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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DEEPAK RAMESH THAKKER,
LISA L. SHAFER, and GREG STEWART

Appeal 2015-004335
Application 13/267,243
Technology Center 1600

Before MELANIE L. McCOLLUM, JEFFREY N. FREDMAN, and
TAWEN CHANG, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal¹ under 35 U.S.C. § 134 involving claims to a method of molecule delivery to cerebrospinal fluid. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

“A variety of agents have been administered to the cerebrospinal fluid (CSF), such as through intracerebroventricular (ICV) or intrathecal (IT) bolus infusion. Typically, these agents are administered acutely through a

¹ Appellants identify the Real Party in Interest as Medtronic, Inc. (*see* App. Br. 3).

single, bolus infusion at flow rates in the range of about 0.5 to 12 ml/min.” (Spec. ¶ 3). “However, at lower flow rates, such as less than 1 ml/day, studies report that the distribution of the agent in the CSF is limited” (Spec. ¶ 4). “[I]t would be desirable to administer an agent at a low flow rate to a subject’s CSF; e.g. when using a chronically implanted infusion device, but achieve broad distribution of the agent in the subject’s CNS [central nervous system]” (Spec. ¶ 5).

The Claims

Claims 1–23 are on appeal. Claim 1 is representative and reads as follows:

1. A method comprising:
selecting a subject for which delivery of a therapeutic or diagnostic molecule to cerebrospinal fluid (CSF) of a brain is desired; and
administering a liquid formulation comprising the molecule to an CSP-containing intrathecal space of the subject at a flow rate of less than 500 microliters per hour, wherein the liquid formulation is administered for a period of time sufficient to reach a steady state concentration in CSF of the brain, and wherein the molecular weight of the molecule is less than 5 kDa, between 15 kDa and 200 kDa, greater than 200 kDa, or a polypeptide or antisense DNA having a molecular weight of between 5 kDa and 15 kDa.

The Issues

A. The Examiner rejected claims 1–23 under 35 U.S.C. § 103(a) as obvious over Heruth² (Final Act. 2–4).

² Heruth et al., US 2004/0220546 A1, published Nov. 4, 2004 (“Heruth”).

B. The Examiner rejected claims 1–3, 5, 7–12, 14–18, and 23 under 35 U.S.C. § 103(a) as obvious over Oldfield³ (Final Act. 5–6).

A. *35 U.S.C. § 103(a) over Heruth*

The Examiner finds:

Heruth discloses a method for delivering a therapeutic molecule to cerebrospinal fluid of a brain of a subject, comprising administering a liquid formulation comprising the molecule to an CSF-containing [intrathecal] space, such as the lumbar space (paragraph 181), the thoracic space (paragraph 123), or the cervical space (paragraph 180), of the subject at a flow rate of less than 50 milliliters per hour (paragraph 37) (which overlaps with “less than 500 microliters per hour”) wherein the liquid formulation is administered for 5 minutes or more (paragraph 37).

(Final Act. 3).

The Examiner finds that during “the course of optimizing the method for maximum efficacy and equitable drug distribution radially, the artisan would find the instant flow rate of less than 500 microl[i]ters per hour through routine experimentation” (Ans. 3).

The issues with respect to this rejection are:

(i) Does the evidence of record support the Examiner’s conclusion that Heruth renders claim 1 obvious?

(ii) If so, have Appellants presented evidence of secondary considerations, that when weighed with the evidence of obviousness, is sufficient to support a conclusion of non-obviousness?

³ Oldfield et al., US 2006/0073101 A1, published Apr. 6, 2006 (“Oldfield”).

Findings of Fact

1. Heruth teaches “a method for delivering a drug to a subject’s brain via the subject’s spinal canal. The method comprises administering . . . a hypobaric solution comprising the drug to the subject’s cerebrospinal fluid (CSF) in a spinal location” (Heruth ¶ 180).

2. Heruth teaches

a method for reducing the amount of a drug that reaches a subject’s brain when introduced intrathecally. The method comprises infusing a hyperbaric drug into the subject’s spine. The method may be advantageous because it may be desirable to keep certain drugs from reaching the brain, where the drug may act to produce side effects. To maximize the amount of drug kept out of the brain, the drug may be infused at a low spinal location, such as the *lumbar region*.

(Heruth ¶ 181; emphasis added).

3. Heruth teaches

infusing the drug solution to an internal body location at a continuous rate of no more than 50 milliliters (ml) per hour for a period of five minutes or more. In variations on this method, the maximum infusion rate may be, e.g., no more than 25 ml per hour, no more than 10 ml per hour, no more than 5 ml per hour, or even potentially *no more than 2 ml* [i.e. 2,000 µl] *per hour*. Variations may also be found in the time period over which the infusion is performed. The period of infusion may alternatively be, e.g., 10 minutes or more, one hour or more, eight hours or more, or even 24 hours or more.

