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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte NESYA GORIS, JOHAN NEYTS, ERWIN BLOMSMA, STEFAAN WERA, AINOLA BILLIET, JOERI AUWERX, VEERLE DEBEURME, MARYLINE ROE, and PASCAL PUIG[1]

Appeal 2019-007002
Application 14/828,365
Technology Center 1600

Before ERIC B. GRIMES, FRANCISCO C. PRATS, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims related to an antiviral composition, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] Appellant identifies the real party in interest as Aratana Therapeutic Inc. Appeal Br. 2. We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42.

STATEMENT OF THE CASE

"Different antiviral compounds are known for the treatment of herpes virus infections. The compound 2-amino-9-[[(1S,2R)-1,2-bis(hydroxy-methyl)cyclopropyl]methyl]-1,9-dihydro-6H-Purin-6-one (also known as 'A-5021') is a potent inhibitor of herpes virus replication." Spec. 1:16–18. "The present invention describes a method for solubilizing A-5021 under isotonic and pH neutral conditions in concentrations between 1–10 mg/ml (0.1 – 1% w/v), allowing the use of A-5021 in stable liquid formulations such as eye-drops." *Id*. at 2:1–3.

Claims 1–15 are on appeal. Claims 1 and 14, reproduced below, are the independent claims:

1. A composition comprising:

- at least 0.1 % w/v 2-amino-9-[[(1S,2R)-1,2-bis(hydroxy-methyl)cyclopropyl]methyl]1,9-dihydro-6H-Purin-6-one; and

- at least 15 % w/v of a cyclodextrin.

14. A method for preparing an ophthalmic solution, comprising the steps of:

a) providing a solution comprising at least 10 % w/v of a cyclodextrin;

b) adding 2-amino-9-[[(1S,2R)-1,2-bis(hydroxymethyl) cyclopropyl]methyl]-1,9-dihydro-6H-Purin-6-one to said solution;

c) solubilizing the 2-amino-9-[[(1S,2R)-1,2-bis(hydroxymethyl)cyclopropyl]methyl]-1,9-dihydro-6H-Purin-6-one added in step b);

d) repeating steps b) and c) until a concentration of 2-amino-9-[[(1S,2R)-1,2-bis(hydroxymethyl)cyclopropyl] methyl]-1,9-dihydro-6H-Purin-6-one in said solution of at least 1 mg/mL is obtained;

e) optionally, adding at least 0.008 mg/mL thiomersal.

OPINION

Claims 1–15 stand rejected under 35 U.S.C. § 103 as obvious based on Itahashi[2] and Loftsson.[3] Final Action[4] 5. The Examiner finds that "Itahashi et al. teaches eye drops comprising 0.1% A-5021." *Id*. The Examiner acknowledges that Itahashi does not teach compositions comprising a cyclodextrin, as claimed, but finds that Loftsson "teaches that '[c]yclodextrins have been added to aqueous eye drop preparations to solubilize water-insoluble drug[s], to increase the chemical stability of drugs, or to reduce local drug irritation in the eye.'" *Id*. The Examiner finds that Loftsson also teaches that "'optimum cyclodextrin concentration in aqueous eye drop solutions is considered to be below about 15%'" and reasons that "[b]elow about 15% would read on 'at least 15 % w/w of cyclodextrin.'" *Id*.

The Examiner concludes that it would have been obvious "to combine the teaching of Itahashi et al. and Loftsson et al. and arrive at the instant claims" because "an advantage or expected beneficial result . . . would have been . . . to improve the stability of the active drug and[/]or reduce local drug irritation of the eye." *Id*.

