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DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a pharmaceutical composition and a method of treating pain, which have been rejected as indefinite, anticipated, and obvious. We have jurisdiction under 35 U.S.C. §§ 6(b) and 306.

We affirm.

STATEMENT OF THE CASE

The Specification of the patent under reexamination states that a local anaesthetic can be administered epidurally for pain relief, as an alternative to treatment with narcotics (Spec. 1:19-32). Such treatment is said to provide
good blockade of pain, but “[t]he drawback is the motor blockade in the legs. . . . Among other effects the motor blockade means that the patient cannot leave his bed without assistance as the legs will not bear.” (Id. at 1:39-45.) The Specification states that “the local anaesthetic agent ropivacaine . . . in form of its hydrochloride can be given to the patient in a dosage which gives pain relief with minimal effect on motor function” (id. at 1:49-52).

Claims 1–10, 18, and 38–55 are on appeal. Claims 1, 9, 38, 39, 45, and 52 are illustrative and read as follows:

1. A method for treating a human experiencing pain, said method comprising: administering to said human a composition comprising a pharmaceutically acceptable salt of ropivacaine, wherein said ropivacaine is present in said composition at a concentration of less than 0.25% by weight.

9. A pharmaceutical composition for use in acute pain management with minimal motor blockade, comprising a pharmaceutically acceptable salt of ropivacaine at a concentration lower than 0.25% by weight.

38. A method for treating a human experiencing pain, said method comprising administering to said human experiencing pain a composition comprising a pharmaceutically acceptable salt of ropivacaine at a concentration of less than 0.25% by weight in an amount effective to treat said pain.

39. A method for treating a human experiencing pain with minimal motor blockade, said method comprising administering to said human experiencing pain a composition comprising a pharmaceutically acceptable salt of ropivacaine at a concentration of less than 0.25% by weight in an amount effective to treat said pain with minimal motor blockade.

45. A pharmaceutical composition comprising a pharmaceutically acceptable salt of ropivacaine at a concentration lower than 0.25% by weight
in an amount effective to manage pain with minimal motor blockade in a human experiencing pain.

52. The pharmaceutical composition of any one of claims 45, 50, or 51, wherein said effective amount is determined by one or more factors selected from the group consisting of said concentration of said pharmaceutically acceptable salt of ropivacaine in the composition, a volume of the composition, a rate of administration, a site of administration, and a desired spread of sensory block.

The claims stand rejected as follows:

Claims 45–55 under 35 U.S.C. § 112, second paragraph, as indefinite (Ans. 8);

Claims 9 and 10 under 35 U.S.C. § 102(b) as anticipated by Åkerman\(^1\) (Ans. 5);

Claims 9 and 10 under 35 U.S.C. § 102(b) as anticipated by Sandberg\(^2\) (Ans. 5);

Claims 45–55 under 35 U.S.C. § 102(b) as anticipated by, or alternatively under 35 U.S.C. § 103(a) as obvious based on, Åkerman with evidence provided by Soni\(^3\) and Lim\(^4\) (Ans. 5); and

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\(^3\) Anil K. Soni et al., *Low Dose Intrathecal Ropivacaine With or Without Sufentanil Provides Effective Analgesia and Does Not Impair Motor Strength During Labour: A Pilot Study*, 48 *CAN. J. ANAESTHESIA* 677 (2001).

Claims 1–8, 18, and 38–44 under 35 U.S.C. § 103(a) as obvious based on Li, Brockway, Thuresson, McCrae, Åkerman, and Moore (Ans. 6).

I.

The Examiner has rejected claims 45–55 as “indefinite in their recitation of ‘an amount effective to manage pain with minimal motor blockade’ because, as evidenced by claims 52 and 55, this amount is affected by volume of the composition, rate of administration, site of administration and desired spread of sensory block, all of which are variable” (Ans. 8). The Examiner concludes that “the claims are essentially drawn to some amount (e.g. some volume of a solution) of ropivacaine having a concentration less than 0.25%. It is not at all clear from the specification how much total mass of ropivacaine constitutes a therapeutic amount.” (Id. at 9.)

