

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 16

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte DAVID BODMER, THOMAS KISSEL,
FRIEDRICH RICHTER, and HARRY TIEMESSEN

Appeal No. 2001-1044
Application No. 08/881,216

ON BRIEF

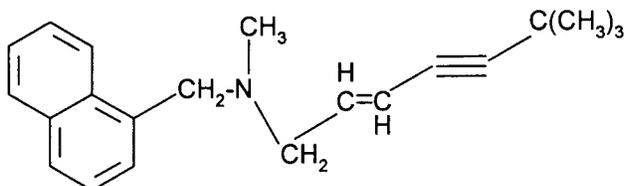
Before WINTERS, SCHEINER, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 18-21 and 23-26, all of the claims remaining. Claims 18 and 23-26 are representative and read as follows:

18. A topical, pharmaceutical composition comprising the compound of formula I



I

in free base form or acid addition salt form, encapsulated in liposomes, which composition contains phospholipid components which are selected from 1) palmitoyl-oleyl-phosphatidyl-choline, 2) dioleoyl-phosphatidyl-glycerol, 3) dioleoyl-phosphatidyl-serine, 4) a mixture of palmitoyl-oleyl-phosphatidyl-choline and palmitoyl-oleyl-phosphatidyl-glycerol, 5) dimyristoyl-phosphatidyl-choline, or 6) a mixture of dimyristoyl-phosphatidyl-choline and dimyristoyl-phosphatidyl-glycerol.

23. A composition of claim 18 comprising phosphatidylethanolamine-polyethyleneglycol.
24. A method for the treatment of fungal infections comprising topically administering an antifungally effective amount of a composition of claim 18 to a subject in need of such treatment.
25. A method of claim 24 for the treatment of pulmonary fungal infections comprising administering an antifungally effective amount of said composition to the lungs of a subject in need of such treatment.
26. A composition of claim 18 which is in lyophilized form comprising as cryoprotectant a disaccharide selected from sucrose, lactose, mannitol, and maltose, or a monosaccharide selected from fructose, glucose, galactose, mannose, xylitol, and sorbitol.

The examiner relies on the following references:

Lopez-Berestein et al. (Lopez-Berestein)	4,812,312	Mar. 14, 1989
Janoff et al. (Janoff)	4,891,208	Jan. 02, 1990
Woodle et al. (Woodle)	5,013,556	May 07, 1991
Knight et al. (Knight)	5,049,388	Sep. 17, 1991
Crowe et al. (Crowe)	WO 86/03938	Jul. 17, 1986

Birnbaum, "Pharmacology of the allylamines," Journal Amer. Acad. Dermatol., Vol. 23, no. 4/ Part 2, Suppl., pp. 782-785 (1990)

Claims 25 and 26 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

Claims 18-21, 24, and 25 stand rejected under 35 U.S.C. § 103 as obvious in view of Birnbaum, Lopez-Berestein, and Janoff.

Claim 23 stands rejected under 35 U.S.C. § 103 as obvious in view of Birnbaum, Lopez-Berestein, Janoff, and Woodle.

Claim 25 stands rejected under 35 U.S.C. § 103 as obvious in view of Birnbaum, Lopez-Berestein, Janoff, and Knight.

Claim 26 stands rejected under 35 U.S.C. § 103 as obvious in view of Birnbaum, Lopez-Berestein, Janoff, and Crowe.

We affirm the indefiniteness rejection and the obviousness rejections of all claims except claim 23.

Background

Terbinafine, the compound of formula I recited in the claims, is a known allylamine anti-mycotic agent. See the specification, pages 1-2. Terbinafine is highly active when administered topically or orally, but its antifungal activity is antagonized by serum. See id., page 2.

It is thus desirable to find a drug delivery system which can improve the bioavailability of [terbinafine] in order to overcome serum binding and/or favourably influence parameters such as pharmacokinetics and tissue distribution and/or reduce side effects and toxicity. . . .

A promising approach meeting the above-mentioned criteria has now been found in the form of liposomes comprising [terbinafine] as the active agent. Thus pharmaceutically acceptable e.g. parenteral dosage form for [terbinafine] has been obtained by means of liposomal preparations.

Id.

