

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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

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*Ex parte* AI J. LIN, JOHN VANHAMONT, WILBUR K. MILHOUS

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Appeal 2007-4552  
Application 10/376,420  
Technology Center 1600

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Decided: November 19, 2007

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Before, DONALD E. ADAMS, DEMETRA J. MILLS, and  
LORA M. GREEN, *Administrative Patent Judges*.

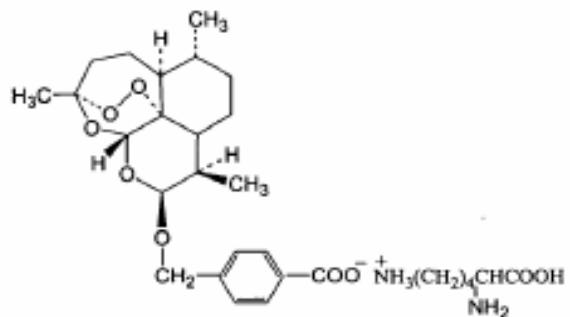
MILLS, *Administrative Patent Judge*.

**DECISION ON APPEAL**

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Claim 1 is representative.

1. A composition comprising artelinic acid/L-lysine salt having the following formula:



### *Grounds of Rejection*

Claims 1-9, 16, and 17 stand rejected under 35 U.S.C. § 103 as obvious over Lin in view of Okada and Fujisawa.

### *Cited References*

Okada ('357)	US 3,925,357	Dec. 9, 1975
Fujisawa ('403)	US 3,984,403	Oct. 5, 1976
Lin ('135)	US 4,791,135	Dec. 13, 1988

## DISCUSSION

### *Background*

“Artelinic acid (AL) was patented in 1988 (Lin, et al., US 4,791,135) as antimalarial agents ... and is currently under development as [a] parenteral drug for treatment of severe and complicated malaria.” (Specification 5 (endnote omitted).) “Unexpectedly, AL formulation has

encountered numerous problems which are unique to artelinic acid and not commonly observed with other acidic drugs.” (*Id.*)

“Artelinic acid is not water soluble until it was converted to a salt form. The most commonly used water soluble salt for acidic drugs is sodium salt. … The freshly prepared sodium artelinate (Na-AL) is highly water soluble (> 60 mg/ml). However, portions of the sodium artelinate were converted to free artelinic acid on exposure to atmospheric carbon dioxide and moisture which formed carbonic acid. The carbonic acid is acidic enough to convert some of the Na-AL salt back to AL free acid.” (Specification 5-6.)

“Similar problems were observed with freshly prepared sodium artelinate aqueous solution which turned turbidity on standing at room temperature because of the formation of free AL on standing.” (Specification 6.) “[O]n standing at room temperature for a longer period of time, white crystalline material (free artelinic acid) crystallized out from all solutions with various concentrations of sodium carbonate. Heating of the solution at 40° C accelerated the crystal formation.” (*Id.*)

### *Obviousness*

Claims 1-9, 16, and 17 stand rejected under 35 U.S.C. § 103 as obvious over Lin ('135) in view of Okada ('357) and Fujisawa ('403). We select claim 1 as representative of the rejection before us since Appellants have not separately argued individual claims. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner finds that Lin teaches artelinic acid and its alkaline earth metal salts as useful in treating malaria (See the abstract and claims 1-

8). (Answer 3.) The Examiner acknowledges that Lin does not expressly teach the L-lysine salt of artelinic acid and that the Lin patent does not expressly teach the method of preparing L-lysine salt of artelinic acid.  
(Answer 4.)

The Examiner relies on Okada and Fujisawa for teaching a method of preparing lysine salts of  $\alpha$ -sulfonylpenicillin as carried in a solvent such as water or mixtures of alcohols such as ethanol '357 also teaches the collection of the lysine salt product being performed by lyophilization or recrystallization (See col. 2, line 60 to col. 3, line 22). '357 also teaches the lysine or D-lysine salt as being more stable, less hygroscopic and less local irritation or pain when injected (See col. 1, lines 59-68, also col. 2, lines 7-11).