Appellant argues that “an amount effective to” is not intrinsically indefinite (Br. 19), and that claims reciting an “effective amount” are not indefinite merely because effectiveness depends on site or length of administration (id. at 14). Appellant also argues that the Specification

5 D.F. Li, A.D. Rees, & M. Rosen, *Continuous Extradural Infusion of 0.0625% or 0.125% Bupivacaine for Pain Relief in Primigravid Labour*, 57 BRITISH J. ANAESTHESIA 264 (1985).
provides general guidance and specific examples of effective amounts of ropivacaine (id. at 14-15), which allow those skilled in the art to understand what amount of ropivacaine is effective to treat pain (id. at 15). Specifically, Appellant argues that the Specification “discloses factors that would allow one of ordinary skill in the art to determine an amount effective to manage pain with minimal motor blockade, such as site of administration, concentration of ropivacaine, volume of ropivacaine, and rate/time of administration” (id. at 20-21).

We agree with the Examiner that claim 45 is indefinite. The Supreme Court has “read § 112, ¶ 2 to require that a patent’s claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty.” Nautilus, Inc. v. Biosig Instruments, Inc., 134 S.Ct. 2120, 2129 (2014). That is, “a patent must be precise enough to afford clear notice of what is claimed, thereby appris[ing] the public of what is still open to them.” Id. (internal quotation marks omitted). See also id. at 2129, n.6: “The statutory requirement of particularity and distinctness in claims is met only when they clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise” (quoting United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942)).

Here, as dependent claim 52 makes clear, the “amount effective to manage pain with minimal motor blockade” recited in claim 45 varies depending on, among other things, how the pharmaceutical composition is administered and the “desired spread of sensory block” (claim 52). Thus, a given volume of pharmaceutical composition, at a given concentration,
could be within the scope of claim 45—because it would be an “amount effective to manage pain with minimal motor blockade”—if it was administered in a certain way and with a certain desired spread of sensory block, but outside the scope of claim 45 if an anesthesiologist chose to administer it in a different way, or with the intention of a different spread of sensory block.

As the Examiner pointed out (Ans. 12), Appellant’s expert Paul F. White, in fact, has confirmed that a particular dose of ropivacaine could be both within and outside the scope of claim 45, depending on how it was used. Dr. White testified that if “2 mL of the 0.2% ropivacaine is administered spinally in a single injection for a total dose of 4 mg. This would be therapeutically effective in preventing or blocking pain.” Second Supplemental White Declaration, filed July 1, 2011, ¶ 17. However, if “2 mL of the 0.2% ropivacaine is administered epidurally in a single injection for a total dose of 4 mg. Here, . . . because the ropivacaine was administered epidurally instead of spinally, the treatment would not produce any therapeutic effect.” Id.

A claim is indefinite if one of skill in the art would not know whether a particular composition standing alone is within the claim scope; the scope of a claimed composition cannot depend on how the composition is used. See Geneva Pharms., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1384 (Fed. Cir. 2003) (under the patentee’s proposed claim construction, “a given embodiment would simultaneously infringe and not infringe the claims, depending on the particular bacteria chosen for analysis. Thus, one of skill would not know from one bacterium to the next whether a particular
composition standing alone is within the claim scope or not. That is the epitome of indefiniteness.”).

The evidence of record shows that a given embodiment could be both within and outside the scope of claim 45 depending on how it is used. The scope of claim 45 is therefore unclear and claim 45 fails to satisfy the definiteness requirement of 35 U.S.C. § 112, second paragraph. Claims 46–55 fall with claim 45 because they were not argued separately. 37 C.F.R. § 41.37(c)(1)(vii).

II.

The Examiner has rejected claims 9 and 10 as anticipated by Åkerman, because “Akerman discloses a 0.125% solution of ropivacaine (Fig. 6A) . . . , in which ropivacaine was provided as the hydrochloride monohydrate (p. 572, col. 2)” (Ans. 5).

We agree with the Examiner’s finding. Åkerman’s Figure 6A shows the effects of intradermal anaesthesia in guinea pigs of solutions of ropivacaine ranging from 0.125% to 0.75% (Åkerman 576, Fig. 6A legend). Åkerman also states that it used the hydrochloride monohydrate form of ropivacaine (id. at 572, right col.).