The specification states that the disclosed liposomal preparations of terbinafine can be administered in a variety of ways. “Administration may be peroral, topical or parenteral. It preferably is topical or parenteral, especially parenteral, particularly pulmonal.” Page 33. “A topical application of liposomes containing [terbinafine] may lead to enhanced accumulation of the drug at the site of administration, in turn leading to enhanced efficacy. . . . On pulmonal application the liposomes comprising [terbinafine] are effective against fungal diseases of the lung such as candidiasis.” Page 2.

Discussion

1. Obviousness

A. Birnbaum, Lopez-Berestein, and Janoff

The examiner rejected claims 18-21, 24, and 25 as obvious in view of Birnbaum, Lopez-Berestein, and Janoff. The examiner accurately characterized Birnbaum as disclosing the allylamines terbinafine and naftifine as antifungal agents, but not in liposomal formulations. Examiner’s Answer, page 5. The examiner cited Lopez-Berestein as disclosing liposomal compositions containing an antifungal agent (specifically, nystatin), and liposomes comprising dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG). Id. Finally, the examiner cited Janoff as teaching liposome-encapsulated naftifine, and suggesting that both naftifine and nystatin were appropriate for liposomal formulation. Id. The examiner concluded that it would have been obvious to combine the terbinafine taught by Birnbaum with the liposomal formulation disclosed by Lopez-Berestein, because Lopez-Berestein

discloses the advantages of liposomal formulation and because Janoff suggests liposomal formulation of the closely related allylamine naftifine. Id.

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness.” In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). “Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have had a reasonable expectation of success.” In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991) (citation omitted).

We agree with the examiner that the cited references support a prima facie case of obviousness. Claim 18, the broadest claim subject to this ground of rejection, is directed to a topical pharmaceutical composition comprising terbinafine encapsulated in liposomes which contain specified phospholipids, including a mixture of dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol.

Birnbaum discloses that terbinafine is a known antifungal agent belonging to the class of allylamines, and is an analog of naftifine, the original allylamine antimycotic. See the abstract. Birnbaum also teaches that terbinafine is active

both topically and orally (abstract) and that it has high lipophilicity (page 785).

Birnbaum does not suggest liposomal formulations of terbinafine.

Lopez-Berestein discloses liposomal formulations of nystatin. In the most preferred embodiment, the liposomes consist essentially of dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol in a ratio of about 7:3. Column 6, lines 10-14. Lopez-Berestein teaches that nystatin was a known antifungal agent of the polyene class (see Table 2) that is tolerated well both orally and topically but could not be used intravenously because of its presumed high toxicity and aqueous insolubility. Column 4, lines 50-53. See also column 5, lines 33-36: "Nystatin . . . has high hydrophobicity, which has precluded its effective systemic administration. It has been used as suspensions . . . administered to the patients orally. However, these studies have generally failed to document a beneficial effect of nystatin administration against systemic fungal infections."

Lopez-Berestein teaches that "[l]iposome-encapsulated nystatin (L-Nys) has a lowered systemic toxicity and an enhanced therapeutic efficacy as compared to free-Nys." Column 6, lines 61-63. Lopez-Berestein also teach that L-Nys can be administered topically "near to sites of localized fungal infection," and that "[a]lthough Nys has been topically used, L-Nys should more effectively inhibit fungal proliferation." Column 8, lines 28-35.

Janoff teaches vesicles (i.e., liposomes) which can contain "[b]ioactive agents, for example, antifungal compounds." Column 12, lines 50-53.

"Antifungal agents which may be present in the formulations of the instant

invention include . . . nystatin [and] naftifine.” Column 12, lines 56-61. Thus, Janoff suggests that both nystatin and the allylamine naftifine are appropriate for encapsulation in liposomes.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the terbinafine taught by Birnbaum with the topical, liposome-encapsulated antifungal formulation taught by Lopez-Berestein. Motivation to replace Lopez-Berestein’s nystatin with Birnbaum’s terbinafine is provided by the following teachings:

- (1) Both nystatin and terbinafine are hydrophobic antifungal agents. See Lopez-Berestein, column 5, lines 33-36; Birnbaum, page 785.
- (2) Both nystatin and terbinafine were known for topical use. See Lopez-Berestein, column 4, lines 47-51; Birnbaum, abstract. Lopez-Berestein teaches that liposome encapsulation was expected to increase the topical efficacy of nystatin. Column 8, lines 34-35.
- (3) Janoff suggests that nystatin and naftifine are both appropriate antifungal agents for inclusion in liposomal formulations. Column 12, lines 53-61. Naftifine is an analog of terbinafine. Birnbaum, abstract.

