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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 2019-002501
Application 13/790,279
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and JOHN G. NEW, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

The claims in this appeal are directed to formulations comprising one or more non-steroidal anti-inflammatory drugs encapsulated in multivesicular liposomes. The Examiner rejected the claims under 35 U.S.C. § 103 as obvious and under the judicially-created doctrine of obvious-type double patenting. Pursuant to 35 U.S.C. § 134, Appellant[1] appeals the Examiner's determination that the claims are unpatentable. We have jurisdiction for the appeal under 35 U.S.C. § 6(b).

We AFFIRM.

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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. 4.

STATEMENT OF THE CASE

The Examiner finally rejected the claims as follows:

1. Claims 74, 78–82, 84, 85, and 106–117 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Weiner et al. (U.S. Pat. No. 6,759,057 B1, issued July 6, 2004) ("Weiner") or McLean et al. (U.S. Pat. App. Publ. 2003/0235610 A1, published Dec. 25, 2003) ("McLean"), Sankaram et al. (U.S. Pat. No. 6,132,766, issued Oct. 17, 2000) ("Sankaram"), Gruber et al. (U.S. Pat. App. Publ. 2010/0035937 A1, published Feb. 11, 2010) ("Gruber"), and Heit et al. (U.S. Pat. No. 8,097,614 B2, issued Jan.17, 2012) ("Heit"). Ans. 2.

2. Claims 74, 78–82, 84, 85, and 106–117 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of Hofland et al. (U.S. Pat. App. Publ. 2004/0224010 A1, published Nov. 11, 2004) ("Hofland"), Cipolla et al. (U.S. Pat. App. Publ. 2012/0244206 A1, published Sept. 27, 2012) ("Cipolla"), Kim et al. (U.S. Pat. No. 5,723,147, issued Mar. 3, 1998) ("Kim"), Gruber, and Heit. Ans. 4.

3. Claim 111 under pre-AIA 35 U.S.C. § 103(a) as obvious in view of 1) Weiner or McLean, Sankaram, Gruber, and Heit; or 2) Hofland, Cipolla, Kim, Gruber, and Heit, and further in view of Shirley et al. (U.S. Pat. No. 6,306,432 B2, issued Oct. 23, 2001) ("Shirley"). Ans. 6.

4. Claims 74, 78–82, 84, 85, and 106–117 provisionally rejected on the ground of obviousness-type double patenting as obvious over claims of co-pending Applications (1) 13/283,450 (rejections appealed to PTAB and reversed in the Decision entered Sept. 16, 2019); (2) 13/787,480 (on appeal to PTAB); and (3) 13/787,462 (issue notification sent Oct. 24, 2018). Ans. 7, 8.

We have identified another co-pending application, Application 13/787,382, which is also on appeal and *concurrently* decided (Appeal 2019-002529).

Claim 74, the only independent claim on appeal, is reproduced below (bracket numbers [1]–[4] added for reference):

> 74. A formulation comprising one or more non-steroidal anti-inflammatory drugs encapsulated in multivesicular liposomes prepared by a process comprising:
>
> [1] providing a volume of first emulsion comprising at least one non-steroidal anti-inflammatory drug selected from the group consisting of diclofenac, piroxicam, meloxicam and ketorolac by mixing a first aqueous phase and a volatile water-immiscible solvent phase, wherein said solvent phase comprises at least one amphipathic lipid and at least one neutral lipid, and wherein said first aqueous phase comprises one or more pH modifiers;
>
> [2] providing a volume of second emulsion comprising a continuous aqueous phase by mixing and emulsifying said first emulsion and a second aqueous phase; and
>
> [3] removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles encapsulating at least one non-steroidal anti-inflammatory drug in the first aqueous phase, [4] wherein the multivesicular liposomal particles are characterized by an internal pH of about 7 or higher.

REJECTIONS 1–3

Claim 74 is directed to a formulation made by the recited process of [1] providing a first emulsion comprising a non-steroidal anti-inflammatory drug (NSAID) selected from a specific list; [2] providing a second emulsion by mixing and emulsifying the first emulsion and an aqueous phase; and [3] removing solvent from the thus formed second emulsion to form multi-vesicular liposomal ("MVL") particles which encapsulate the NSAID. The

claim requires the MVL particles to have [4] "an internal pH of about 7 or higher."

