

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 45

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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

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Ex parte MICHAEL S. KOPRESKI, BERYL ASP,  
BO FREDHOLM and PER-OLV GUNNARSSON

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Appeal No. 2004-0670  
Application No. 09/276,741

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ON BRIEF<sup>1</sup>

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Before WINTERS, ADAMS, and GREEN, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-8, 48, 49 and 73, which are all the claims pending in the application.

Claims 1 and 73 are illustrative of the subject matter on appeal and are reproduced below:

1. A method of administering estramustine phosphate as an intravenous dose, whereby the dosage of a single infusion exceeds 1300 mg.
73. A method of administering estramustine phosphate, wherein estramustine phosphate is first encapsulated within liposomes, and then administered intravenously.

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<sup>1</sup> Appellants waived their request for oral hearing. Paper No. 44, received April 29, 2004. Accordingly, we considered this appeal on Brief.

The references relied upon by the examiner are:

Rahman et al. (Rahman)	5,424,073	Jun. 13, 1995
Bishop et al. (Bishop)	5,795,882	Aug. 18, 1995
Ramu	5,780,446	Jul. 14, 1998

Maier et al. (Maier), "Estramustine Phosphate in Secondary Hormone-Resistant Carcinoma of the Prostate," Eur. Urol., Vol. 17, pp. 216-218 (1990)

#### GROUND OF REJECTION

Claims 1-8, 48, 49 and 73 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Bishop, Ramu, Rahman and Maier.

We reverse.

#### DISCUSSION

According to the examiner (Answer, page 4), "[t]he use of estramustine phosphate as an antineoplastic agent is well known in the art." In support of this assertion the examiner relies on Bishop, Ramu and Maier. In addition, the examiner finds (id.), Maier teach a method of administering estramustine phosphate intravenously.

With reference to Ramu, the examiner also finds (Answer, page 5), "[l]ike taxol, estramustine phosphate has a number of drawbacks including the fact that it is a local irritant." In this regard, the examiner finds (id.), Rahman teach "encapsulation of a pharmaceutical agent within a liposome minimizes some of its side effects or drawbacks such as the ability to administer the compound as a bolus ... as well as reduction in irritation caused by said pharmaceutical."

The rejection of claims 1-8, 48 and 49:

Based on the foregoing evidence, the examiner finds (Answer, page 4),

[t]he instant claims differ from the prior art by reciting a dosage exceeding 1300 mg. However, the determination of dosages is dependent on a number of factors including age, sex, weight and/or severity and type of illness. In the medical art, said determination is routine and, thus, is well within the level of skill of the ordinary artisan in the art. Thus, depending on the patient to be treated, it is within the level of the skill of the ordinary artisan to administer estramustine phosphate intravenously at a dose exceeding 1300 mg or  $950 \text{ mg/m}^2$ .<sup>[2]</sup>

However, as set forth in In re Sebek, 465 F.2d 904, 907, 175 USPQ 93, 95 (CCPA 1972), “while it may ordinarily be the case that the determination of optimum values for the parameters of a prior art process would be at least prima facie obvious, that conclusion depends upon what the prior art discloses with respect to those parameters.” As appellants point out (Brief, page 4), Bishop teaches away from administering a dosage of estramustine phosphate (EM) that exceeds 1300 mg as set forth in claims 1-8, 48 and 49, by teaching that such an agent should be administered in an amount of only 0.1 to 1  $\mu\text{g/kg/day}$ . According to appellants (id.), “[e]ven for a 250 lb person, this recommended dosage is only about 11.3 to 113  $\mu\text{g/day}$  or 0.0113 to 0.113  $\text{mg/day}$ ....” Similarly, appellants argue (Brief, page 5), Maier “discloses the intravenous administration of EM at a dosage of 300, 600 or 900  $\text{mg}$ ....” As for Ramu and Rahman appellants point out (Brief, pages 4 and 5), that neither reference suggests administering EM at a dose that exceeds 1300 mg.