Thus, a person of ordinary skill in the art would have been motivated to replace Lopez-Berestein’s nystatin with Birnbaum’s terbinafine because both agents were known to be hydrophobic antifungal agents, because Janoff suggests that the terbinafine analog naftifine is suitable for liposomal encapsulation, and because Lopez-Berestein suggests that liposomal encapsulation would be expected to increase the antifungal efficacy of a topical composition. These teachings would also have led a skilled artisan to

reasonably expect that combining the cited references would produce a topical pharmaceutical composition of liposome-encapsulated terbinafine. We therefore conclude that the examiner has met the initial burden of showing prima facie obviousness.

Appellants argue that the references would not have led a person of ordinary skill in the art to combine their respective teachings. See the Appeal Brief, pages 3-4:

Nystatin is a macrolide antibiotic compound and is thus wholly different from terbinafine. First, there would be no motivation to encapsulate a molecule of a different structural class based on Berestein. . . . Nor is it obvious what the results of such modification would be. Second, it is clear that a reason for encapsulating nystatin in liposomes is to reduce systemic toxicity (col. 6, lines 61-62). . . . [T]oxicity is not an issue with terbinafine. Therefore, there is no motivation to prepare a liposome-encapsulated terbinafine composition.

This argument is not persuasive. It is true that nystatin and terbinafine belong to different classes of antimycotics. However, as discussed above, a person of ordinary skill in the art would have been motivated to replace Lopez-Berestein's nystatin with terbinafine in view of the similar hydrophobic nature of the two antimycotics, by Janoff's suggestion that the terbinafine analog naftifine was suitable for incorporation in liposomes, and by Lopez-Berestein's suggestion that liposome encapsulation would be expected to increase the topical efficacy of nystatin. We therefore find that the references would have provided the required "reason, suggestion, or motivation" to combine their respective teachings.

See Pro-Mold and Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

Appellants also argue that the references do not provide the requisite expectation of success. See the Appeal Brief, page 4:

Berestein would provide no basis for predicting the properties of liposomes containing terbinafine. This is especially true with terbinafine since it was well known prior to this invention that terbinafine is highly lipophilic and binds strongly to lipoproteins in plasma. . . . Therefore, at the time of this invention, the expectation would have been that terbinafine in liposomes would have bound to the lipid component of the liposomes. Consequently, the expectation would have been that formulating terbinafine in liposomes would have offered not only no improvement but possibly a reduced or total lack of efficacy.

This argument is not persuasive. As previously discussed, the cited references taught that both nystatin and terbinafine were hydrophobic antifungal agents, that naftifine (an analog of terbinafine) was suitable for use in liposomes, and that liposome encapsulation was expected to increase the topical efficacy of the hydrophobic antimycotic nystatin. These teachings would have led those of ordinary skill in the art to reasonably expect that liposome-encapsulated terbinafine would at least retain its antifungal activity. “Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.” In re O’Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). The references would have provided the required reasonable expectation of success.

Finally, Appellants point to the specification’s Examples 3 and 7 as providing evidence of unexpected results to rebut any prima facie case based on the examiner’s references. See the Appeal Brief, pages 4-5.

This argument is also unpersuasive. The specification's Examples 3 and 7 provide no evidence that the claimed compositions have any unexpected properties compared to the closest prior art (i.e., free terbinafine). Example 3 discloses the results of administering an intravenous pharmaceutical composition of liposome-encapsulated terbinafine to treat systemic candidiasis, and concludes that "[s]urprisingly, 10 out of 20 animals survived to day 21." These data do not overcome the rejection of record for two reasons. First, the experiment provides no comparison of the liposome-encapsulated terbinafine with any other antifungal agent to support the conclusion that the observed results were surprising. "[I]t is well settled that unexpected results must be established by factual evidence. 'Mere argument or conclusory statements in the specification does not suffice.'" In re Geisler, 116 F.3d 1465, 1470, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997). See also In re Baxter-Travenol Labs., 952 F.2d 388, 392, 21 USPQ2d 1281, 1285 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

Second, the claims on appeal are directed to topical compositions and methods of topically treating fungal infection; there is no evidence of record that the results seen on intravenous treatment would also apply to the claimed topical compositions and methods. See In re Fenn, 639 F.2d 762, 765, 208 USPQ 470, 472 (CCPA 1981) ("Although it is well settled that comparative test data showing an unexpected result will rebut a prima facie case of obviousness, the

comparative testing must be between the claimed invention and the closest prior art.” (emphasis added)).