Rejection 1

The Examiner found that Weiner and McLean each disclose liposomal formulations comprising NSAIDs, including piroxicam which is specifically claimed. Ans. 2. However, the Examiner acknowledged that Weiner and McLean do not disclose the NSAIDS encapsulated in MVLs as required by the claim ("formulation comprising one or more non-steroidal anti-inflammatory drugs encapsulated in multivesicular liposomes"). Ans. 3. To meet this deficiency, the Examiner relied on Sankaram for its description of a process for encapsulating drugs in MVLs. *Id.*

To meet the pH requirement of the claim, the Examiner further cited the publications by Gruber and Heit.

FF1.[2] The Examiner found that Gruber discloses that "NSAIDs can be solubilized if the pH of the composition is from 7-10" and describes using bases to do so. Ans. 3.

FF2. Gruber teaches that "active ingredient is selected from the family of NSAIDs which contain at least one carboxylic group," and identifies diclofenac as one such NSAID. Gruber ¶ 25. Diclofenac is one of the NSAIDS listed in the claims.

FF3. The Examiner also relied upon Heit for teaching that meloxicam, one of the claimed NSAIDs, is soluble in alkaline solutions and precipitates below pH 8. Ans. 3; Heit 36:26–30 ("The solution was then acidified to a pH of 7 with 0.2 M HCl, whereupon the meloxicam was

[2] "FF" is a Finding of Fact.

observed to precipitate. Additional 1 M NaOH was added, adjusting the pH to 8, and the meloxicam redissolved and remained in solution.").

FF4. Neither of Gruber or Heit teach liposomal preparations.

Based on these findings, the Examiner concluded that it would have been obvious to one of ordinary skill in the art "to encapsulate NSAIDs of Weiner or McLean in the multivesicular liposomes since Sankaram teaches the advantages of multivesicular liposomes." Ans. 3. The Examiner further concluded that, when encapsulating an NSAID, "it would have been obvious to one of ordinary skill in the art to increase the pH of NSAID since such an increase would enable the NSAID to solubilize as taught by Gruber and Heit (meloxicam)." Ans. 4.

Rejection 2

The Examiner found that Hofland teaches liposomes comprising NSAIDs, including the claimed diclofenac and ketorolac. Ans. 4. Although Hofland's examples make unilamellar liposomes, the Examiner found that Hofland also discloses MVLs, making it obvious to use MVLs to deliver NSAIDS as required by claim 74. *Id.* Hofland, however, does not describe how to make MVLs. The Examiner also found that Cipolla describes delivering NSAIDS in MLVs to increase encapsulation efficiency. Ans. 4–5. Cipolla also describes several of the claimed NSAIDs. *Id.*

The Examiner concluded it would have been obvious to one of ordinary skill in the art "to use multivesicular liposomes in Cipolla or in [Hofland] since Cipolla teaches that the encapsulation efficiency is higher in multivesicular liposomes." Ans. 5.

The Examiner further found that Kim teaches that "multivesicular liposomes provide high encapsulation efficiency, controlled release of the encapsulated substance, well defined, reproducible size distribution among the liposomes, adjustable average size that can be easily controlled," providing further reason to utilize MLV to encapsulate NSAIDs. Ans. 5–6.

With respect to the [4] pH limitation of the claims, the Examiner relied on Gruber and Heit as in Rejection 1, namely, for teaching solubilizing NSAIDS in alkaline solutions. Ans. 5.

Discussion

Appellant contends that there would have been no reason to encapsulate NSAIDS in MLVs as described in Sankaram and Kim (the "MVL references") at an alkaline pH as taught by Gruber and Heit because "the acidic internal environment required by the MVL references to effectively control the release rate of the encapsulated active agent is incompatible with the teaching of Gruber and Heit regarding the use of bases to solubilize NSAIDs" and "both Gruber and Heit disclose formulations that are not compatible with the manufacture of MVLs." Appeal Br. 14.

Appellant cites the following evidence to support this argument:

FF5.

