¹⁰

¹⁰ We note, it appears the compounds identified in the Specification as Batch A and Batch B (Spec. 37) are not identical to the starting material of the claims. For example, the Specification's Batches A and B include SO_4 and Na_2SO_4 in the pre-calcinated starting material, but the formula (II)

In view of the somewhat ambiguous teachings of the prior art cited against the claims here and the prior art combination's sometimes conflicting teachings concerning relevant subject matter, we conclude that the balance of evidence on appeal favors Appellant's position. There is a lack of definitive evidence that the cited prior art would have been modified to utilize the claimed heat treatment parameters for the claimed starting material to produce the claimed final composition, which is used as, e.g., a pharmaceutical. Furthermore, the evidence of unexpected results appears to be sufficient when considered alongside the evidence of obviousness to outweigh any case for obviousness, if indeed a prima facie case was made in the first instance. In view of the above, we conclude the balance of evidence supports Appellant and we reverse the Examiner's rejections for obviousness.

CONCLUSION

The anticipation rejection of claims 38 and 39 is reversed.

The obviousness rejection of claims 38 and 39 is reversed.

The obviousness rejection of claims 1, 3, 5, 6, 26, 28, 32, 34, 35, and 37-42 is reversed.

starting material of the claims does not. Further, the amounts of H₂O are not the same when comparing Batches A and B to the elected species. However, the significance of such differences is not apparent and the Examiner does not contend that Appellant's evidence of unexpected results is not commensurate in scope with the claims.

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
38, 39	102(b)	Hibino		38, 39
38, 39	103(a)	Hibino, Forano, Fernández		38, 39
1, 3, 5, 6, 26, 28, 32, 34, 35, 37–42	103(a)	Hibino, Zhu, Forano, Châtelet, Roberts, Miyata, and Ansel		1, 3, 5, 6, 26, 28, 32, 34, 35, 37–42
Overall Outcome				1, 3, 5, 6, 26, 28, 32, 34, 35, 37–42

REVERSED