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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte YUHUA LI and BENJAMIN CHIEN

Appeal 2015-004031
Application 11/653,636¹
Technology Center 1600

Before JEFFREY N. FREDMAN, JOHN G. NEW, and DAVID COTTA,
Administrative Patent Judges.

COTTA, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an injectable polymeric composition. The Examiner rejected the claims on appeal as obvious under 35 U.S.C. § 103(a).

We affirm.

¹ According to Appellants, the real party in interest is Foresee Pharmaceuticals, Inc. App. Br. 2.

STATEMENT OF THE CASE

Claims 1–7 and 11–28 are on appeal. Claims 1 and 27, the only independent claims on appeal, read as follows:

1. An injectable polymeric composition comprising:
 - a) a salt of a peptide agent formed with a strong acid selected from the group consisting of hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, chromic acid, methanesulfonic acid, trifluoromethane sulfonic acid, trichloroacetic acid, dichloroacetic acid, bromoacetic acid, chloroacetic acid, cyanoacetic acid, 2-chloropropanoic acid, 2-oxobutanoic acid, 2-chlorobutanoic acid, 4-cyanobutanoic acid, perchloric acid, and phosphoric acid;
 - b) a biodegradable polymer;
 - c) a pharmaceutically acceptable organic solvent, which dissolves the biodegradable polymer and is miscible or dispersible in aqueous or biological fluid; and
 - d) optionally one or more pharmaceutically acceptable excipients; wherein the composition does not contain excess strong acid in addition to the strong acid used to form the salt of the peptide agent.

27. An injectable polymeric composition comprising:
 - a) a hydrochloride or mesylate salt of a LHRH agonist or antagonist;
 - b) a poly(lactide-co-glycolide) copolymer, wherein the ratio of lactide:glycolide of the copolymer is from 50:50 to about 100:0;
 - c) N-methyl-2-pyrrolidone (NMP); and
 - d) A triglyceride and/or vitamin E, wherein the composition does not contain hydrochloric acid or methanesulfonic acid in addition to the acid used to form the salt of the LHRH agonist or antagonist.

As the result of a restriction requirement, Appellants elected the following species for initial examination:

An injectable polymeric composition comprising:
a) a mesylate salt of leuprolide;
b) a poly(lactide-co-glycolide) copolymer, wherein the ratio of lactide:glycolide of the copolymer is from 50:50 to about 100:0;
c) N-methyl-2-pyrrolidone (NMP); and
d) optionally one or more pharmaceutically acceptable excipients;
wherein the composition does not contain methanesulfonic acid in addition to the acid used to form the salt of the leuprolide.

App. Br. 3.

The claims stand rejected as follows:

Claims 1–7 and 13–22 under 35 U.S.C. § 103(a) over the combination of Dunn,² Thanoo,³ and Bastin.⁴

Claims 11–12 under 35 U.S.C. § 103(a) over the combination of Dunn, Thanoo, Bastin and Burov.⁵

Claims 21–24 under 35 U.S.C. § 103(a) over the combination of Dunn, Thanoo, Bastin, and Gibson.⁶

² Dunn et al., US Patent No. 6,773,714 B2, issued Aug. 10, 2004 (“Dunn”).

³ Thanoo et al., US Patent Publication No. 2005/0042294 A1, published Feb 24, 2005 (“Thanoo”).

⁴ Bastin et al., *Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities*, 4 *Organic Process Research & Development* 427–435 (2000) (“Bastin”).

⁵ Burov et al., *Hybrid Antitumor Compounds Containing LH-RH Analog and 5-Fluorouracil*, Proceedings of the European Peptide Symposium, Peptides 1996 (“Burov”).

⁶ Gibson et al., US Patent Publication No. 2009/0004273 A1, published Jan. 1, 2009 (“Gibson”).

Claims 25 and 26 under 35 U.S.C. § 103(a) over the combination of Dunn, Thanoo, Bastin and Falotico.⁷

Claims 27 and 28 under 35 U.S.C. § 103(a) over the combination of Dunn, Thanoo, Bastin and Gibson.