Appellant argues that “[n]one of the compositions of Akerman are [ ] ‘pharmaceutical compositions’ as required by claim 9 but were understood as mere scientific tools to elucidate the properties of the test molecule” (Br. 38).

This argument is not persuasive. Appellant has pointed to no definition in the Specification, or to any evidence showing the understanding of those skilled in the art, that distinguishes the claimed “pharmaceutical
composition” from the composition administered intradermally by Åkerman. Åkerman discloses that its compositions contained ropivacaine in 0.9% saline, and had a pH of 5.3 to 7.0 (Åkerman 572, right col.). Appellant has provided no evidence to show that this composition would not be considered a “pharmaceutical composition” by those of skill in the art.

Appellant also argues that Åkerman’s compositions could not be used for “acute pain management with minimal motor blockade,” as recited in claim 9, because “Akerman teaches preparing 0.005 ml - 0.25 ml solutions (Akerman at, e.g., p. 572). Such small volumes would be unacceptable for acute pain management.” (Br. 39.) Appellant also argues that Åkerman teaches prevention, not treatment, of pain (id.); that animal studies are unreliable indicators of pain (id.); and that Åkerman does not discuss motor blockade (id.).

These arguments are all unpersuasive because they are based on the intended use of the composition of claim 9, and the intended use of the claimed composition does not structurally distinguish it from the composition disclosed by Åkerman. See Rowe v. Dror, 112 F.3d 473, 478 (Fed. Cir. 1997) (“Where . . . a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation.”); IMS Tech., Inc. v. Haas Automation, Inc., 206 F.3d 1422, 1434 (Fed. Cir. 2000) (“If the preamble adds no limitations to those in the body of the claim, the preamble is not itself a claim limitation and is irrelevant to proper construction of the claim.”).

We affirm the rejection of claims 9 and 10 as anticipated by Åkerman.
III.

The Examiner has rejected claims 9 and 10 as anticipated by Sandberg, because “Sandberg discloses ropivacaine hydrochloride formulated in concentrations as low as 0.125% (col. 2, lines 49-53)” (Ans. 5).

Appellant argues that Sandberg discloses a range of concentrations that corresponds to a range of 0.125% by weight to 1.5% by weight but its only specific examples are at concentrations of 0.264% by weight and 0.529% by weight (Br. 31). Appellant argues that “Sandberg does not have any explicit examples falling within the claimed range, and the claimed subject matter of claims 9 and 10 is not disclosed with sufficient specificity to render claims 9 and 10 anticipated” (id.).

We agree with Appellant that the Examiner has not shown that Sandberg identically discloses the composition of claim 9 on appeal. The Examiner points to Sandberg’s disclosure that

\[\text{for the preparation of pharmaceutical preparations [ropivacaine] ... is dissolved in a liquid diluent, which is suitable for injection. The preparations used are aqueous solutions which contain between 1.25 and 15.0 mg/ml of the active compound calculated as the hydrochloride salt.}\]

(Sandberg, col. 2, ll. 47-52.) The Examiner finds that this disclosure anticipates claim 9 because “Sandberg specifically discloses 0.125% (1.25 mg/ml) ropivacaine hydrochloride (col. 2, lines 51-53), which is in the claimed range of ‘lower than 0.25% by weight’” (Ans. 17).

However, as Appellant has pointed out, Sandberg discloses 0.125% by weight ropivacaine as the endpoint of a range of potential concentrations, not as the concentration of an actual pharmaceutical preparation. The
disclosure of a range is not an anticipating disclosure of any value within the range, including the recited endpoints. See Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 1000 (Fed. Cir. 2006):

the disclosure of a range of 150 to 350 °C does not constitute a specific disclosure of the endpoints of that range, i.e., 150 °C and 350 °C. . . . The disclosure is only that of a range, not a specific temperature in that range, and the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points.

The Examiner argues that Atofina is off-point, and that the more pertinent case is Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985), which held that “'[i]t is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is “anticipated” if one of them is in the prior art’” (Ans. 17, quoting Titanium Metals).