(Heruth ¶ 37; emphasis added).

4. Heruth teaches “[e]xemplary opioid agonists include morphine and hydromorphone. Ranges of effective daily doses of such drugs are known by physicians” (Heruth ¶ 172).

5. The Examiner finds that morphine has “a molecular weight of less than 5 kDa” (Ans. 2).

Principles of Law

“In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003).

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). This rule is limited to cases in which the optimized variable is a “result-effective variable.” *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (*citing In re Antonie*, 559 F.2d 618, 620 (CCPA 1977)).

Analysis

We adopt the Examiner’s findings of fact and reasoning regarding the scope and content of the prior art (Final Act. 2–4; FF 1–5) and agree that the claims are rendered obvious by Heruth. We address Appellants’ arguments below.

Appellants contend that “one of skill in the art would not read Heruth as teaching or suggesting that even lower flow rates (less than 500 microliters per hour) would be of any use for achieving broad distribution of the drug in CSF, or to achieve distribution in the CSF of the brain via intrathecal administration” (App. Br. 10). Appellants further contend that “Heruth teaches that the higher the flow rate, the broader the distribution . . .

For a drug to reach the brain via intrathecal infusion (infusion into the CSF in the spinal canal) broad distribution would be desired” (App. Br. 11).

We do not find these arguments persuasive because Heruth specifically teaches flow rates of no more than 2 ml [i.e. 2,000 μ l] per hour (FF 3), a range overlapping the “less than 500 microliters per hour” range of claim 1. Heruth further evidences that the flow rate is an optimizable variable, as is the delivery dose of drugs (FF 3–4), rendering it obvious to routinely optimize the flow rate.

Moreover, Appellants’ baseline assumption regarding “broad distribution of the drug in CSF” is not a limitation of claim 1, which does not require any degree of distribution in the CSF, nor does claim 1 require any specific concentration to be obtained in the brain. Moreover, Heruth also does not require a broad distribution as evidenced by Heruth’s teaching of “reducing the amount of a drug that reaches a subject’s brain when introduced intrathecally” by administering to the lumbar region (FF 2). Therefore, the ordinary artisan, interested in reducing the amount of drug reaching a subject’s brain, would have reasonably considered optimizing Heruth to reduce the flow rate as expressly suggested by Heruth (FF 3). Heruth does teach administering for periods of more than 24 hours (FF 2), a time period reasonably sufficient to satisfy the “steady state” requirement of claim 1 consistent with Specification’s teaching that administration for 1 day was sufficient to cause wide distribution (*see* Spec. ¶ 50) in the absence of any contrary evidence presented by Appellants.

Appellants contend

the inventors have surprisingly and unpredictably demonstrated that broad distribution within the CSF may be achieved by

infusing liquid formulations that include therapeutic or diagnostic agents to the CSF at low flow rates over prolonged periods of time, particularly for a duration that allows steady state levels of the agents in the CSF. See ¶¶06-07 of the present application.

(App. Br. 11–12).

We do not find this argument persuasive because neither paragraph 6 nor 7 of the Specification identifies the breadth of distribution as “surprising” or unexpected (see Spec. ¶¶ 6–7). “It is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an *unexpected* difference” *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972).

Appellants do not identify any other evidence such as a Declaration which suggests that the distribution is surprising or unexpected. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements... [does] not suffice.”); *also see In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974) (“Attorney’s argument in a brief cannot take the place of evidence.”).

Appellants contend that “Heruth teaches away from [distributions as recited in the claims]. Accordingly, one would not have administered molecules at the claimed rates for the claimed period of times to patients for which the claimed distributions were desired based on the teachings of Heruth” (App. Br. 12).

We find the teaching away argument unpersuasive. A teaching away requires a reference to actually criticize, discredit, or otherwise discourage

the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (“The prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed”). Appellants do not identify, and we do not find, any teaching in Heruth that administration of less than 500 microliters for periods of time necessary to reach steady state concentrations in the CSF as undesirable in any way. In fact, Heruth directly suggests administration of 2,000 microliters or less for periods up to 24 hours (FF 3). Likewise, although Heruth teaches that reducing the amount of a drug that reaches the brain may be desirable under some circumstances (FF 2), claim 1 does not require any specific concentration of the molecule to be obtained in the brain, as discussed above.

Conclusion of Law

(i) The evidence of record supports the Examiner’s conclusion that Heruth renders claim 1 obvious.

(ii) Appellants have not presented evidence of secondary considerations, that when weighed with the evidence of obviousness, is sufficient to support a conclusion of non-obviousness.