As for the specification’s Example 7, that example is prophetic and discloses no actual data whatever. In no way can Example 7 be relied on to show factual evidence of unexpected results.

All of the claims subject to this rejection stand or fall together. Appeal Brief, page 2. We have concluded that claim 18 is rendered obvious by the prior art, and therefore claims 19-21, 24, and 25 fall with claim 18. Since claim 25 falls with claim 18, we need not address the examiner’s additional rejection of claim 25 over Birnbaum, Lopez-Berestein, Janoff, and Knight.

B. Birnbaum, Lopez-Berestein, Janoff, and Crowe

The examiner rejected claim 26 as obvious in view of the disclosures of Birnbaum, Lopez-Berestein, Janoff, and Crowe. Claim 26 is directed to the composition of claim 18 in lyophilized form and further comprising one of several listed disaccharides or monosaccharides. The examiner relied on Birnbaum, Lopez-Berestein, and Janoff for the same teachings discussed above. Crowe was relied on to meet the additional limitation.

Crowe teaches “a method for preserving liposomes containing biologically active molecules using a preserving agent.” Page 4. “Preferred preserving agents include carbohydrates having at least two monosaccharide units, and especially preferred compounds include the disaccharides sucrose, maltose, and trehalose.” Pages 3-4. “The method involves either freeze-drying liposomes in

the presence of a preserving agent, or freeze-drying liposomes which contain a preserving agent internally.” Page 4.¹

The examiner concluded that it would have been obvious to a person of ordinary skill in the art to combine the terbinafine-containing liposomes made obvious by Birnbaum, Lopez-Berestein, and Janoff, with the method of lyophilization in the presence of a disaccharide (e.g., maltose), taught by Crowe, because Crowe teaches that this method preserves the liposome composition without degradation. Examiner’s Answer, page 8. We agree with the examiner’s reasoning and conclusion.

Appellants argue that “the three primary references do not suggest the composition of the invention. . . . Lyophilizing an unobvious invention cannot be obvious even if there is teaching of lyophilizing related compositions.” Appeal Brief, page 6. This argument is not convincing, because we have already concluded that the composition of claim 18 would have been obvious in view of Birnbaum, Lopez-Berestein, and Janoff. Since we disagree with the premise of Appellants’ argument, we also disagree with their conclusion.

Appellants also argue that “Crowe discloses preservation of liposomes by lyophilisation; however, the thrust is towards trehalose as the preserving agent (see text and examples).” Appeal Brief, page 6. This argument is also unpersuasive. Crowe discloses that maltose and sucrose are “especially preferred” preserving agents, along with trehalose. Thus, it would have been

¹ “Lyophilization” and “freeze-drying” are synonymous. See Crowe, abstract (“In a preferred embodiment, trehalose is used as a preserving agent, both inside the liposomes . . . and

obvious to use any one of these agents in the disclosed preservation method.

“[A]ll disclosures of the prior art, including unpreferred embodiments, must be considered.” In re Lamberti, 545 F.2d 747, 750 192 USPQ 278, 280 (CCPA 1976).

C. Birnbaum, Lopez-Berestein, Janoff, and Woodle

The examiner rejected claim 23 as obvious in view of the disclosures of Birnbaum, Lopez-Berestein, Janoff, and Woodle. Claim 23 is directed to the composition of claim 18, comprising phosphatidylethanolamine-polyethyleneglycol (PEG-PE). The examiner relied on Birnbaum, Lopez-Berestein, and Janoff for the same teachings discussed above, and cited Woodle as teaching liposomal formulations comprising the antifungal agent amphotericin B, as well as teaching that “PEG derivatized PE in liposomes enhances their circulation time.” Examiner’s Answer, page 8. The examiner reasoned that it would have been obvious to use PEG-PE in the terbinafine-containing liposome formulation made obvious by Birnbaum, Lopez-Berestein, and Janoff, “since such a use increases the circulation time of liposomes.” Id.

Appellants argue that “there are no data on antifungal agents generally or terbinafine specifically. The representative drugs disclosed at col. 12, lines 28-34, do not suggest terbinafine. There is no motivation to combine Woodle with the other references.” Appeal Brief, page 6.

externally, in solution, during freeze-drying. The invention also includes a lyophilized composition prepared by the disclosed method.”).