As the Atofina court itself pointed out, however, the cited holding of Titanium Metals merely stands for the proposition that a prior art species anticipates a claimed genus. Atofina, 441 F.3d at 999. Here, the Examiner has not pointed to any specific composition disclosed by Sandberg with a concentration of ropivacaine within the range required by claim 9. We therefore reverse the rejection of claims 9 and 10 as anticipated by Sandberg.

IV.

The Examiner has rejected claims 45–55 as anticipated by, or alternatively as obvious based on, Åkerman with evidence provided by Soni and Lim (Ans. 5). The Examiner calculates that the experiments shown in Åkerman’s Figures 6A and 6B required a total of 3.75 mg of ropivacaine in
solution, and cites Soni and Lim as evidence that 3.75 mg of ropivacaine is a therapeutically effective amount ($id.$ at 5-6)

As discussed in section I above, however, we conclude that claims 45–55 are indefinite because a given volume of a ropivacaine composition, even at a given concentration of ropivacaine, could be within or outside the scope of the claims depending on how it is used. Because we are unable to determine whether any particular ropivacaine composition is encompassed by claims 45–55, we are unable to find, by a preponderance of the evidence, that Åkerman discloses or suggests a composition within the scope of these claims. For this reason, we reverse the rejection of claims 45–55 as anticipated by, or alternatively as obvious in view of, Åkerman with evidence provided by Soni and Lim.

V.

Issue

The Examiner has rejected claims 1–8, 18, and 38–44 as obvious based on the disclosures of Li, Brockway, Thuresson, McCrae, Åkerman, and Moore (Ans. 6). The Examiner finds that Li discloses epidural (a.k.a. extradural) administration of bupivacaine for relief of labor pain at concentrations of 0.0625% or 0.125% ($id.$) and “Brockway compared extradural administration of ropivacaine and bupivacaine in humans . . . [and] concluded that ropivacaine is suitable for epidural anesthesia in man, producing a sensory block similar to bupivacaine, but with a lesser motor block” ($id.$).

The Examiner finds that Thuresson discloses that ropivacaine is “strikingly superior” to bupivacaine and that it is the “optimal anesthetic”
among that series of compounds (id. at 7). The Examiner finds that McCrae compares epidural ropivacaine and bupivacaine, and administered 10 ml of a 0.25% solution when further analgesia was requested (id.). The Examiner finds that McCrae concluded that ropivacaine worked as well as bupivacaine.

The Examiner finds that Åkerman discloses 0.125% ropivacaine for intradermal administration and 0.5% ropivacaine for epidural administration (id.). The Examiner finds that Moore reviews clinical experience with bupivacaine and teaches that injection of 0.25% bupivacaine produced complete sensory block but minimal or no motor block (id.).

The Examiner concludes that it would have been obvious “to modify the methods of Li by replacing bupivacaine (administered as 0.125% or 0.0625% solution) with its homolog, ropivacaine. One would have been motivated to do so given the knowledge that ropivacaine has certain advantages, such as less intense motor block (Brockway) and lower toxicity (Akerman, Thuresson).” (Id. at 8.) The Examiner also concludes that “[t]here would have been a reasonable expectation of success, knowing that ropivacaine and bupivacaine are equally effective in obstetric epidural analgesia at concentrations as low as 0.25%, as taught by McCrae” (id.).

Appellant contends that, for a variety of reasons that will be addressed in detail below, the Examiner has not made out a prima facie case that claim 1 would have been obvious based on the cited references (Br. 45-71). Appellant separately argues that claims 7, 38, and 39 would not have been obvious based on the cited references (id. at 64-65, 71-77, 85). Finally, Appellant argues that several secondary considerations of nonobviousness
weigh against a conclusion that the claims would have been obvious based on the cited references (id. at 97-103).

