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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte LOUIE DANIEL GARCIA, LIANGJIN ZHU, WILLIAM JOSEPH LAMBERT, and GARY PATOU

Appeal 2018-007990
Application 13/283,450[1]
Technology Center 1600

Before DONALD E. ADAMS, JOHN G. NEW, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an Appeal under 35 U.S.C. § 134 involving claims to a formulation of one or more non-steroidal anti-inflammatory drugs, which have been rejected as obvious. 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 Pacira Pharmaceuticals, Inc. (Appeal Br. 3.)

STATEMENT OF THE CASE

Non-steroidal anti-inflammatory drugs (NSAIDs) are administered both orally and intravenously. (Spec. ¶ 3.) "Oral NSAID treatment, however, has been linked to a variety of serious gastrointestinal complications, including peptic ulcer, digestive perforation, hemorrhage, colonic ulcer, and colitis." (*Id.*) "GI toxicity is attributable to the magnitude and duration of drug exposure both in the GI tract following oral dosing and with high systemic levels of drug required to achieve efficacious drug levels at the synovial site of action[[2]]." (*Id.* ¶ 4.)

Appellant's invention is directed at a formulation of the NSAIDs meloxicam and/or piroxicam encapsulated in a multivesicular liposome[3] which minimize the side effects of NSAIDs while maintaining or improving efficacy. (*See id.* ¶¶ 8, 28, claim 1)

Claims 1, 62, 64, 68, 70, 71, 73, 74, 111, 112, 115–122, and 136 are on appeal. Claim 1 is representative and reads as follows:

> 1. A formulation of one or more non-steroidal anti-inflammatory drugs, comprising:
>
> one or more non-steroidal anti-inflammatory drugs selected from the group consisting of meloxicam and piroxicam; and
>
> multivesicular liposomes,
>
> wherein the multivesicular liposomes comprise a first aqueous phase and a second aqueous phase;

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[2] "[D]rugs are typically cleared in a matter of hours from the synovial fluid." (*Id.* ¶ 5.)

[3] "Topologically, multivesicular liposomes ["MVLs"] are defined as having multiple non-concentric chambers within each particle, resembling a 'foam-like' matrix; whereas multilamellar vesicles contain multiple concentric chambers within each liposome particle, resembling the 'layers of an onion.'" (*Id.* ¶ 35.)

> wherein the one or more non-steroidal anti-inflammatory drugs are encapsulated in the first aqueous phase of the multi vesicular liposomes; and
>
> wherein the first aqueous phase comprises at least one pH modifier, said pH modifier comprises an organic acid or an organic base, or a combination thereof.

(Appeal Br. 17.)

The following grounds of rejection by the Examiner are before us on review:

Claims 1, 62, 64, 68, 70, 71, 73, 74, 111, 112, 115–122, and 136 under 35 U.S.C. § 103 as unpatentable over Weiner[4] or McLean,[5] Sankaram,[6] and Gruber.[7]

Claims 1, 62, 64, 68, 70, 71, 73, 74, 111, 112, and 115–122[8] under 35 U.S.C. § 103 as unpatentable over Weiner or McLean, Kim '573,[9] and Gruber.

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[4] Weiner et al., US 6,759,057 B1, issued July 6, 2004.
[5] McLean et al., US 2003/0235610 A1, published Dec. 25, 2003.
[6] Sankaram et al., US 6,132,766, issued Oct. 17, 2000.
[7] Gruber et al., US 2010/0035937 A1, published Feb. 11, 2010.
[8] Additional claims were rejected by the Examiner in the Office Action from which the appeal was taken, but those claims had been canceled prior to issuance of that Office Action, and thus, are no longer pending in the Application on Appeal. (*See* Amendment and Response to Office Action dated April 20, 2017 (cancelling claims 20, 65–67, 69, 87, 89–91, 93–97, 99–102, 107, 108, 110, 123–125, and 128–135).)
[9] Kim, U.S. Patent No. 5,759,573, issued June 2, 1998.

Claims 1, 62, 64, 68, 70, 71, 73, 74, 111, 112, 115–122, and 136 under 35 U.S.C. § 103 as unpatentable over Hofland,[10] Cipolla[11], Kim '147,[12] and Gruber.

DISCUSSION

Weiner, McLean, Sankaram, and Gruber

The Examiner finds that Weiner and McLean both teach liposomal formulations that contain a non-steroidal anti-inflammatory drug (NSAID), where piroxicam is identified as one such NSAID. (Final Action 2.) The Examiner recognizes that neither reference teaches encapsulation of the NSAID in a MVL. (*Id.*)

The Examiner finds, however, that Sankaram teaches a variety of drugs encapsulated in MVLs. (*Id.* at 3.) The Examiner finds that Sankaram indicates that the internal membranes of the MVL "serve to cover increased mechanical strength to the vesicle, while still maintaining a high volume lipid ratio compared to multi-lamellar vesicles." (*Id.* (citing Sankaram 2:28–39).) According to the Examiner, it would have been obvious to one of ordinary skill in the art "to encapsulate NSAIDS of Weiner or McLean in the [MVL] and treat inflammation since Sankaram teaches the advantages of [MVL]" and/or because "Sankaram teaches that any drug can be encapsulated within the [MVL] and NSAIDS are known to be encapsulated within liposomes as evident from Weiner and McLean." (*Id.*)

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[10] Hofland et al., US 2004/0224010 A1, published Nov. 11, 2004.
[11] Cipolla et al., US 2012/0244206 A1, published Sept. 27, 2012.
[12] Kim et al., US 5,723,147, issued Mar. 3, 1998.