REJECTION OF CLAIMS 1–7 AND 13–22 OVER THE COMBINATION
OF DUNN, THANOO AND BASTIN

The Examiner found that Dunn disclosed a polymeric composition comprising the elected peptide agent (leuprolide), the elected biodegradable polymer (poly(lactide-co-glycolide) (“PLGA”)), and the elected solvent (N-methyl-2-pyrrolidone (“NMP”)). Ans. 3–4. The Examiner further found that Dunn’s leuprolide composition did not contain an excess of strong acid. *Id.* at 3. The Examiner found, however, that Dunn did not disclose the elected mesylate salt of the peptide agent leuprolide, or any other salt formed from the strong acid species recited in claim 1. *Id.* at 5.

The Examiner found that Thanoo taught that most polypeptide drugs are available as their salts, that leuprolide, ornitide and octreotide are available as acetate salts, and that “although the acetate molecule is believed to form an ion pair with the amino groups of the polypeptide it has been found that the nucleophilic groups in the polypeptide, even as the acetate salt form, catalyze the polymer (e.g., PLGA) degradation.” Ans. 6 (citing Thanoo ¶ 49). The Examiner further found that Thanoo taught that adding a small amount of a low pKa acid helped to partially overcome this stability issue. *Id.*; *see also*, Thanoo ¶ 51.

⁷ Falotico et al., US Patent Publication No. 2005/0272806 A1, published Dec. 8, 2005 (“Falotico”).

Finally, the Examiner found that Bastin taught that selection of salt form for new chemical entities modifies aqueous solubility as well as a “range of other properties such as hygroscopicity, chemical stability, dissolution rate and mechanical properties.” *Id.* at 7. Bastin also teaches that “a range of salts should be prepared for each new substance and their properties compared in order to allow for the selection of the optimum salt,” and provides a table of approximately 30 of the most common pharmaceutical anion salts – including hydrochloride and mesylate salts. *Id.*

Based on the combined teachings of Dunn, Thanoo and Bastin, the Examiner concluded:

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to modify the leuprolide acetate in the injectable composition of Dunn and Thanoo with an alternative salt form of leuprolide; specifically the hydrochloride or methanesulfonate (i.e. salts of leuprolide formed from a stoichiometric amount of the lower pKa acids hydrochloric acid and methanesulfonic acid).

One would have been motivated to do so because 1) Thanoo teaches that injectable compositions comprising the acetate salt and the polymer PLGA are unstable and exhibit undesirable polymer molecular weight reduction (i.e. PLGA degradation) as a result of attack from the nucleophilic groups in the polypeptide (leuprolide), 2) Thanoo teaches, that said degradation can be at least partially overcome by adding a small amount of a low pKa acid additive, wherein said additives include hydrochloric acid and methanesulfonic acid, 3) Bastin teaches that salts influence a range of properties such as hygroscopicity, chemical stability, dissolution rate and mechanical properties and that, where possible, a range of salts should be prepared and their properties compared for each new substance and 4) Bastin teaches, [that]

hydrochloride and mesylate are among ~ 30 of the more frequently used common pharmaceutical anionic salts.

Ans. 7–8.

Appellants challenge the Examiner’s rejections on multiple grounds. First, Appellants argue that the claimed composition exhibits unexpected results, citing to the Specification as support. App. Br. 6. The Specification provides a comparison of polymeric compositions containing PLGA and three different salts of leuprolide, the hydrochloride salt, the mesylate salt, and the acetate salt. Specification ¶ 111. It reports that after 18 months at 4° C, 23% of leuprolide in a composition containing leuprolide acetate was degraded while only 2% was degraded in formulations of leuprolide mesylate and leuprolide hydrochloride. *Id.* Similarly, after 12 months at room temperature, 35% of leuprolide in compositions containing leuprolide acetate was degraded while only about 11% was degraded in composition containing leuprolide hydrochloride and leuprolide mesylate. *Id.*