**Findings of Fact**

1. Li discloses epidural administration of bupivacaine for relief of labor pain\(^{10}\) (Li 264).
   2. In Li’s procedure, mothers were given an initial epidural injection of 0.5% bupivacaine (10 ml) and, starting 10-15 minutes later, an infusion of either 0.0625% bupivacaine or 0.125% bupivacaine (id. at 265, left col.).
   3. Li concludes that “[t]he optimum infusion rate was 0.125% bupivacaine 10 ml h\(^{-1}\)” (id. at 264 (Summary)).
   4. Li discloses that “[p]revious studies have shown the effectiveness of a continuous infusion with either 0.25% or 0.375% bupivacaine,” although this approach carries the risk of a dural puncture (id. at 264, left col.).
   5. Li discloses that “a compromise between efficacy and safety has been sought by using a ‘safe’ volume of a solution of lower concentration” (id.).
   6. Brockway discloses a comparison of epidural administration of ropivacaine (0.5%, 0.75%, or 1.0%) and bupivacaine (0.5% or 0.75%) (Brockway 31).

\(^{10}\) Li refers to “extradural” rather than “epidural” administration but Appellant does not dispute that the two terms are equivalent. *See* Br. 47 (In Li, “bupivacaine . . . [was] administered at least 10-15 minutes *after* an initial epidural injection.”).
7. Brockway concludes that the “duration of analgesia was increased by increasing the concentration of both drugs, but this had minimal effect on onset time or extent of block. When the same concentration of each drug was administered, there were inconsistent differences in duration of sensory block, none of which was statistically significant” (id.).

8. Brockway concludes that “[r]opivacaine produced a slower onset, shorter duration and less intense motor block than the same concentration of bupivacaine” (id.).

9. Brockway discloses that ropivacaine has “lesser cardiotoxicity” than bupivacaine (id. at 36, right col.).

10. Thuresson discloses that ropivacaine is “markedly superior as a local anesthetic for mammals including humans to other known homologues of these compounds including . . . Bupivacaine” (Thuresson 2:17-21).11

11. Thuresson discloses that ropivacaine “is strikingly superior to Bupivacaine, being both a far better anesthetic and much less toxic” (id. at 13:13-15).

12. Thuresson discloses that ropivacaine “is the optimal anesthetic within this homologous series” (id. at 16:16-17).


11 Thuresson refers to ropivacaine by its chemical name but Appellant does not dispute that the compound referred to is ropivacaine. See Br. 54 (“Thuresson is a study of, amongst other things, the ability of ropivacaine to prevent pain.”).
14. McCrae states that “[i]n non-pregnant patients onset and duration of sensory blockade and overall clinical efficacy are comparable after the two drugs” are administered (id.).

15. McCrae discloses that women who had requested epidural analgesia were administered an initial dose of 4 ml of 0.5% bupivacaine or 0.5% ropivacaine, followed 5 minutes later by an additional dose of 6 ml (id., Methods).

16. McCrae discloses that when “further analgesia was requested . . . a ‘top-up’ of 10ml 0.25% of the same local anaesthetic solution was given” (id.).

17. McCrae discloses that all of the patients who received ropivacaine were administered the 0.25% “top-up” dosage (see id., Table (showing n=20 both for patients receiving the loading dose and top-up dose of ropivacaine).)

18. McCrae discloses that “[p]ain was assessed . . . after the epidural using a 100mm visual analog scale” (id., Methods). “Efficacy was assessed by the median VAS at 30-60 minutes after the loading and top-up doses” (id., Results).

19. McCrae discloses that the “pre-epid VAS (mm)” was 69.5 for patients receiving a bupivacaine loading dose and 84 for patients receiving a ropivacaine loading dose, while the corresponding numbers for patients receiving a top-up dose of each drug were 31.5 and 42, respectively (id., Table).

20. McCrae discloses that the “median VAS (mm)” was 12 for patients receiving a bupivacaine loading dose and 18 for patients receiving a
ropivacaine loading dose, while the corresponding numbers for patients receiving a top-up dose of each drug were 7 and 9, respectively (id.).

21. McCrae concludes that “10ml of 0.5% bupivacaine or ropivacaine followed by a top-up of 10ml of 0.25% solution produces effective and well tolerated pain relief in labour. There were no significant differences between the groups, apart from shorter time to onset of pain relief with bupivacaine after the loading dose.” (Id., Conclusion.)

22. Åkerman discloses administration of ropivacaine at 0.125% intradermally, and 0.5% epidurally, to guinea pigs (Åkerman, Figs. 6A and 5, respectively)

23. Moore reviews the use of “[b]upivacaine . . . in concentrations of 0.25, 0.5, or 0.75 percent . . . for caudal, epidural (peridural), or peripheral nerve block for 11,080 surgical, obstetrical, diagnostic, or therapeutic procedures” (Moore 42 (abstract)).