Appellant argues that "Itahashi states 'A-5021 eyedrops significantly suppressed both corneal epithelial and stromal lesions at all concentrations used.' This statement in Itahashi casts doubt on the Examiner's contention

[2] Itahashi et al., "A-5021: a new acyclovir analogue inhibits murine herpetic keratitis," Cornea 27:334–338 (2008) (abstract only).
[3] Loftsson et al., "Effect of Cyclodextrins on Topical Drug Delivery to the Eye," Drug Dev. Indus. Pharm. 23:473–481 (1997).
[4] Office Action mailed April 19, 2018.

that it would have been obvious to place the claimed active compound into a composition with a cyclodextrin" because it "shows that A-5021 was able to penetrate into corneal tissue in order to suppress herpetic lesions. The skilled artisan, after learning of this quality, would not believe that A-5021 would need to be placed into a cyclodextrin [composition] in order to show clinical efficacy." Appeal Br. 4–5.

Appellant also argues that "the Examiner has not demonstrated that Loftsson teaches or suggests that cyclodextrin can solubilize or increase the stability, for example, of *any and all* drugs, and that combining cyclodextrin with A-5021 in a formulation would be expected to have any type of predicted or expected effect." *Id*. at 6.

In response to the Examiner's statement that "Applicant admits in the reply filed on 6/14/2017 at page 5, that the composition of Itahashi has 'poor stability,' which would suggest the need to . . . incorporate Itahashi [sic, Loftsson]" (Ans. 4), Appellant argues that the reply referred to the Specification's statement that Itahashi's composition has poor stability. Reply Br. 2. Thus, Appellant argues, "the Examiner has pegged the rejection on impermissible hindsight reconstruction using information solely gleaned from the Appellant's specification to justify the rejection." *Id*. at 3. Appellant argues that "Itahashi . . . makes no statements as to the stability of the composition." *Id*.

We agree with Appellant that the Examiner has not shown that the claimed composition would have been obvious to a skilled artisan based on Itahashi and Loftsson. Itahashi describes a comparison of A-5021 eye drops with acyclovir in treating corneal herpes simplex virus infections in mice.

Itahashi, abstract. Itahashi reports that "[c]linical scores on the epithelium and stroma treated with 0.1% A-5021 were equivalent to those with 3% acyclovir treatment." *Id*. Itahashi concludes that "A-5021 eyedrops, which are easily applied onto the affected cornea, ameliorated clinical scores and suppressed virus growth. It is a promising alternative treatment of herpetic keratitis." *Id*.

Loftsson states that "[c]yclodextrins have been added to aqueous eye drop preparations to solubilize lipophilic water-insoluble drug[s], to increase the chemical stability of drugs, or to reduce local drug irritation in the eye." Loftsson 473, abstract. The Examiner concludes that this disclosure would have led a person of ordinary skill in the art to incorporate a "cyclodextrin into the eye drop composition as taught by Itahashi et al. to improve the stability of the active drug and[/]or reduce local drug irritation of the eye." Final Action 5.

However, as Appellant has pointed out (Reply Br. 3), Itahashi does not describe its A-5021 composition as requiring improved stability. And, although the Examiner states that "Applicant admits" that Itahashi's composition has poor stability (Ans. 4), Appellant correctly notes that the statement relied on by the Examiner was summarizing what is stated in the Specification, not in the prior art. *See* Response filed June 14, 2017, page 5. Thus, the Examiner has not shown that a person of ordinary skill in the art would have been aware, without the benefit of Appellant's disclosure, of a need to improve the stability of Itahashi's composition.

The Examiner also cites "reduc[ing] local drug irritation of the eye" as a reason to include a cyclodextrin in Itahashi's composition. Final Action 5.

However, the Examiner has not pointed to any evidence to show that Itahashi's eye drops caused any local drug irritation. Itahashi states that "A-5021 eyedrops . . . are easily applied onto the affected cornea" and are "a promising alternative treatment of herpetic keratitis." Itahashi, abstract. Thus, the evidence of record does not support combining a cyclodextrin with Itahashi's eye drops in order to reduce local drug irritation.

In summary, the Examiner has not shown, by evidence or sound technical reasoning, that a person of ordinary skill in the art would have had a reason to combine Loftsson's cyclodextrin with Itahashi's A-5021 composition. We therefore reverse the rejection of claims 1–15 under 35 U.S.C. § 103 based on Itahashi and Loftsson.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–15	103	Itahashi, Loftsson		1–15

REVERSED