

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte STEFAN HIRSCH, DIETER BECKER, PATRICE GUITARD,
and ANDREAS CARL EUGSTER

Appeal 2008-5267
Application 10/181,639
Technology Center 1600

Decided: December 16, 2008

Before ERIC GRIMES, RICHARD M. LEBOVITZ, and JEFFREY N.
FREDMAN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to terbinafine compositions and methods of using them. The Examiner has rejected the claims as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part but designate the affirmances as new grounds of rejection. We also enter a new rejection for obviousness.

BACKGROUND

“Terbinafine . . . belongs to the class of allylamine anti-mycotics. It is . . . commercially available under the trade name Lamisil®. Terbinafine is highly active upon both topical and oral administration.” (Spec. 1.) “One particular difficulty in the formulation of terbinafine in oral pharmaceutical compositions is its unpleasant, e.g. bitter, taste and/or low physical integrity” (*id.*).

The Specification discloses that “pharmaceutically acceptable solid dosage forms of terbinafine showing rapid disintegration in aqueous medium, e.g. upon oral administration, and having an acceptable taste can been [sic] obtained by formulating buffered pharmaceutical compositions . . . comprising terbinafine as the active agent and one or more disintegrants” and that “inclusion of a suitable buffer in a sufficient amount provided taste-masking properties to the compositions of the invention” (*id.*).

DISCUSSION

1. CLAIMS

Claims 13-27 are pending and on appeal. Claim 27 is representative and reads as follows:

Claim 27: A solid pharmaceutical composition for oral administration having a disintegration time of 90 seconds or less in an aqueous medium and comprising
terbinafine,
a buffering component singly or in any suitable combination and
one or more disintegrants,
wherein the buffering component is capable of maintaining a pH of 5 to 6 on treatment with excess water.

2. ANTICIPATION

Claims 13-17, 20, and 27 stand rejected under 35 U.S.C. § 102(b) as anticipated by Gadebusch,¹ with Spesfeed News² cited for evidence.

The Examiner finds that Gadebusch discloses “a solid pharmaceutical composition … for oral administration comprising terbinafine, a buffering component (dibasic calcium phosphate hydrous), binders, a disintegrant (starch, lactose) and a sweetening compound (sugar) in a tablet useful for treatment of fungal infections (column 11-column 12; examples I, II)” (Ans. 3). The Examiner cites Spesfeed News as evidence that “the dibasic calcium phosphate hydrous utilized by Gadebusch et al. is a buffer” (*id.* at 4).

Appellants argue that “[n]either Example I or Example II of Gadebusch et al. describes each and every element of Applicant’s claim. It appears that the Examiner is [improperly] combining the elements from Example I and Example II to formulate an anticipatory rejection” (App. Br. 3).

We agree with Appellants that the Examiner has not adequately explained how the reference anticipates claim 27, which defines a composition comprising terbinafine, a buffering component, and a disintegrant. Gadebusch discloses a composition containing ketoconazole, starch (a disintegrant), and dibasic calcium phosphate hydrous (a buffering component) (Example I) and a separate composition containing

¹ Gadebusch et al., US 4,894,375, Jan. 16, 1990.

² Spesfeed News, Autumn 1998, Richard Miles, “Feed Phosphorus Explained,” http://www.spesfeed.co.za/autumn_1998.

ketoconazole, terbinafine, starch, and lactose (Example II) (*id.* at col. 11, l. 37 through col. 12, l. 9).

Although Gadebusch discloses a first composition that contains terbinafine and a disintegrant (Example II) and a second composition that contains ketoconazole, a disintegrant, and a buffering component (Example I), it does not disclose a composition comprising terbinafine, a disintegrant, and a buffering component. Thus, we find that Gadebusch's disclosure is too general and nonspecific to anticipate claim 27. As stated in *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972), an anticipatory reference under 35 U.S.C. § 102

. . . must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.

In our view, the Examiner's finding that Gadebusch discloses the limitations of claim 27 relies on the type of picking, choosing, and combining various disclosures that is foreclosed by *Arkley*. Thus, we agree with Appellants that the Examiner has not adequately shown that Gadebusch discloses an embodiment meeting all the limitations of claim 27, and the rejection of independent claim 27 and dependent claims 13-17 and 20 as anticipated by Gadebusch is reversed.

3. NEW GROUND OF REJECTION

Although we find that the Examiner has not adequately shown that Gadebusch anticipates claims 13-17, 20 and 27, we conclude that these claims would have been obvious in view of Gadebusch, with evidence

provided by Spesfeed News. Thus, under the provisions of 37 C.F.R. § 41.50(b), we enter the following new ground of rejection: claims 13-17, 20 and 27 are rejected under 35 U.S.C. § 103 as obvious in view of Gadebusch, with evidence provided by Spesfeed News.