24. Moore discloses “times required for onset of analgesia and for establishment of complete operative anesthesia, as well as duration of both surgical anesthesia and postoperative analgesia” (id. at 42, left col.).

25. Moore summarizes “Safe Adequate Dosages (Volumes and Concentrations) of Bupivacaine and Their Indications in Adults for Single-Injection Regional Block” (id. at 44, Table 3).

26. Moore discloses that epidural administration of 8-30 ml of 0.25% bupivacaine is indicated for at least lower extremity, diagnostic blocks, and therapeutic blocks (id.) and results in “Complete” sensory block and “Minimal to moderate” motor block (id.).
Analysis

Claim 1 is directed to a method for treating a human experiencing pain comprising administering a composition comprising less than 0.25% by weight of a pharmaceutically acceptable salt of ropivacaine. We will begin with claim interpretation.

“[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification.” In re Hyatt, 211 F.3d 1367, 1372 (Fed. Cir. 2000). In this case, the broadest reasonable interpretation of claim 1 is that it requires treating a human patient who is experiencing pain, as opposed to treating a patient to prevent pain at a later time. This interpretation follows from the preamble language stating that the method is “for treating a human experiencing pain,” followed by the active step of “administering to said human” the recited ropivacaine composition. See Pitney Bowes Inc. v. Hewlett Packard Co., 182 F.3d 1298, 1305 (Fed. Cir. 1999) (“If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning, and vitality’ to the claim, then the claim preamble should be construed as if in the balance of the claim.”); Eaton Corp. v. Rockwell Int’l Corp., 323 F.3d 1332, 1339 (Fed. Cir. 2003) (“When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention.”).

However, claim 1 is directed to a method “comprising” the recited step, and therefore encompasses methods that include that step along with any other steps. See Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364,
The transition ‘comprising’ in a method claim indicates that the claim is open-ended and allows for additional steps. Claim 1 uses the open-ended transition ‘comprising’ to introduce the recited steps. Thus the claim signals to patent practitioners that claim 1 allows activity . . . before the recited steps.” (Citations omitted.)

Thus, claim 1 reads on any method of treating pain in a human that includes a step of administering a pharmaceutically acceptable salt of ropivacaine at a concentration of less than 0.25% by weight, even if that administration follows a step of administering something else, such as a higher dose of ropivacaine. As long as one of the steps in a pain-relieving method is the step recited in claim 1, the method as a whole is encompassed by claim 1. We note that this claim interpretation is consistent with the Examiner’s reading of the claim language. See Ans. 29 (“[T]he open language of claims 1-8 does not exclude methods in which administration of ropivacaine at < 0.25% is preceded by administration of ropivacaine at a higher concentration.”).

We agree with the Examiner that the cited references would have made obvious a method that is encompassed by claim 1. Li discloses a method of relieving labor pain by administering an initial dose of 0.5% bupivacaine, followed by an infusion of bupivacaine (either 0.0625% 0.125%) (FFs 1, 2). Li concludes that the optimal infusion rate is 10 ml per hour (FF 3). Åkerman discloses a 0.125% solution of ropivacaine, which was used in Åkerman for intradermal administration to guinea pigs (FF 22).

Brockway discloses that, in epidural administration, there is no statistically significant difference in duration of sensory block between
ropivacaine and bupivacaine (FFs 6, 7) but the motor block produced by ropivacaine is shorter and less intense than that produced by bupivacaine (FF 8). Brockway also states that ropivacaine is less cardiotoxic than bupivacaine (FF 9). Similarly, Thuresson discloses that ropivacaine is superior to bupivacaine, “being both a far better anesthetic and much less toxic” (FF 11).