We find that these results are within the range of properties that a person of ordinary skill in the art would have expected in view of Bastin’s teachings that: 1) “[s]election of an appropriate salt form for a new chemical entity provides the pharmaceutical chemist and formulation scientist with the opportunity to modify the characteristics of the potential drug substance,” 2) salt forms influence a range of properties including, “aqueous solubility . . . melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, crystal form, and mechanical properties,” and 3) “[w]here possible, a range of salts should be prepared for each new substance and their properties compared during a suitable preformulation program.” Bastin Abstract. Given these teachings, the person of ordinary skill in the art would have

expected various salt forms to exhibit different properties with respect to polymer degradation. The improved degradation characteristics of the mesylate and hydrochloride salts are consistent with expected variation among salts, and represent a differences in degree not in kind. *See, In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (a “32--43% increase in stress-rupture life, however, does not represent a ‘difference in kind’ that is required to show unexpected results.”).

Appellants argue that Bastin is “outside the context of a polymeric composition” and includes “no discussion of peptides.” App. Br. 10. Appellants try to distinguish the case, at hand, from *Pfizer v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007) – which found that it would be routine to optimize among 53 different prior art salt forms of a pharmaceutical drug – on this basis, arguing “there is no prior art reference as in the *Pfizer v. Apotex* case that discloses a genus of peptide salts.” *Id.* at 11. Appellants, however, do not offer any persuasive evidence or argument to support a conclusion that salts of peptides are fundamentally different from salts of any other drug compounds. Nor do Appellants offer persuasive evidence or argument to support a conclusion that the person of ordinary skill in the art would be unable to apply the teachings of Bastin to peptide drugs. Accordingly we find that the preponderance of the evidence supports the Examiner’s finding that the teachings of Bastin regarding optimization of salt forms of pharmaceutical drugs would apply to peptide drugs.

Appellants contend that Thanoo teaches that “the acetate salt of octreotide does not prevent the reduction of polymer molecular weight at all,” and thus, that Thanoo “teaches away from the sole use of the salt of a peptide agent.” App. Br. 8. Appellants, however, do not identify any

specific teaching in Thanoo which discourages the use of alternative salt forms of leuprolide. Accordingly, we find that Thanoo does not teach away from the optimization among alternative salt forms of peptides. *See, DyStar Textilfarben GmbH & Co. Deutschland Kg v. C.H. Patrick Co.*, 464 F.3d 1356, 1364 (Fed. Cir. 2006) (“[M]ere failure to discuss immediate use of his leuco indigo *solution* for dyeing is not the same thing as Brochet stating in his article that . . . his leuco indigo solution may only be concentrated in paste form. We will not read into a reference a teaching away from a process where no such language exists.”). To the contrary, we find that Thanoo’s identification of problems with the acetate salt of peptides (including leuprolide) would have motivated the person of ordinary skill in the art to explore alternative salt candidates. *See, Pfizer v. Apotex*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (“one skilled in the art, facing the problems including the stickiness of the tablet form of the maleate acid addition salt, would have been motivated to combine the teachings of the '909 patent, Berge, and other prior art, to produce the besylate salt of amlodipine”).

Appellants argue that Thanoo’s teaching of degradation problems when an acetate salt of a peptide is used without a small amount of acid “directly contracts” the Examiner’s interpretation of Bastin as teaching that “a salt of a peptide agent can be selected to reduce the degradation of a polymer.” App. Br. 9. But the teachings of Thanoo and Bastin are not in conflict. Thanoo teaches that the acetate salt may create degradation issues, Bastin teaches that different salts may have different properties.

Finally, Appellants assert “according to a commercial manufacturer, ScinoPharm Taiwan Ltd., leuprolide mesylate (a salt of a peptide agent formed with a strong acid) is more hygroscopic than leuprolide acetate.”

