



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/296,153	12/06/2005	Gershon Golomb	92114.003US4	1175
75004	7590	12/02/2016	EXAMINER	
CADWALADER, WICKERSHAM & TAFT LLP ONE WORLD FINANCIAL CENTER NEW YORK, NY 10281			FRAZIER, BARBARA S	
			ART UNIT	PAPER NUMBER
			1611	
			NOTIFICATION DATE	DELIVERY MODE
			12/02/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOROTHY.AUTH@CWT.COM
DOCKETING@CWT.COM
JENNIFER.CHICK@CWT.COM

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte GERSHON GOLOMB and HAIM DANENBERG

Appeal 2015-006625
Application 11/296,153¹
Technology Center 1600

Before RICHARD M. LEBOVITZ, JOHN G. NEW, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims directed to pharmaceutical compositions comprising a bisphosphonate for intravenous administration. The compositions are useful for treatment or prevention of restenosis. The Examiner rejected the claims under 35 U.S.C. § 103(a). We have jurisdiction under 35 U.S.C. § 134(a). The Examiner's decision is reversed. New grounds of rejection are set forth pursuant 37 C.F.R. § 41.50(b).

¹ The real party in interest listed in the Appeal Brief is BIOrest Ltd.

STATEMENT OF THE CASE

Claims 1, 3, 4, 6, 15, 22, and 24–26 stand finally rejected by the Examiner under 35 U.S.C. § 103(a) as obvious in view of DE '890 (DE 196 37 890 A1, publ. Mar. 19, 1998), and Mönkkönen (1994) (“The effects of liposome surface charge and size on the intracellular delivery of clodronate and gallium in vitro,” *International Journal of Pharmaceutics*, 107: 189–197). Ans. 2.

Claim 1 is representative and reads as follows (*see* Appeal Br. 22 for the complete structural formula of the bisphosphonate):

1. A pharmaceutical composition for intravenous administration useful for treatment or prevention of restenosis comprising a bisphosphonate having a formula:

[FORMULA OMITTED]

in an aqueous liposome dispersion and having a size of 0.15 to 300 nanometers, wherein the liposome dispersion comprises distearoyl phosphatidylcholine (DSPC), distearoyl-phosphatidylglycerol (DSPG), and cholesterol in a molar ratio of 3:1:2;

wherein said composition contains an effective amount of said bisphosphonate for the treatment or prevention of restenosis.

REJECTION

Claims 1, 3, 4, 6, 15, 22, and 24–26 stand rejected by the Examiner as obvious in view of DE '890 and Mönkkönen (1994). The Examiner found it obvious to have modified the teachings in DE '980 with the teachings in Mönkkönen (1994). Ans. 2–4.

We reverse the rejection. Claim 1 is directed to a liposome dispersion comprising “an effective amount of said bisphosphonate for the treatment or

prevention of restenosis.” DE '890 describes a liposome composition comprising clodronate as useful to prevent kidney rejection. DE '890, p. 2. Mönkkönen (1994) teaches liposomes comprising clodronate as useful in inflammatory disease. Mönkkönen, Abstract. The Examiner did not provide adequate evidence that the composition in DE '890 comprises “an effective amount of said bisphosphonate for the treatment or prevention of restenosis” as required by all the rejected claims. *See* Ans. 5. The Examiner also did not provide sufficient reason to use the amounts of clodronate described in Mönkkönen in DE '890, which administers a liposome for a different purpose than disclosed by Mönkkönen.

NEW GROUNDS OF REJECTION

New grounds of rejection pursuant to 37 C.F.R. § 41.50(b) are set forth below.

1. Claims 1, 3, and 6 are rejected under 35 U.S.C. § 102(b) (pre-AIA) as anticipated by, or alternatively, under 35 U.S.C. § 103(a) (pre-AIA) as obvious in view of, Mönkkönen (1994). Medford (U.S. Pat. No. 5,380,747, patented Jan. 10, 1995) is cited as evidence.