McCrae states that ropivacaine and bupivacaine were known to provide comparable sensory blockade and overall clinical efficacy in non-pregnant patients (FF 14) and compared their effects on “relief of pain in labour” when administered epidurally (FF 13). McCrae’s procedure began with administration of a dose (10 ml at 0.5%) of either ropivacaine or bupivacaine, followed when further analgesia was requested by 10 ml of 0.25% of the same drug (FFs 15, 16). McCrae found that, as assessed by a visual analog scale (VAS) (FF 18), the procedure “produces effective and well tolerated pain relief in labour” using either ropivacaine or bupivacaine (FF 21).

Moore discloses that bupivacaine had been epidurally administered at a concentration of 0.25% (FF 23) and had been used for both surgical anesthesia and postoperative analgesia (FF 24). Moore discloses that epidural administration of 0.25% bupivacaine, in a specified range of dosages, produces complete sensory block and minimal to moderate motor block (FF 25).

We agree with the Examiner that, based on these teachings, a person of ordinary skill in the art would have considered it obvious to substitute ropivacaine for the bupivacaine used by Li, and therefore administer an
initial dose of 0.5% ropivacaine, followed by an infusion of 0.125% ropivacaine at a rate of 10 ml per hour. Motivation to make the substitution is provided by the teachings of Brockway and Thuresson that ropivacaine is less toxic than bupivacaine. A skilled worker would have reasonably expected that ropivacaine would be at least as effective as bupivacaine in providing relief from labor pain based on Thuresson’s disclosure that ropivacaine is a far better anesthetic than bupivacaine, as well as McCrae’s disclosure that epidural administration of the same dosage of either drug provides effective pain relief in labor. We conclude that the method of claim 1, considered as a whole, would have been obvious based on the cited prior art.

Appellant reviews each of the cited references individually, and notes what it views as the deficiencies of each reference in disclosing the claimed method (Br. 45-55). Appellant concludes that “there is not a single reference that describes or suggests the treatment of already existing pain using concentrations of ropivacaine (or any other drug) at below 0.25% by weight, as required by the claims” (id. at 56). Even assuming this statement is accurate, however, it does not provide a basis for concluding that the claimed method would not have been obvious based on the combined teachings of the references. See In re Merck & Co., 800 F.2d 1091, 1097 (Fed. Cir. 1986) (“Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references.”); In re Young, 927 F.2d 588, 591 (Fed. Cir. 1991) (“The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art.”).
Appellant similarly argues that “the Examiners have not shown that the combined references teach or suggest treatment of already existing pain in humans by administering ropivacaine at a concentration of less than 0.25% by weight” (Br. 63). This argument, while it refers appropriately to what is suggested by the combined references, does not accurately reflect what is required by claim 1. As discussed in our claim interpretation above, claim 1 requires only that a pain-relief method include a step of administering ropivacaine at less than 0.25% by weight. The claim language does not exclude an initial step of administering ropivacaine at a higher concentration, so long as both steps are part of the same pain-relief procedure. Li teaches such a method, except that bupivacaine is administered instead of ropivacaine and, for the reasons discussed above, a person of ordinary skill in the art would have considered it obvious to modify Li’s method by using ropivacaine instead, with a reasonable expectation of success.

Appellant argues, however, that the method taught by Li is for prevention of pain, not treatment of existing pain (Br. 47, 64, 66). This argument, however, relies on Appellant’s claim interpretation, which would require an administration of less than 0.25% by weight ropivacaine by itself for relieving pain. See id. at 66 (“[W]hen the bupivacaine was given at the 0.0625% or 0.125% concentrations, 10-15 minutes after treatment with 0.5% bupivacaine, the patients were not experiencing pain.”). Appellant also argues that “there is no disclosure in McCrae that suggests that pain existed before or at the time of the administration of the ropivacaine at 0.25%” (id. at 69). As discussed above, however, the method defined by claim 1 can
include steps in addition to the single step actually recited. Appellant’s argument that Dr. White’s testimony supports their position regarding McCrae (*id.* at 95-97) is similarly unavailing because it fails to take into consideration the full scope of claim 1.

Another argument that is based on Appellant’s erroneous claim interpretation takes the following form: treating existing pain is more difficult than preventing pain before it occurs, so it was generally believed that higher concentrations and doses of drugs were required to treat rather than prevent pain (Br. 57-58), and therefore “there was no reason for a person of ordinary skill in the art to believe that a concentration of the drug used in preventing or blocking pain could also be effective in treating already-existing pain” (*id.* at 65). Because it is based on an improperly narrow reading of the claim language, this argument is unpersuasive.