> The process for producing these MVL compositions comprises (a) forming an emulsion from a lipid component comprising at least one organic solvent, at least one amphipathic lipid, at least one neutral lipid, and an immiscible first aqueous component comprising at least one biologically active substance and, in *the presence of at least one nonhydrohalic acid*, (b) mixing the emulsion with a second aqueous component to form solvent spherules, (c) removing the organic solvent from the solvent spherules to form

> multivesicular liposomes. *According to the present invention, addition of one or more non-hydrohalic acids is effective in controlling the release rate of the encapsulated biologically active substance into biological fluids and in vivo*.

Sankaram 3:27–41 (emphasis added).

FF6.

> The non-hydrohalic acid present when the MVL is formed is effective in controlling the rate of release of the encapsulated biologically active substance from the MVL into biological fluids and in vivo.

Sankaram 4:49–52.

FF7.

> The present invention provides a multivesicular liposome containing a biologically active substance encapsulated *in the presence of a hydrochloride*, which is used to effectively modulate the release rate of the encapsulated biologically active substance.

Kim 3: 21–25 (emphasis added).

FF8.

> According to the present invention, the addition of sufficient hydrochloride effective for high encapsulation efficiency and for controlled release rate of encapsulated biologically active substances in biological fluids and in vivo is *essential*.

Kim 5:33–37 (emphasis added).

FF9.

> The term "hydrochloride" as used herein means hydrochloric acid or a hydrochloric acid salt of an organic base or a combination thereof.

Kim 4:50–52.

FF10. Table 7 shows that organic bases and hydrochloric acid produce acidic salts, listing, for example, Arginine HCl, Histidine HCl, and Lysine HCl. Kim 13:20–30; Appeal Br. 15.

These findings provide evidence that each of Sankaram and Kim teach the essentiality of the acid to control release of the biologically active substance from the MLV.

Appellant also provided a declaration under 37 C.F.R. § 1.132 by Kathleen Los, Director of Formulation Development at Pacira Pharmaceutical, the real party in interest of the application involved in this Appeal ("Los Decl."). Ms. Los stated in her declaration:

FF11.

> Previous work in the development of the MVL manufacturing process done by Kim, Sankaram, etc. all requires an acidic internal environment to achieve high encapsulation efficiencies and to facilitate the sustained release of the active agents. For example, Sankaram discloses processes for preparing multivesicular liposomes ("MVLs") where the encapsulation of the biologically active substance is in an acidic environment. Sankaram discloses the processes of preparing MVLs encapsulating a biologically active substance containing at least one acid other than a hydrohalic acid. *See* Sankaram at Abstract. Sankaram teaches the use of an acid or an acidic salt for controlling the release rate of the encapsulated biologically active substance from the MVLs into biological fluids *in vivo*.

Los Decl. ¶ 5.

FF12.

> Second, high pH environments may cause lipid hydrolysis in the MVL membranes, and decrease the long term storage stability of the MVL particles. Third, MVLs with a highly basic internal pH would be undesirable for local injection into a human body.

Los Decl. ¶ 6.

Discussion

Rejections 1 and 2 are both based on the determination that it would have been obvious to one of ordinary skill in the art to encapsulate the recited NSAIDs in MLVs at "an internal pH of about 7 or higher" (an alkaline pH) because both Gruber and Heit teach utilizing an alkaline pH to solubilize NSAIDs which fall within the scope of claim 74. However, as argued by Appellant, Sankaram teaches the addition of acid (below pH 7) to control the release of the encapsulated biological active substance (FF5, FF6) and Kim teaches the presence of an acid ("hydrochloride") is "essential" for high encapsulation efficiency and controlled release (FF7, FF8, FF10). The testimony of Ms. Los in her § 1.132 declaration is consistent with these findings. FF11. Ms. Los also provided additional reasons as to why alkaline pH would be undesirable in MVL membranes. FF12.

> "When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references." *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Stated another way, the prior art as a whole must "suggest the desirability" of the combination. *In re Beattie*, 974 F.2d 1309, 1311 (Fed. Cir. 1992) (internal quotation omitted).

In re Fulton, 391 F.3d 1195, 1200 (Fed. Cir. 2004).

