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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte GAETANO BRAMBILLA,
PAOLO COLOMBO, FRANCESCA BUTTINI, and
MICHELE MIOZZI

Appeal 2020-000726
Application 15/152,835
Technology Center 1600

Before RICHARD M. LEBOVITZ, RYAN H. FLAX, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

The Examiner rejected claim 12, 13, and 21 under 35 U.S.C. § 103 as obvious. Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject the claims. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Chiesi Farmaceutici S.p.A. Appeal Br. 2.

STATEMENT OF THE CASE

An oral hearing was held in this appeal on September 14, 2020. A written transcript of the hearing has been entered into the record.

The Examiner rejected claims 12, 13, and 21 in the Office Action ("Office Act.") under U.S.C. § 103(a) as obvious in view of Hipkiss,[2] Eck,[3] Amighi,[4] Batycky,[5] Badyal,[6] Abiko,[7] Crooke,[8] Rairkar,[9] da Rocha,[10] and Banowski.[11] Office Act. 3.

Claim 12, the only independent claim on appeal, is reproduced below:

> 12. A process for preparing chemically stable crystalline microparticles, comprising formoterol fumarate dehydrate coated with myristic acid in an amount of 1.0 to 2.0% by weight based on a total weight of the crystalline microparticles, the process comprising:
>
> (a) preparing a solution of myristic acid in a fluorinated model propellant in which the formoterol fumarate dihydrate is

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[2] Ruecroft et al., WO 2010/007447 A1, published Jan. 21, 2010 ("Hipkiss"; last listed inventor). We follow the Examiner's convention of, at times, identifying the cited prior art references by other than first-named inventors.
[3] Eck, US 2007/0009445 Al, published Jan. 11, 2007 ("Eck").
[4] Vanderbist et al., EP 2 050 437 A1, published Apr. 22, 2009 ("Amighi"; 3rd listed inventor).
[5] Batycky et al., US 2003/0180283 Al, published Sept. 25, 2003 ("Batycky").
[6] Badyal and Rogueda, US 2005/0106335 A1, published May 19, 2005 ("Badyal").
[7] Abiko and Kamaishi, US 4,259,905, issued Apr. 7, 1981 ("Abiko").
[8] Crooke and Graham, US 2006/0009410 A1, published Jan. 12, 2006 ("Crooke").
[9] Rairkar et al., US 2006/0286038 A1, published Dec. 21, 2006 ("Rairkar").
[10] da Rocha et al, "Science and Technology of Pressurized Metered-Dose Inhalers," 165, 170 in Smyth et al., ed., 2011, Controlled Release Society: New York ("da Rocha").
[11] Banowski et al., US 2010/0047296 A1, published Feb. 25, 2010 ("Banowski").

> substantially insoluble, selected from the group consisting of perfluoropentane, 2H,3H-perfluoropentane (HPFP), perfluorohexane, and 1H-perfluorohexane;
>
> (b) adding the formoterol fumarate dihydrate as a micronized powder to the solution of myristic acid, to obtain a mixture;
>
> (c) mixing the mixture to obtain a homogeneous suspension;
>
> (d) subjecting the suspension to spray-drying, to obtain the coated microparticles, the myristic acid forming a continuous film on a surface of the microparticles;
>
> (e) preparing a pharmaceutical aerosol formulation comprising the coated microparticles in suspension in a liquefied propellant gas; and
>
> (f) filling the pharmaceutical aerosol formulation into a pressurized metered dose inhaler.

REJECTION

Claim 12 is directed to a process of preparing a pharmaceutical aerosol formulation comprising formoterol fumarate dihydrate ("FF") microparticles coated with myristic acid, which are filled into a pressurized metered dose inhaler ("pMDI"). Formoterol is a beta2-agonist administered to the lungs by inhalation to treat reversible airway obstruction, inflammation and hyper-responsiveness. Spec. 1–2.

In the first step (a) of the claim, a solution of myristic acid is prepared in a fluorinated model propellant. The propellant is selected from a group consisting of four specific fluorinate propellants. The FF is required by the claim to be substantially insoluble in the propellant.

The FF is added to the myristic acid solution (step (b)), mixed to obtain a suspension (step (c)), and then subjected to spray-drying (step (d)). The spray-drying results in the formation of a continuous film of myristic acid on the surface of the FF microparticles.

An aerosol formulation is prepared in step (e) in which the coated FF microparticles are suspended in a liquefied propellant gas and then filled into a pMDI in the last step (f) of the claim.