Gadebusch discloses that an “unexpected synergistic and fungicidal effect” results from combining “inhibitors of 14 α -methyl demethylase and inhibitors of squalene epoxidase” (Gadebusch, col. 1, ll. 45-51). Gadebusch also discloses that 14 α -methyl demethylase inhibitors include ketoconazole (*id.* at col. 2, ll. 9-21) and that inhibitors of squalene epoxidase include terbinafine and naftifine (*id.* at col. 2, l. 67 to col. 3, l. 3).

As set forth above, Gadebusch discloses a composition containing ketoconazole, naftifine, dibasic calcium phosphate hydrous, and starch (*id.* at col. 11, ll. 39-54). The instant Specification states that starch is a disintegrant (Spec. 2: 9-15) and that buffering agents include phosphate salts of calcium (*id.* at 3: 4-6).

Given the suggestion in Gadebusch that ketoconazole be used together in an antifungal composition with either naftifine or terbinafine, one of skill in the art would have considered it obvious to substitute terbinafine for the naftifine in the composition of Gadebusch’s Example I. The resulting composition would comprise terbinafine, a disintegrant (starch), and a buffering component (dibasic calcium phosphate hydrous).

Gadebusch discloses that its compositions can be used to treat human mycotic infections (*id.* at col. 1, ll. 31-36). Gadebusch also discloses that the compositions of the invention may be prepared for solid dosage formats and that, “for solid preparations such as capsules and tablets,” the

components are mixed with “solid carriers such as starches, sugars, kaolin, ethyl cellulose, generally with lubricant such as calcium stearate, together with binders, disintegrating agents (Gadebusch at col. 11, ll. 7-16). Thus, Gadebusch would have suggested the compositions and methods of claims 13-17 and 20 to a person of ordinary skill in the art.

Given that the suggested composition includes a buffering agent and a disintegrating agent, it is reasonable to expect that the suggested composition would have the claimed disintegration properties and that the buffer would meet the claimed functional limitation (see the discussion below).

Appellants argue that the Spesfeed News “reference is non-analogous art and that one of ordinary skill in the pharmaceutical sciences would not look to an article directed to pig/poultry feed to find a suitable buffer for a pharmaceutical agent” (App. Br. 5).

We are not persuaded by this argument. The claimed compositions would have been obvious based on the disclosure of Gadebusch alone. The Spesfeed News article is cited only as evidence that the dibasic calcium phosphate hydrate of Gadebusch would inherently meet the limitation of a “buffering component ... capable of maintaining a pH of 5 to 6 on treatment with excess water.” Thus, the argument that the Spesfeed News article is non-analogous art is not applicable.

Appellants also argue that “the industry standard reference manual Handbook of Pharmaceutical Excipients[³] ... shows that dibasic calcium

³ Handbook of Pharmaceutical Excipients, 4th ed., 2003, edited by Rowe et al., Royal Pharmaceutical Society of Great Britain, London, UK)

phosphate hydrous is not a buffering agent in pharmaceutical compounds” and that Schmidt⁴ discloses that “dibasic calcium phosphate is used namely as a binder and filler for direct tableting” (App. Br. 5).

This argument is not persuasive. While the references cited by Appellants show that dibasic calcium phosphate can be used as a binder or diluent in tableting compositions, they do not state that it lacks the capacity to act as a buffer. Spesfeed News discloses that dibasic phosphate converts to monobasic phosphate (and vice versa) depending on pH: at pH 7.4, 80% is in the dibasic form, but at pHs below that level, more of the molecules in the dibasic form will accept an additional proton and convert to the monobasic form (Spesfeed News, page 6). The evidence of record therefore supports the Examiner’s position that dibasic calcium phosphate is a buffering agent.

Appellants further argue that with “monobasic and dibasic forms of phosphates, the range where buffering occurs is about 7.4. Therefore, even if the mentioned phosphate buffer system of Spesfeed News would have been applied to a terbinafine comprising composition, this would not result in a product of the present invention” (App. Br. 4). As we understand it, Appellants’ argument is that the dibasic calcium phosphate hydrous of Gadebusch is not a buffering component “capable of maintaining a pH of 5 to 6 on treatment with excess water,” as specified in claim 27.

We are not persuaded by this argument. Once a *prima facie* case has been established that a claimed product is in the prior art, Appellants bear the burden of proving “that the prior art products do not necessarily or

⁴ Schmidt et al., *Pharm. World Sci.* 15(3):105-15 (1993).

inherently possess the characteristics of his claimed product.” *Id.* at 698 (quoting *In re Fitzgerald*, 619 F.2d 67, 70 (CCPA 1980); *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977)).