'403 teaches lysine salt[s] of cephalosporins that have superior stability, increased solubilities and reduced pain of injection (See the abstract and col. 1, lines 5-30). '403 also teaches the method of preparing lysine salts as reacting the lysine and the acidic cephalosporins in aqueous medium or with additional organic solvents (See col. 3, lines 17-46).

(Answer 4.)

The Examiner concludes

[i]t would have been obvious to one of ordinary skill in the art at the time of invention to employ the methods of '357 and/or '403 to prepare the composition comprising lysine salts of artelinic acid.

One of ordinary skill in the art would have been motivated to employ the methods of '357 and/or '403 to prepare the composition comprising lysine salts of artelinic acid. Examiner notes that the pharmaceutically acceptable salts of artelinic acid are known. It is also known in the art that lysine salt of antibiotic can increase stability and solubilities, as well as reduce pain of injection. Therefore, possessing the teachings

of the cited prior arts, one of ordinary skill I[n] the art would have been reasonably expected to formulate the L-lysine salts of artelinic acid in the manner described in '357 and '403 to increase stability and solubilities, as well as reduce pain of injection. Furthermore, formulating the L-lysine salt of artelinic acid with conventional carriers, such as 5% glucose or saline, into a conventional parenteral formulation is obvious as being within the purview of the skilled artisan.

(Answer 4-5.)

The Examiner further relies on the case law of *Pfizer v. Apotex*, 480 F. 3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007) in support of a prima facie case of obviousness in the present case. (Answer 6.)

We agree that the Examiner has provided sufficient evidence to support a prima facie case of obviousness. We further agree with the Examiner that the *Pfizer* case is particularly relevant to the facts of the obviousness rejection before us.

In *Pfizer*, the primary reference disclosed pharmaceutically acceptable salts of amlodipine, but did not expressly disclose the claimed benzene sulfonate (besylate) salt. (*Id.*, at 1361.) The secondary references disclosed besylate salts of pharmaceutical compounds and indicated that the besylate salt had good stability, good solubility, nonhygroscopicity and good processability. (*Id.*, at 1355.) Like Appellants in the present case, *Pfizer* argued there was no motivation to combine the cited references because the pharmaceutical compound besylate salts of the secondary references were unrelated to the claimed compound, amlodipine. (*Id.*, at 1362.) In *Pfizer*, there was “irrefutable evidence that a skilled chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active

ingredient with which he or she was working at the time.” (*Id.*, at 1362.) The court held that one skilled in the art facing the problem of the inventor would have been motivated to combine the teachings of the prior art to produce the besylate salt of amlodipine. (*Id.*, at 1364.)

Like *Pfizer*, in the present case, the prior art describes pharmaceutical salts of artelinic acid and lysine salts of pharmaceutical compounds unrelated to artelinic acid, and also describes advantages associated with the use of lysine salts of the unrelated pharmaceutical compounds. In particular, the prior art cites the advantages of water solubility and stability of alkaline earth metal salts of artelinic acid (Lin, col. 9, ll. 33-37). The prior art further describes good solubility, stability and reduced pain when lysine salts of unrelated pharmaceutical compounds are injected intramuscularly or subcutaneously (Fujisawa, col. 1, ll. 5-30; Okada col. 1, ll. 10-15, 30-58).

Each of Lin, Okada and Fujisawa teach subcutaneous administration of a pharmaceutical salt. (Lin, col. 10, ll. 20-34; Okada, col. 3, ll. 40-47; Fujisawa, col. 1, ll. 8-30.) Okada and Fujisawa each teach that one of ordinary skill in the art addressing the problem of pain associated with subcutaneous injection would look to prior art pharmaceutically acceptable salts, such as lysine salts, which have good solubility and stability properties as well as properties that do not cause pain upon subcutaneous injection. We find that one of ordinary skill in the art desiring to administer artelinic acid subcutaneously as set forth in Lin (Lin, col. 10, ll. 20-24) would look to prior art pharmaceutically acceptable salts, such as lysine salts, which have good solubility and stability properties as well as properties that do not cause pain upon subcutaneous injection. (Lin, col. 10, ll. 20-34; Okada, col. 3, ll.