App. Br. 10. Appellants contend that leuprolide mesylate can absorb up to 25%w/w of water, while leuprolide acetate can absorb only 14%w/w of water. *Id.* Appellants then argue this would have discouraged the person of ordinary skill in the art from “select[ing] a salt of a peptide agent formed with a strong acid” because Bastin teaches that “higher hygroscopicity is undesirable as it makes leuprolide mesylate much more difficult to handle.” *Id.*

As an initial matter, Appellants do not provide any evidence in support of their (or ScinoPharm Taiwan Ltd.’s) assertions regarding the hygroscopicity of leuprolide mesylate. These assertions, thus, amount to nothing more than attorney argument, which cannot take the place of evidence. *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997); *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). Moreover, hydroscopicity is only one of multiple factors that Bastin teaches should be considered in optimizing among salt candidates. Bastin 428–29. Further, there is no evidence that the difference between 14% and 25% hygroscopicity is meaningful in any way.

Accordingly, we affirm the Examiner’s rejection of claims 1–7 and 13–22 as unpatentable over the combination of Dunn, Thanoo and Bastin.

REJECTION OF CLAIMS 11 AND 12 OVER THE COMBINATION OF
DUNN, THANOO, BASTIN AND BUROV

Appellants do not offer any new arguments with respect to the Examiner’s rejection of claims 11 and 12 over the combination of Dunn, Thanoo, Bastin and Burov. *See*, App. Br. 12. Instead Appellants rely exclusively on the same arguments raised with respect to the Examiner’s rejection of claims 1–7 and 13–22 based on the combination of Dunn,

Thanoo and Bastin. *Id.* Accordingly, we affirm the Examiner's rejection of claims 11 and 12 for the reasons discussed above with respect to the Examiner's rejection of claims 1–7 and 13–22.

REJECTION OF CLAIMS 21–24 OVER THE COMBINATION OF
DUNN, THANOO, BASTIN AND GIBSON

Appellants do not offer any new arguments with respect to the Examiner's rejection of claims 21–24 over the combination of Dunn, Thanoo, Bastin and Gibson. *See*, App. Br. 12–13. Instead Appellants rely exclusively on the same arguments raised with respect to the Examiner's rejection of claims 1–7 and 13–22 based on the combination of Dunn, Thanoo and Bastin. *Id.* Accordingly, we affirm the Examiner's rejection of claims 21–24 for the reasons discussed above with respect to the Examiner's rejection of claims 1–7 and 13–22.

REJECTION OF CLAIMS 25 AND 26 OVER THE COMBINATION OF
DUNN, THANOO, BASTIN AND FALOTICO

Appellants do not offer any new arguments with respect to the Examiner's rejection of claims 25 and 26 over the combination of Dunn, Thanoo, Bastin and Falotico. *See*, App. Br. 13. Instead Appellants rely exclusively on the same arguments raised with respect to the Examiner's rejection of claims 1–7 and 13–22 based on the combination of Dunn, Thanoo and Bastin. *Id.* Accordingly, we affirm the Examiner's rejection of claims 25 and 26 for the reasons discussed above with respect to the Examiner's rejection of claims 1–7 and 13–22.

REJECTION OF CLAIMS 27 AND 28 OVER THE COMBINATION OF
DUNN, THANOO, BASTIN AND GIBSON.

Appellants do not offer any new arguments with respect to the Examiner's rejection of claims 27 and 28 over the combination of Dunn, Thanoo, Bastin and Gibson. *See*, App. Br. 14. Instead Appellants rely exclusively on the same arguments raised with respect to the Examiner's rejection of claims 1–7 and 13–22 based on the combination of Dunn, Thanoo and Bastin. *Id.* Accordingly, we affirm the Examiner's rejection of claims 27 and 28 for the reasons discussed above with respect to the Examiner's rejection of claims 1–7 and 13–22.

SUMMARY

For these reasons and those set forth in the Examiner's Answer, the Examiner's final decision to reject claims 1–7 and 11–28 is affirmed.

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).

AFFIRMED