The Specification discloses that “[e]xamples of suitable buffers for use in this invention include carbonate, citrate, acetate, *phosphate*, phthalate, tartrate *salts* of the alkali and alkaline earth metal cations, such as sodium, potassium, magnesium and *calcium*” (Spec. 3: 4-6; emphases added). Spesfeed News provides evidence that dibasic calcium phosphate has buffering capacity at pHs near 7.4 (Spesfeed News 3-6). Thus, as recognized by the Examiner, given the disclosure in the Specification that “phosphate . . . salts of . . . calcium” are suitable buffers in accordance with the invention and given the evidence in Spesfeed News that dibasic calcium phosphate is a buffer at pHs near 7.4, it would be reasonably expected that the terbinafine/dibasic calcium phosphate combination suggested by Gadebusch would inherently have the property of a “buffering component . . . capable of maintaining a pH of 5 to 6 on treatment with excess water.”

3. OBVIOUSNESS I

Claims 18 and 19 stand rejected under 35 U.S.C. § 103 as obvious in view of Gadebusch. Claims 18 and 19 are directed to methods of administering the composition of claim 27 comprising dissolving the composition before administration.

The Examiner finds that Gadebusch discloses that “the composition may be in solution form and, further, that it may be in a solid (powder) form that can be reconstituted with a suitable vehicle prior to administration” (Ans. 4). The Examiner also finds that “reconstituting a powder form . . .

encompasses the act of dissolving the composition” (*id.* at 4-5). The Examiner reasons that “[o]ne of ordinary skill in the art would have been motivated to formulate a solution by reconstituting a powdered formulation of the prior art to achieve the therapeutic benefit of avoiding unpleasant feeling of the powder form in the mouth” (*id.* at 5).

We agree with the Examiner that Gadebusch would have made obvious the method of claims 18 and 19. Gadebusch expressly suggests administering its compositions in solution form, which can be made by reconstituting a powder with a suitable vehicle (Gadebusch, col. 10, ll. 55-61). It therefore would have been obvious to administer the composition suggested by Gadebusch by dissolving it prior to administration, as required by claims 18 and 19.

Appellants do not provide any additional arguments directed to the specific limitations of claim 18 or 19.

4. OBVIOUSNESS II

Claims 21-26 stand rejected under 35 U.S.C. § 103 as obvious in view of Gadebusch and Physicians’ Desk Reference (PDR).⁵ Claims 21-26 are directed to the composition of claim 27, and methods of administering it, comprising terbinafine in an acid addition salt form or the hydrochloride salt form.

The Examiner finds that Gadebusch does “not teach the specified acid addition salt form (e.g. terbinafine hydrochloride)” (Ans. 5). The Examiner

⁵ Physicians’ Desk Reference, 53rd Edition, Medical Economics Co., Montvale, NJ (1999), page 2038.

relies on the PDR as disclosing a “terbinafine hydrochloride tablet (i.e. solid salt) form for treatment of fungal infection” (*id.*).

The Examiner concludes that it “would have been obvious to one of ordinary skill in the art to utilize terbinafine hydrochloride as taught by the PDR to formulate a solid oral dosage form because terbinafine hydrochloride is readily available commercially in solid form for treatment of a fungal infection as taught by PDR” (*id.*). We agree with the Examiner’s reasoning and conclusion.

Appellants argue that the Physician’s Desk Reference “does not compensate for that which is lacking in the primary reference of Gadebusch et al., namely the absence of a buffering agent” (App. Br. 6).

We are not persuaded by this argument for the reasons discussed above.

SUMMARY

We agree with Appellants that the Examiner has not made out a *prima facie* case of anticipation based on Gadebusch, and we therefore reverse the rejection of claims 13-17, 20, and 27 under 35 U.S.C. § 102(b). However, we enter a new ground of rejection of claims 13-17, 20, and 27 under 35 U.S.C. § 103 as being obvious in view of Gadebusch, with evidence provided by Spesfeed News. We affirm the Examiner’s rejections of claims 18, 19, and 21-26 under 35 U.S.C. § 103 but designate the affirmances as new grounds of rejection, in order to give Appellants a fair opportunity to address the rationale on which we rely.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides “[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review.

37 C.F.R. § 41.50(b) also provides that the Appellant(s), 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 proceeding will be remanded to the Examiner

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record

AFFIRMED-IN-PART; 37 C.F.R. § 41.50(b)

Ssc:

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