B. 35 U.S.C. § 103(a) over Oldfield

The Examiner finds Oldfield teaches

administering a liquid formulation comprising the molecule to an CSF-containing intrathecal space of the subject at a flow rate of 1.9 ml in 32 hours (0.059 ml/hour, or 59 microliters/hour) (paragraph 124), wherein the therapeutic agent may be aminoglutethimide (molecular weight = 232 Da) (paragraph 71). Although Oldfield does not appreciate that 7 hours is a

period of time sufficient to reach a steady state concentration in CSF of the brain, the specification states that over 1 day is an exemplified time period

(Ans. 5). The Examiner acknowledges that “Oldfield fails to teach a specific example wherein aminoglutethimide is administered at 59 microliters/hour” but finds it obvious to “administer aminoglutethimide at a flow rate of 59 microliters/hour, as this is one embodiment taught by Oldfield to provide efficacious administration of aminoglutethimide to the CSF of a brain” (*Id.*).

The issue with respect to this rejection is: Does the evidence of record support the Examiner’s conclusion that Oldfield renders claim 1 obvious?

Findings of Fact

6. Oldfield teaches “a method of monitoring the distribution of therapeutic agents as they move through solid tissue during CED [convection enhanced delivery]” (Oldfield ¶ 2). Oldfield explains that “CED delivery relies on bulk flow to distribute substances within the interstitial spaces of the CNS. Unlike intraventricular delivery, which relies on diffusion, convection is not limited by the infusate’s molecular weight, concentration, or diffusivity” (Oldfield ¶ 100).

7. Oldfield teaches

Delivery of therapeutic agents to large targeted volumes (and substantially only to those targeted volumes) of the brain offers great potential for treatment of many neurological disorders . . . potential target areas should be completely perfused by infusing 0.4 ml over a 7 hour period, or 1.9 ml over a course of 32 hours, assuming a flow rate of 1 μ gl/min and a volume of distribution equal to four.

(Oldfield ¶ 124).

8. The Examiner finds that aminoglutethimide has a molecular weight of 232 Da (*see* Ans. 5).

9. Oldfield teaches:

Factors that influence delivery of a therapeutic agent by CED include the type of tissue infused (for example, white or gray matter) and the tissue binding properties, metabolism and microvascular permeability of the agent. In addition, the volumetric flow rate, duration of infusion, and the size of the cannula (or catheter) used to deliver an infusate may affect the distribution of therapeutic agents delivered by CED.

(Oldfield ¶ 5).

Principles of Law

A prima facie case for obviousness “requires a suggestion of all limitations in a claim,” *CFMT, Inc. v. Yieldup Int’l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Analysis

Appellants contend

Oldfield relates to CED to infuse substances directly into the interstitial space of a solid tissue. One of skill in the art at the time the present application was filed would learn nothing from Oldfield with regard to infusion rates or times that could be used for infusing an agent into the fluid filled CSF space of a subject for broad distribution within the CSF space.

(App. Br. 13).

The Examiner responds “Oldfield teaches administration of its liquid formulation to the brain. The brain, even though it is a semi-solid, contains cerebrospinal fluid (CSF). Therefore administration into the brain is administration into a CSF-containing intrathecal space” (Ans. 7).

We find that Appellants have the better position. The definition of “intrathecal” is “[w]ithin a sheath, specifically, the spinal canal—in the subarachnoid or subdural space).”⁴ Claim 1 specifically requires administration to a “CSF-containing intrathecal space”. Therefore, even if the Examiner is correct that Oldfield administers to the CSF in the brain, that administration does not constitute an “intrathecal space” as required by claim 1. The Examiner provides no reason why administration to the intrathecal space in the spine would have been obvious over the teachings of Oldfield.

Claim 10 requires “administering a liquid formulation comprising the molecule to the CSF”. We agree with Appellants that Oldfield’s administration by CED to the brain is not reasonably interpreted as “administering” the liquid to the CSF, even if some of the liquid may be transported through the brain tissue to the CSF (*see* App. Br. 13). The Examiner does not establish that an ordinary artisan would reasonably interpret Oldfield’s administration to solid tissue as “administering a liquid” to the CSF.

⁴ Intrathecal. (n.d.) *McGraw-Hill Concise Dictionary of Modern Medicine*. (2002). Retrieved November 16 2016 from <http://medical-dictionary.thefreedictionary.com/intrathecal>

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that Oldfield renders claim 1 obvious.

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Heruth. Claims 2–23 fall with claim 1.

We reverse the rejection of claims 1 and 10, and of claims 2, 3, 5, 7–9, 11, 12, 14–18, and 23, which directly or indirectly depend from claims 1 or 10, under 35 U.S.C. § 103(a) as obvious over Oldfield.

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