Regarding encapsulation of NSAIDs in an aqueous phase of the MVL rather than in the lipid layers of the liposomes of Weiner and McLean, the Examiner notes that Gruber teaches NSAIDs, such as naproxen and diclofenac which are water insoluble hydrophobic compounds, "can be converted into salt form to obtain soluble forms." (*Id.* at 3–4.) According to the Examiner, it would have been obvious to make the NSAID into a salt form "since such [a] procedure makes the NSAID soluble as taught by Gruber" (*id.* at 3), and then encapsulate the NSAID in the aqueous compartment of the MVL "instead of sequestering them into [the] lipid bilayer of the liposomes" (*id.* at 4).

We disagree with the Examiner's conclusion of obviousness. As Appellant points out, Gruber teaches a solubilized NSAID salt where the NSAID contains "at least one carboxylic group." (Gruber ¶ 25; Appeal Br. 13 (citing Declaration of Kathleen Los[13] ¶ 7).) The Examiner did not address this argument directly. (Ans. 3–5.) Instead, the Examiner argued that generally increasing the pH to dissolve NSAIDs "is suggested by Gruber [and] determining the solubility conditions of any compound is within the skill of the art of [the] highly developed field of chemistry." (*Id.* at 6.)

We disagree that one of ordinary skill in the art would have had a reasonable expectation of success in solubilizing meloxicam or piroxicam by making a salt form using the method described by Gruber. Gruber notes that "[a] common disadvantage of this group of drugs[, i.e., NSAIDs,] is their poor solubility." (Gruber ¶ 2.) Yet Gruber only discloses making water-

[13] The Los Declaration is dated April 19, 2017.

soluble salt forms of NSAIDs that contain at least one carboxylic group. (Gruber ¶¶ 24–25.) We determine that one of ordinary skill in the art would have reasonably concluded from this disclosure that not all NSAIDs may be provided as a water-soluble salt form, and thus, we disagree with the Examiner that increasing the pH to dissolve any NSAID is suggested by Gruber (Ans. 6).

As Ms. Los attests (Los Declaration ¶ 7), and the Examiner does not dispute, neither meloxicam nor piroxicam have a carboxylic group. Thus, we agree with Appellant (Reply Br. 7), that in light of Gruber's narrow disclosure of the NSAIDs that could be made into solubilized salts as NSAIDS having a carboxylic group, one of ordinary skill in the art would not have had a reasonable expectation of success in achieving a soluble salt form of meloxicam or piroxicam by simply solubilizing those compounds "at an alkaline pH as taught by Gruber" (Final Action 5). Consequently, we reverse the Examiner's rejection of the claims as being obvious over Weiner, McLean, Sankaram, and Gruber.

Weiner, McLean, Kim, and Gruber

The Examiner's rejection under this ground relies on Gruber for the same principle as discussed above. (*See* Final Action 6.) For the reasons just discussed, we disagree that one of ordinary skill in the art would have had a reasonable expectation of success in solubilizing meloxicam or piroxicam by making a salt form as described by Gruber. Thus, we reverse the Examiner's obviousness rejection under this ground.

Hofland, Cipolla, Kim, and Gruber

The Examiner's rejection under this ground relies on Gruber for the same principle as discussed above. (*See* Final Action 7–8; Ans. 6.) For the reasons just discussed we disagree that one of ordinary skill in the art would have had a reasonable expectation of success in solubilizing meloxicam or piroxicam by making a salt form as described by Gruber. Thus, we reverse the Examiner's obviousness rejection under this ground.

SUMMARY

In summary:

Claims Rejected	Basis	Affirmed	Reversed
1, 62, 64, 68, 70, 71, 73, 74, 111, 112, 115–122, and 136	§ 103 over Weiner or McLean, Sankaram, and Gruber		1, 62, 64, 68, 70, 71, 73, 74, 111, 112, 115–122, and 136
1, 62, 64, 68, 70, 71, 73, 74, 111, 112, and 115–122	§ 103 over Weiner or McLean, Kim '573, and Gruber		1, 62, 64, 68, 70, 71, 73, 74, 111, 112, and 115–122
1, 62, 64, 68, 70, 71, 73, 74, 111, 112, 115–122, and 136	§ 103 over Hofland, Cipolla, Kim '147, and Gruber		1, 62, 64, 68, 70, 71, 73, 74, 111, 112, 115–122, and 136
Overall Outcome			1, 62, 64, 68, 70, 71, 73, 74, 111, 112, 115–122, and 136

REVERSED