The Examiner found that Hipkiss describes FF particles prepared in a fluorinated propellant as recited in steps (a) and (b) of claim 12, but not coated with myristic acid as the claim requires. Office Act. 3. To reach this limitation of the claim, the Examiner cited Eck (Office Act. 4) for its teaching of coating fine drug particles with a surfactant by adding the surfactant to a hydrofluoroalkane ("HFA") and then adding the drug as in steps (b) and (c) of the claim. Eck ¶ 45. The Examiner further cited Amighi for describing the "preparation of coated particles for inhalation where a suspension of the core particle is prepared in a solution of the coating material that is then spray dried to yield coated particles," corresponding to step (d) of the claim. Office Act. 5.

The Examiner recognized that Eck does not disclose myristic acid as the surfactant, but instead discloses coating the drug particles with omega-3 and/or omega-6 fatty acids. Eck ¶ 7. Eck also does not disclose any of the propellants listed in claim 12, step (a), that are used to make the myristic acid solution.

To meet these limitations of the claims, the Examiner cited Batycky as teaching that fatty acids may be used to coat drug particles to reduce particle agglomeration (Batycky ¶¶ 161, 162). Office Act. 5–6. While Batycky does not disclose that the fatty acid is myristic acid as required by step (a) of claim 12, the Examiner found that Rairkar and Crooke disclose that myristic acid is compatible with the lung. *Id.* at 6.

The Examiner found that Hipkiss and Eck teach using an HFA to prepare drug particles, such as FF particles, but acknowledged that neither publication describes one of the listed propellants in claim 12, step (a) that are used to make the myristic acid solution used to coat the FF particles in steps (b)–(d) of the claim. The Examiner cited Badyal for teaching that HPFP, a propellant of claim 12, can be used in place of HFA 227, the particular propellant described in each of Hipkiss and Eck. Office Act. 6.

The Examiner also found that Abiko teaches that, when making toner for waterless printing plates, it is preferred to make a uniform solution of the polymeric material and organopolysiloxane that comprise the toner. Abiko 3:20–13; Office Act. 6. To do so, Abiko teaches "it is preferable that the difference in solubility parameter between the polymeric material and the organopolysiloxane is smaller than 2 (cal/cm^{-3})." Abiko 3:13–16. The Examiner found it would have been obvious to one of ordinary skill in the art to apply this teaching to Eck to determine whether myristic acid is soluble in HPFP. Final Act. 6. The Examiner looked up the solubility parameters of myristic acid and HPFP in Banowski and da Rocha, respectively, and using Abiko's teaching, determined that myristic acid is soluble in HPFP. *Id.*

DISCUSSION

A prima facie case for obviousness "requires a suggestion of all limitations in a claim," *CFMT, Inc. v. Yieldup Int'l Corp*., 349 F.3d 1333, 1342 (Fed. Cir. 2003) and "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 418 (2007). To establish obviousness under 35 U.S.C. § 103, one of ordinary

skill in the art must also have a reasonable expectation that the prior art, when combined, would succeed in making the claimed invention. *See, e.g.*, *Acorda Therapeutics, Inc. v. Roxane Laboratories, Inc*., 903 F.3d 1310, 1333 (Fed. Cir. 2018). "'Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*.' [citing *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)]." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009). In some cases, however, "the evidentiary basis for an inference of reasonable expectation of success may be inadequate." *Accorda*, 903 F.3d at 1333–34.

In this appeal, the issue is whether one of ordinary skill in the art would have had reason to select myristic acid as the surfactant with a reasonable expectation of success that it would uniformly coat the FF microparticles when present in a solution of HPFP and spray-dried as required by steps (a) and (d) of claim 12.

There is no express teaching in the cited publications of using myristic acid to coat drug particles. However, Batycky generally teaches using surfactants to coat drug particles to reduce agglomeration,[12] and specifically discloses fatty acids as an example.[13] Rairkar teaches that myristic acid is a

[12] "In another embodiment of the invention particles include a surfactant. . . Surfactants generally possess a hydrophilic moiety and a lipophilic moiety, such that, upon absorbing to microparticles, they tend to present moieties to the external environment that do not attract similarly-coated particles, thus reducing particle agglomeration. Surfactants may also promote absorption of a therapeutic or diagnostic agent and increase bioavailability of the agent." Batycky ¶ 161.

[13] "In addition to lung surfactants, such as, for example, the phospholipids discussed above, suitable surfactants include but are not limited to hexadecanol; fatty alcohols such as polyethylene glycol (PEG);

fatty acid used as a surfactant in the lungs (Rairkar ¶¶ 8, 55). Although, the teaching is in a different context than how the fatty acids are used as particle coatings in Eck and Batycky, the teaching by Rairkar indicates myristic acid is compatible with the lung, the target for the aerosolized coated drug particles of claim 12.