In response, the examiner asserts (Answer, bridging paragraph, pages 5-6),

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<sup>2</sup> Appellants’ claim 2 is drawn to “[a] method of administering estramustine phosphate as an intravenous dose, whereby the dosage of a single infusion exceeds  $950 \text{ mg/m}^2$ . According to appellants’ specification (page 7),  $\text{mg/m}^2$  refers to milligrams per square meter of body surface area. According to page 8 of appellants’ specification, a dose of  $900 \text{ mg/m}^2$  is generally greater than 1300 mg per dose. Accordingly, we limit our discussion to a dose in excess of 1300 mg.

[t]he recitation of the amount of estramustine phosphate does not lend patentability to said method of administration of estramustine phosphate. The determination of the amount of estramustine phosphate given to a patient is dependent on a number of factors such as the age, sex and weight of the patient as well as the severity and type of illness. Said determination as well as the determination of the dose of estramustine phosphate that would provide maximum effect with minimum adverse effects in a patient are within the level of skill of the ordinary artisan in the medical art and is done routinely in the medical art.

The examiner, however, has not addressed appellants' assertions that the prior art of record fails to teach a dose of estramustine phosphate in excess of 1300 mg as is required by the claimed invention. To the extent that the examiner would assert that it is within the skill of the art to simply increase the dose of estramustine phosphate above that taught in the prior art, we note that Bishop teach (column 15, lines 12-20):

[A]s a significantly increased growth inhibitory effect is obtained with the above disclosed combinations utilizing lower concentrations of the anticancer drugs compared to the treatment regimes in which the drugs are used alone, there is the potential to provide therapy wherein adverse side effects associated with the anticancer drugs are considerably reduced than normally observed with the anticancer drugs used alone in larger doses.

Accordingly, Bishop teach the use of estramustine phosphate in combination with another drug, and at a dosage range below the amount set forth in the claimed invention.

As set forth in In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988), "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a

reasonable likelihood of success, viewed in the light of the prior art.” In our opinion, the examiner has failed to demonstrate that the prior art suggests appellants’ claimed dosage. In this regard, we remind the examiner that “[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.” W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

For the foregoing reasons, we reverse the rejection of claims 1-8, 48 and 49 under 35 U.S.C. § 103 as being unpatentable over the combination of Bishop, Ramu, Rahman and Maier.

Claim 73:

Unlike claims 1-8, 48 and 49, claim 73 does not require the administration of a particular dosage of estramustine phosphate. To the contrary, claim 73 requires the intravenous administration of liposome encapsulated estramustine phosphate.

As both the examiner (Answer, page 4), and appellants (Brief, page 5) recognize, Maier teach the intravenous administration of estramustine phosphate. Similarly, Ramu teaches (column 1, lines 32-33), “[m]ost antineoplastic drugs are administered by intravenous injection of infusion.” In addition, Ramu teaches (id., lines 33-45), “[m]any of these [antineoplastic] drugs are vesicants or local irritants and produce severe soft tissue damage upon

infiltration or extravasation into tissue surrounding an injection or infusion site.

Vesicant compounds include ... estramustine phosphate ... [and] taxol.”

However, as appellants point out (Brief, page 4, emphasis removed), “the purpose of Ramu is to treat or prevent extravasation injury caused by intravenous administration of even conventional dosages of vesicant compounds.” While Ramu teach photochemical methods to address this issue, the examiner asserts (Answer, page 5), Rahman<sup>3</sup> teach “encapsulation of a pharmaceutical agent within a liposome minimizes some of its side effects or drawbacks such as the ability to administer the compound as a bolus ... as well as reduction in irritation caused by said pharmaceutical agent.” Thus, according to the examiner (id.), “the encapsulation of estramustine phosphate would have been prima facie [sic] obvious to the ordinary artisan in the art.”