40-47; Fujisawa, col. 1, ll. 8-30.) Thus, we find one of ordinary skill in the art facing the problem of subcutaneous injection of a pharmaceutical compound such as artelinic acid, would have been motivated to combine the teachings of the prior art to make the claimed lysine salt of artelinic acid. The motivation to combine references does not have to be identical to patent owner's to establish obviousness. *In re Kemps*, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996).

We acknowledge that Appellants' primary emphasis is on intravenous delivery of the claimed artelinic acid lysine salt (Br. 4-5). While Appellants argue their composition is for intravenous administration, Appellants' composition claim, which we have selected as a representative claim, is not so limited. Moreover, an intended use, such as intravenous administration, that merely states the purpose of the claimed subject matter, without adding additional structure to it, is generally not treated as limiting the scope of the claim. See *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345, 65 USPQ2d 1961, 1964-65 (Fed. Cir. 2003); *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997). In the present case one of ordinary skill in the art, desiring to administer the artelinic acid compound of Lin subcutaneously, would have been motivated by the prior art of Okada and Fujisawa to administer the lysine salt of artelinic acid, which lessen the pain of subcutaneous injection.

Thus, the cited prior art references provide motivation to one of ordinary skill in the art to prepare and administer the claimed lysine salt subcutaneously, and that is sufficient to support a prima facie case of obviousness of the claimed artelinic acid lysine salt composition.

Where the prior art, as here, gives reason or motivation to make the claimed invention, the burden then falls on Appellants to rebut that prima facie case. Such rebuttal or argument can consist of any other argument or presentation of evidence that is pertinent. *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc).

Appellants contend that

[a]lthough '135 indicates that its dyhydroartemisinin salts can be used for intravenous administration (1988), it was later found that they had problems. It has since been found that when dihydroartemisinin-succinic acid monoester (artesunic acid) was used for the treatment of malaria, it penetrated into the cerebral fluid after IV administration and was toxic in the cerebral fluid over time. Further, '135 does not indicate that L-lysine salts or any other salt other than its disclosed alkali and alkaline earth metal salts (col. 2, lines 66-68) would be suitable for the treatment of malaria or for intravenous administration. This motivation is necessary for arriving at the present invention.

(Br. 3.)

Appellants argue that Fujisawa teaches the use of lysine salts of cephalosporins and that cephalosporines are taught to be antibacterial agents and that malaria parasites are not bacteria. (Br. 3.) Appellants argue that a lysine salt of a cephalosporine is different in chemical structure than a lysine salt of artelinic acid. (Br. 4.) “Still further, the cephalosporin salts of '403 are only disclosed to be for intramuscular (IM) or subcutaneous injection (column 1, line 9) and not for intravenous injection.” (Br. 4.) Appellants argue that the prior art states that their lysine salts give no local pain or irritation with intramuscular injection or subcutaneous injection, but neither indicate that they would not cause a negative reaction inside of the vein.

(*Id.*) Appellants argue that “[o]ne of ordinary skill in the art would have known that not all substances that are safe for IM or subcutaneous injection are safe for intravenous injection. The tissue inside of the vein walls is different than muscle or skin tissue.” (Br. 4.)

For the reasons discussed herein, we find it of no consequence to the Examiner’s *prima facie* case that the lysine salts of the prior art, Fujisawa and Okada, are for antibacterial agents having a chemical structure unrelated to artelinic acid, and are not for the treatment of malaria. As discussed in *Pfizer*, “a skilled chemist at the time would simply make *known* pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time.” (*Pfizer*, 480 F. 3d at 1362.) For the reasons herein, we find that one of ordinary skill in the art facing the problem of pain associated with subcutaneous injection of a pharmaceutical compound such as artelinic acid, would have been motivated to combine the teachings of the prior art, Okada and Fujisawa, to make the claimed lysine salt of artelinic acid, as lysine salt is taught in the prior art to alleviate the pain of subcutaneous injection.

In view of the above, the rejection of the claim 1 for obviousness is affirmed. Claims 2-9, 16 and 17 fall with claim 1.

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## SUMMARY

The rejection of claims 1-9 and 16-17 under 35 U.S.C. § 103 as obvious over Lin in view of Okada and Fujisawa is affirmed.

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

AFFIRMED

Ssc:

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