Based on Batycky, the Examiner found that all fatty acids would be equivalent in being effective to coat a drug particle in the HPFP solution. Office Act. 4, 6–7. However, in the second declaration under 37 C.F.R. § 1.132 by Francesca Buttini, Ph.D. ("2nd Buttini Decl."), a co-inventor of the appealed claims, Dr. Buttini states that while the myristic acid concentration could be increased from 0.5% by weight of the total weight of the crystalline microparticles to the claimed amount of "1.0 to 2.0% by weight based on a total weight of the crystalline microparticles," two other fatty acids tested by her had limitations. 2nd Buttini Decl. ¶ 12. Specifically, Dr. Buttini states that "[t]he amount of lauric acid could not be increased [from 0.5 %] because at higher concentrations lauric acid is toxic to the lungs and mucous membranes" and that palmitic acid "could not be dissolved in HPFP at concentrations higher than 0.5%." *Id.* ¶ 15. Thus, Dr. Buttini undermines the Examiner's finding that all fatty acids would behave similarly and could be formulated in the claimed amounts of "1.0 to 2.0% by weight based on a total weight of the crystalline microparticles."

The Examiner cited Abiko's teaching about using the solubility parameters to determine whether myristic acid is soluble in HPFP. However, we agree with Appellant that one of ordinary skill in the art would not have

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polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid." Batycky ¶ 162.

considered Abiko's teaching of using a solubility difference of 2 cal/cm^{-3} to determine whether a polymeric material and organopolysiloxane can make a uniform toner solution for waterless printing as providing a reasonable expectation of success of making a coated drug particle of a drug coated with myristic acid as claimed. First, the Examiner did not provide evidence that the difference of 2 cal/cm^{-3} in solubility of compounds used in the toner printing art is applicable to determining the solubility of a fatty acid in HPFP. Second, the Examiner did not establish that Abiko is reasonably pertinent to the drug coating teachings of Eck and Batycky. A reference is "reasonably pertinent" to the inventor's particular problem when the reference "is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *In re Klein*, 647 F.3d 1343, 1348 (Fed. Cir. 2011) (citation omitted). The Examiner did not explain why one of ordinary skill in the art would have looked to waterless planographic printing plates as described in Abiko for guidance in selecting fatty acids and solvents for drug formulation. The Examiner provided no reasoning as to why Abiko would been considered pertinent to the problem of making drug particles coated with myristic acid. Ans. 7–8; Office Act. 6.

The Examiner relied on Badyal for finding that HPFP is a substitute propellant for HFA 227, the propellant described in Eck, for coating the drug particles. Office Act. 6. However, the Examiner's finding is misplaced. HFA 227 is used in Eck, not as a propellant, but as the *solvent* to *coat* the drug particle with the omega-3 and/or omega-6 fatty acid.[14] Badyal, however,

[14] "The invention also provides methods for preparing omega-3 and/or omega-6 fatty acid-coated particles, as well as methods for preparing and

uses the HPFA as a *propellant* to *aerosolize* the particles and deliver to the lungs, not as a solvent to coat drug particles with fatty acid. Badyal describes the problem of particles sticking to the surface of a delivery device when using HFA propellants to administer drug particles to the lung. Badyal ¶¶ 2, 3. Badyal treated the surface of the delivery device (Badyal ¶ 8) and determined adhesion between the particles and the drug surface:

> The extent of the adhesion between the particles and the treated surfaces was tested in a fluorinated solvent, 2H, 3H perfluoropentane (abbreviated as HPFP). This liquid is a very good substitute for both propellants HFA227 and BFA134a. It is used when tests can not be performed in situ in pressurised liquids, such as AFM.

Badyal ¶ 26.

Thus, there is no teaching by Badyal that HPFP is a substitute for HFA 227 as the *solvent* to coat the FF particle with myristic acid as required by the claims (*see* steps (a) and (d) of claim 12).

In view of these deficiencies, we conclude that the Examiner did not establish that it would have been obvious to one of ordinary skill to coat FF microparticles with myristic acid using HPFP as required by all the rejected claims.

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isolating the coated particles. For example, omega-3 linoleic acid isopropyl ester is solubilized in HFA 134a or HFA227, a fine particle medicament is added and the suspension is homogenized and coated particles are isolated by filtration or spray drying." Eck ¶ 45.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)	Affirmed	Reversed
12, 13, 21	103	Hipkiss, Eck, Amighi, Batycky, Badyal, Abiko, Crooke, Rairkar, da Rocha, Banowski		12, 13, 21

REVERSED