However, contrary to the examiner’s assertion, Rahman does not broadly teach “encapsulation of a pharmaceutical agent within a liposome,” instead, Rahman teach liposomal-encapsulated taxol. Furthermore, contrary to the examiner’s assertion Rahman does not teach that liposomal-encapsulation of a vesicant compound will result in a reduction of the irritation caused by the vesicant compound. Instead, Rahman teach (column 1, lines 60-65), “[i]n clinical trials, a consistent problem of anaphylactoid reaction, dyspnea, hypertension and flushing have been encountered [with taxol treatment]. The cardiac toxicity of taxol is treatment limiting and because of this the patient has to be hospitalized

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<sup>3</sup> Contrary to appellants’ assertion (Brief, page 10), Rahman is not limited to parenteral administration of liposomal formulations. To the contrary, Rahman teach the liposomal formulations are generally administered intravenously or intraperitoneally. Rahman, column 8, lines 37-40.

for continuous infusion of the drug.” Rahman teach (column 2, lines 4-9), “[a]ttempts to prevent taxol cardiotoxicity and anaphylactoid reaction have included reliance on pretreatment of patients with antihistamine and corticosteroids, and by prolonging the infusion time from six to twenty four hours.” Accordingly, the Rahman invention provides for a taxol delivery system which is characterized by, inter alia, “avoidance of anaphylactoid reactions and cardiotoxicity, ... [and the] ability to administer taxol as a bolus or short infusion rather than extended (24-hour) infusion of free taxol.” See id., at lines 60-68. The examiner, however, failed to establish a nexus between estramustine phosphate administration, and the anaphylactoid reactions and cardiotoxicity attributed to taxol administration. The same is true of the other advantages attributed to Rahman’s liposomal-encapsulated taxol, such as the avoidance of solubility problems of taxol, improved taxol stability, increased therapeutic efficacy of taxol, and modulation of multidrug resistance in cancer cells. See Rahman, column 2, lines 60-68.

While the examiner asserts (Answer, page 5), Rahman teach “reduction in irritation caused by said pharmaceutical agent,” at best, we find<sup>4</sup> the only suggestion in Rahman of irritation caused by taxol administration is that “[n]o further injections could be given in mice which received free taxol because of the sclerosis of the vein.” Rahman, column 5, lines 25-27. Rahman, however, is silent as to the effect of liposomal-encapsulation on the irritation caused by taxol administration. Rather than acknowledging any effect on taxol induced irritation,

Rahman conclude (column 5, lines 27-31), “[a]s shown in FIG. 2 by day 12, three mice in the free taxol group died because of toxicity whereas no toxicity or mortality was observed in mice which were injected with taxol encapsulated in liposomes.” On reflection, it is our opinion that the examiner failed to support her assertion with evidence on this record. In this regard, we remind the examiner that findings of fact and conclusions of law must be made in accordance with the Administrative Procedure Act, 5 U.S.C. 706 (A), (E) (1994). See Zurko v. Dickinson, 527 U.S. 150, 158, 119 S.Ct. 1816, 1821, 50 USPQ2d 1930, 1934 (1999). Findings of fact relied upon in making the obviousness rejection must be supported by substantial evidence within the record. In re Gartside, 203 F.3d 1305, 1315, 53 USPQ2d 1769, 1775 (Fed. Cir. 2000) (“because our review of the board’s decision is confined to the factual record compiled by the board ... the ‘substantial evidence’ standard is appropriate for our review of board fact

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<sup>4</sup> The examiner failed to identify any portion of the Rahman patent that supports her assertion that “encapsulation of a pharmaceutical agent within a liposome ... [results in a] reduction of irritation caused by said pharmaceutical agent.”

findings, see 5 U.S.C. § 706(2)(E)”). See also In re Lee, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002) (board decision denying patent must be founded on necessary findings and must provide an administrative record showing the evidence which the findings are based; the board must assure the requisite findings are made, based on evidence of record).

In our opinion, the examiner failed to provide the evidence necessary to establish a prima facie case of obviousness. Accordingly, we reverse the rejection of claim 73 under 35 U.S.C. § 103 as being unpatentable over the combination of Bishop, Ramu, Rahman and Maier. Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Hudes Declaration relied on by appellants to rebut any such prima facie case.

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

REVERSED

Sherman D. Winters	)	
Administrative Patent Judge	)	
	)	BOARD OF PATENT
	)	
Donald E. Adams	)	APPEALS AND
Administrative Patent Judge	)	
	)	INTERFERENCES
	)	
Lora M. Green	)	
Administrative Patent Judge	)	

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