We agree with Appellants that the examiner has not made out a prima facie case of obviousness with respect to claim 23. While it is true that Woodle discloses liposomes containing PEG-PE (column 4, lines 46-51) and discloses that such liposomes have enhanced circulation time in the blood (column 4, lines 34-36), Woodle's liposome formulations are disclosed for use in intravenous administration. See column 11, lines 35-41 (“[T]he liposome composition is designed for sustained release of a liposome-associated drug into the bloodstream by long-life circulating liposomes.”) and column 12, lines 35-36 (“For sustained drug-release via the blood stream, the liposome composition is administered intravenously.”).

The composition of claim 23, and the composition made obvious by the other cited references, is a topical composition. The examiner has not adequately explained why a modification disclosed to provide enhanced circulation time in the bloodstream, for a composition administered intravenously, would have suggested the same modification for a composition applied topically.

An adequate showing of motivation to combine requires “evidence that ‘a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.’” Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000). Such evidence is lacking with respect to the instant rejection. We therefore reverse the rejection of claim 23.

2. Indefiniteness

The examiner rejected claims 25 and 26 under 35 U.S.C. § 112, second paragraph, as indefinite. The examiner reasoned that claim 25 is indefinite because it is directed to a method comprising administering a terbinafine-containing composition to the lungs of a subject, but depends on claim 24, which is directed to a method of topically administering a composition to a patient. The examiner reasoned that claim 25 is inconsistent with the claim from which it depends, because topical administration does not include administration to the lungs (by inhalation). The examiner also rejected claim 26 as indefinite, on the basis that “xyliit” and “sorbit” are not “monosaccharide[s]” as recited in the claim.

We affirm these rejections as well. With respect to claim 25, the specification makes clear that “topical” administration differs from administration to the lung. See page 2, last paragraph (distinguishing “topical” administration from “pulmonary” or “pulmonal” administration); page 33, second full paragraph (“Administration may be peroral, topical or parenteral. It preferably is topical or parenteral, especially parenteral, particularly pulmonal.”); page 34, first full paragraph (“Topical administration is effected with liposomal preparations such as lotions, gels, creams or ointments. Local administration may also be effected by the inhalation route, especially to the lung.”). Thus, the specification makes clear that “local” administration includes both “topical” administration and “pulmonal” or “pulmonary” administration, i.e., administration to the lung.

The specification does not make clear that Appellants intended the phrase “topical administration” to include all methods of local administration, particularly

administration to the lung. See Optical Disc Corp. v. Del Mar Avionics, 208 F.3d 1324, 1334, 54 USPQ2d 1289, 1295 (Fed. Cir. 2000) (“Without evidence in the patent specification of an express intent to impart a novel meaning to a claim term, the term takes on its ordinary meaning.”). Thus, we agree with the examiner that topical administration does not include administration to the lung.

With respect to claim 26, Appellants have admitted that the “xylit” and “sorbit” recited in the claims are not monosaccharides, as required by the claim’s Markush language. Although Appellants proposed amending the claim to recite “xylitol” and “sorbitol,” that amendment was proposed after the final rejection and was refused entry by the examiner. See Paper No. 10, filed Oct. 14, 1998 (proposing to amend claim 26) and Paper No. 11, mailed Nov. 2, 1998 (refusing entry of Paper No. 10).

With respect to the rejection of claim 25, Appellants argue that “[t]here is nothing inconsistent with a topical composition/method and a pulmonary infection. Page 34, lines 4-7 [of the specification] recites local (i.e., topical) administration to the lungs (i.e., the site of a pulmonary infection).” Appeal Brief, page 7.

This argument is not persuasive. The portion of the specification that Appellants rely on (page 34, first full paragraph) is quoted above. For the reasons discussed above, we do not agree with Appellants’ position that the specification uses the phrases “topical administration” and “local administration” as synonyms. Rather, the specification makes clear that “topical” administration is one form of “local” administration, while administration to the lungs is another,

different form of "local" administration. Thus, topical administration does not include administration to the lungs.

Summary

We affirm the rejection of claims 18-21 and 24-26 for obviousness because the cited references support a prima facie case under 35 U.S.C. § 103, which has not effectively been rebutted. We also affirm the rejection of claims 25 and 26 as indefinite. However, we reverse the rejection of claim 23 because the prior art does not provide motivation to combine the modification taught by Woodle with the composition made obvious by the other references. Thus, claim 23 is not subject to any outstanding rejection.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 § 1.136(a).

AFFIRMED IN PART

Sherman D. Winters)
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