2. Claims 4, 15, 22, and 24–26 are rejected under 35 U.S.C. § 103(a) (pre-AIA) as obvious in view of Mönkkönen (1994), Rogers (“Bisphosphonates Induces Apoptosis in Mouse Macrophage-like Cells In Vitro by a Nitric Oxide-Independent Mechanism,” *Journal of Bone and Mineral Research*, 11(10):1482–1491, 1996), and Medford.

1. ANTICIPATION BY MÖNKKÖNEN

Findings of Fact

The following findings of fact (“FF”) are pertinent to the determination that Mönkkönen anticipates claims 1, 3, and 6.

Specification of Application 11/296,153 involved in this appeal

FF1. The Specification discloses that the claimed bisphosphonate “affects restenosis by inhibiting phagocytic cells involved in the restenotic cascade, such as macrophages/monocytes and fibroblasts.” Spec. 3:6–9.

FF2. The Specification also discloses:

In a further embodiment, the present invention includes a method of treating or preventing restenosis by administering to an individual, an effective amount of any compound or composite known to inactivate or inhibit blood monocytes and tissue macrophages, thereby treating or preventing restenosis.

Id. at 3:16–19.

Mönkkönen

FF3. Mönkkönen describes a liposome comprising clodronate. Mönkkönen, Abstract, 192 (Table 1).

FF4. Mönkkönen teaches liposomes prepared from a 200 mM stock solution, and, phospholipid and cholesterol in a proportion of 67:33 or about 2:1. *Id.* at 190 (“2.2 Preparation of liposomes”). The liposomes comprising the phospholipid/cholesterol in the 2:1 ratio are described by Mönkkönen as having different proportions of DSPC and DSPG, including in a ratio of 75:25 (3:1) of DSPC to DSPG (Fig. 1 (unfilled triangles)).

FF5. A liposome having the amounts of DSPC/DSPG/cholesterol described in FF4 is equivalent to a molar ratio of 3:1:2. Final Rej. 5.

FF6. Mönkkönen teaches that the liposome comprising the clodronate (FF3–FF5) are macrophage suppressive agents that may be useful in the treatment of inflammatory diseases. *Id.* at 190 (col. 1, first full paragraph).

FF7. Mönkkönen teaches that the size of its liposomes having 75:25 of DSPC to DSPG is 190 nanometers. *Id.* at 192 (Table 1).

Medford

FF8. Medford teaches, *inter alia*, that an inflammatory response leads to clinically significant restenosis. Medford, col. 4, ll. 45–49.

Discussion

Claim 1 is directed to a pharmaceutical composition for intravenous administration comprising a bisphosphonate of a specifically recited formula in an aqueous liposome dispersion. The liposome dispersion comprises (1) DSPC, DSPG, and cholesterol in a molar ratio of 3:1:2. The composition also comprises (2) an effective amount of the bisphosphonate for the treatment of restenosis. Claim 6, which depends from claim 1, recites that the (3) “bisphosphonate is clodronate, etidronate, tiludronate, pamidronate or alendronate.” The liposomes have (4) a size of 0.15 to 300 nanometers.

Mönkkönen describes a liposome with the same molar ratio of (1) DSPC, DSPG, and cholesterol as claimed (FF4, FF5), where (3) the bisphosphonate is clodronate (FF3, FF6).

Mönkkönen teaches that its liposomes comprising clodronate are macrophage suppressive agents (FF6). Mönkkönen also teaches that its liposomes comprising clodronate may be useful to treat inflammatory disease (FF6). Consequently, Mönkkönen’s liposomes comprise an

effective amount of clodronate to suppress macrophages and treat inflammation. Mönkkönen, however, does not expressly teach that its liposomes comprise (2) an effective amount of the bisphosphonate for the treatment of restenosis as required by claim 1.

When the limitations of a claim are not expressly described in the prior art, the PTO must show “sound basis for believing” that despite the failure of the prior art to describe them, the limitations are inherently present and “the products of the applicant and the prior art are the same.” *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990). We find that a person of ordinary skill in the art would realize that Mönkkönen’s liposome preparation comprising clodronate would be effective to treat or prevent restenosis because the Specification discloses that the efficacy of the bisphosphonates in treating restenosis is associated with macrophage inhibition or inactivation (FF1, FF2), the same mechanism described by Mönkkönen for its liposomes (FF6). Because the mechanisms are the same, the skilled worker would have reasonably expected that Mönkkönen’s liposome preparation would contain an effective amount of clodronate to treat or prevent restenosis.