"[A] finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination." *Id*. However, as explained in *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994):

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

In this case, the cited prior art publications, Sankaram and Kim, in describing MLV preparations, teach that acid is needed to control the release rate and encapsulation efficiency of biological active substances in the MLV preparations. FF5–FF8. Ms. Los's testimony is consistent with these findings. FF11. The result sought by each of these publications, to increase encapsulation and controlled release efficiency, is achieved utilizing an acid. Acid is not described as being omitted from the MLVs, or the effect on the MLV if it were left out. The claims, instead use a pH above about pH 7. Therefore, one of ordinary skill in the art would have been "led in a direction divergent from the path that was taken by the applicant" because Sankaram and Kim describe using an acid, but the claims exclude it. This is not simply a case where omitting the acid is "less desirable." The Examiner did not direct us to embodiments in Sankaram and Kim where the acid had been left out when preparing the MLVs. In contrast, in *Gurley* it was established that

the epoxy that had been used in the prior art in the same way as claimed, but the prior art had improved on it. *Gurley*, 27 F.3d. at 553.

In response to Appellant's arguments, the Examiner stated "it is within the skill of the art if the goal is to encapsulate NSAIDs which are soluble only at pH 7–10 and if fast-release rate is not required to use a basic pH instead of an acidic pH of a non-hydrohalic acid." Ans. 11. However, our difficulty with the Examiner's reasoning is that there is no evidence before us that a skilled worker would have gone against the express teachings in Sankaram and Kim to use acid when preparing MLVs, and to defeat their objective "to effectively modulate the release rate of the encapsulated biologically active substance" and achieve high encapsulation efficiency (FF8). The teachings in Gruber and Heit about pH and alkalinity pertain to non-liposomal preparations (FF4) and therefore do not provide sufficient reason to modify the teachings in Sankaram and Kim about the presence of an acid.

For the foregoing reasons, the rejection of claim 74, and dependent claims 78–82, 84, 85, 106–110, and 112–117 is reversed.

Dependent claim 111, rejected under Ground 3, is reversed for the same reasons.

4. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

Appellant did not provide specific arguments as to why the claims are patentable in view of the cited patent applications. Appeal Br. 23–24. Rather, Appellant requests that the rejections not be summarily affirmed

based on *Ex Parte Moncla* (Appeal No. 2009-006448, Application No. 10/925,693; BPAI; decided June 22, 2010).

In *Moncla*, the Board had reversed the rejections under §§ 102 and 103, and the only remaining rejection was a provisional judicially-created obviousness-type double patenting rejection. The application claims in the appeal were rejected over claims of a *later-filed* co-pending application. *Moncla* 2. The Board stated that "in this circumstance it was premature for the original Board panel to address the Examiner's provisional rejection of the claims." *Moncla* 3.

Appellant has not established that the co-pending applications which serve as the basis for the obviousness-type double-patenting rejections are "later-filed, co-pending" applications. In addition, one of these applications, Application No. 13/787,462, was sent an issue notification on October 24, 2018, indicating it would issue as a patent. Therefore, Appellant has not established that the same situation as in *Moncla* exists here. Accordingly, we summarily affirm the three obviousness-type double-patenting rejections.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/ Basis	Affirmed	Reversed
74, 78–82, 84, 85, 106–117	103	Weiner, McLean, Sankaram, Gruber, Heit		74, 78–82, 84, 85, 106–117
74, 78–82, 84, 85, 106–117	103	Hofland, Cipolla, Kim, Gruber, Heit		74, 78–82, 84, 85, 106–117

111	103	Weiner, McLean, Sankaram, Gruber, Heit, Shirley; or, Hofland, Cipolla, Kim, Gruber, Heit, Shirley		111
74, 78–82, 84, 85, 106–117	101	Obvious-type double-patenting, Application 13/283,450	74, 78–82, 84, 85, 106–117	
74, 78–82, 84, 85, 106–117	101	Obvious-type double-patenting, Application 13/787,480	74, 78–82, 84, 85, and 106–117	
74, 78–82, 84, 85, 106–117	101	Obvious-type double-patenting, Application 13/787,462	74, 78–82, 84, 85, 106–117	
Overall Outcome			74, 78–82, 84, 85, 106–117	

TIME PERIOD FOR RESPONSE

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

AFFIRMED