Furthermore, restenosis is an inflammatory response (FF8), and Mönkkönen teaches that its liposomes comprising clodronate are useful for treating inflammatory disease (FF6), providing further basis to believe that Mönkkönen’s liposomes contain an effective amount of the bisphosphonate to treat restenosis.

Mönkkönen describes that its liposomes are 190 nm (FF7) which falls within the recited range of liposomes having (4) a size of 0.15 to 300 nanometers.

With respect to claim 3, which depends from claim 1, and further comprises a diluent, Mönkkönen teaches that the clodronate is prepared as a 200 mM stock solution (FF4) which would necessarily require a diluent to make a solution.

Even if the amount of clodronate in Mönkkönen's liposomes is not anticipatory, it would have been obvious to have formulated the liposomes with amounts effective to suppress macrophages and treat inflammation because Mönkkönen teaches that this is the purpose of its liposomes (FF6). As discussed above, such amounts would treat restenosis because the mechanism of action described by Mönkkönen (FF6) and in the Specification are the same (FF1, FF2).

2. OBVIOUSNESS

Mönkkönen does not describe a bisphosphonate which is alendronate as recited in claims 15 and 24–26.

FF9. However, Rogers discloses a number of bisphosphonates including clodronate and alendronate, and teaches that alendronate causes apoptosis in a macrophage-like cell line. Rogers, Abstract; Fig. 2 (Fig. 2). *See* also Spec. 11:14–18.

It would have been obvious to one of ordinary skill in the art to have utilized the bisphosphonate alendronate in place of the bisphosphonate clodronate for alendronate's expected macrophage suppressing affect, i.e., apoptosis would result in the cell's death, thereby suppressing its function. It is obvious to utilize a prior art element for its established function. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

With respect to claims 24–26, which recites that the alendronate is a salt:

FF10. DE '890 teaches that bisphosphonates can be in salt form. DE '890, p. 2, ¶¶ 1, 3, 6.

Claims 4, 22

Dependent claims 4 and 22 recite that the composition of claims 1 and 15, respectively, further comprises a stabilizer.

FF11. DE '890 teaches “saccharose” (sucrose) and sodium carbonate buffer in clodronate liposomes. *Id.* at 3 (“Example”).

The Specification does not limit the stabilizers utilized in its liposomes. Spec. 3:20–24. Consequently, we find, as the Examiner did (Final Rej. 6), that sucrose and buffer can serve as stabilizers. It would have been obvious to one of ordinary skill in the art to have included sucrose and buffer in liposomes because DE '890 teaches that they are conventional components of a liposome preparation.

SUMMARY

1. The § 103 rejection of claims 1, 3, 4, 6, 15, 22, and 24–26 as obvious in view of DE '890 and Mönkkönen (1994) is reversed.

Pursuant to 37 C.F.R. § 41.50(b):

2. Claims 1, 3, and 6 are rejected under 35 U.S.C. § 102(b) as anticipated by, or alternatively, under 35 U.S.C. § 103(a) as obvious in view of, Mönkkönen (1994). Medford is cited as evidence.

4. Claims 4, 15, 22, and 24–26 are rejected under 35 U.S.C. § 103 as obvious in view of Mönkkönen (1994), Rogers, and Medford.

NEW GROUNDS OF REJECTION

This Decision contains new grounds 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 that “[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 Appellants, 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. . .

The amendment and/or new evidence under 37 C.F.R. § 41.50(b)(1), or the request for rehearing under 37 C.F.R. § 41.50(b)(2), must be filed within 2 months from the date of the Board’s decision. In accordance with 37 C.F.R. § 41.50(f), this 2-month time period may not be extended by the filing of a petition and fee under 37 C.F.R. § 1.136(a), but only under the provisions of 37 C.F.R. § 1.136(b).

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)(iv).

Appeal 2015-006625
Application 11/296,153

REVERSED; 37 C.F.R. § 41.50(b)