Appellant also argues that a skilled worker would not extrapolate a dosage of ropivacaine from known dosages of bupivacaine, for two reasons (Br. 58-61, 78-84). First, Appellant argues, even structurally similar compounds differ in structure and therefore also differ in their chemical properties, so “one of ordinary skill in the art would not have extrapolated doses used for one drug (e.g., bupivacaine), to another, untested drug (e.g., ropivacaine), based on, for example, chemical similarity” (*id.* at 59, 83).

Second, Appellant argues, Åkerman and Brockway show that ropivacaine was recognized as less potent than bupivacaine at the time of the invention, and thus a skilled worker would use higher concentrations of ropivacaine than had been used for bupivacaine (*id.* at 60-61, 78-79, 83-84). Appellant concludes that those of ordinary skill in the art would not have had a
reasonable expectation of success in using ropivacaine at the same dosage as had been used for bupivacaine.

This argument is not persuasive, because it fails to take into consideration the express teachings in the cited references that ropivacaine has pain-relieving activity that is either substantially the same as, or actually superior to, that of bupivacaine. See FF 7 (“inconsistent differences in duration of sensory block, none of which was statistically significant” when the two drugs were used at the same concentration); FF 11 (ropivacaine “is strikingly superior to Bupivacaine, being . . . a far better anesthetic”); FF 14 (“onset and duration of sensory blockade and overall clinical efficacy are comparable” for both drugs); FF 21 (each of the drugs, administered at the same dosage, “produces effective and well tolerated pain relief in labour”).

Appellant cites Åkerman and Brockway as supporting its position that ropivacaine was known to be less potent than bupivacaine. We do not find the evidence provided by these references to support Appellant’s position. Appellant argues that Brockway shows that ropivacaine was recognized as less potent because it “tested concentrations of ropivacaine at 0.5%, 0.75% and 1.0%, but only compared those to bupivacaine at 0.5% and 0.75%” (Br. 80), and it also found a higher incidence of unsatisfactory sensory blocks with 0.5% ropivacaine compared to 0.5% bupivacaine (id. at 60).

However, as noted immediately above, Brockway’s conclusion from its comparison is that “[w]hen the same concentration of each drug was administered, there were inconsistent differences in duration of sensory block, none of which was statistically significant” (FF 7). Brockway’s Table I does show that administering 0.5% ropivacaine resulted in 7 instances of
unsatisfactory analgesia blocks, compared to 3 with the same concentration of bupivacaine (among 22 patients) (Brockway 33), and Brockway states that “there were more unsatisfactory blocks and general anaesthetics required with 0.5% ropivacaine” (id. at 34). Brockway, however, expressly states that the increased number of unsatisfactory blocks was not significant: “[s]ubjective assessment of the suitability of the blocks for surgery revealed no significant differences between the groups” (id.). Brockway concludes that “[t]here were no significant differences in duration of sensory block at any dermatomal level when equal concentrations of the two drugs were compared” (id. at 35). Brockway therefore would not have led a skilled worker to conclude that ropivacaine is less potent than bupivacaine.

Appellant also cites Åkerman as support for its position: “Akerman observed that for concentrations of 0.5% and greater, a higher concentration of ropivacaine than bupivacaine is needed to achieve the same physiological effect” (Br. 60). The context of Åkerman’s statement, however, makes clear that it refers to the duration, not the extent, of sensory block produced by the two drugs. Åkerman states that “[t]he results indicate that ropivacaine is a long-acting agent with a profile which is essentially similar to that of bupivacaine, apart from some variations mainly in duration of action depending on the site of administration” (Åkerman 578, left col.). Åkerman’s data (id. at 575, Fig. 5) and its discussion of the results of epidural administration (id. at 574, right col.) likewise address only the duration of sensory and motor block caused by ropivacaine and bupivacaine, not the extent of the blocks. Åkerman therefore does not support
Appellant’s position that ropivacaine was recognized as less potent than bupivacaine.

Appellant also argues that animal studies, like those of Åkerman, “are not reliable predictors of responses in humans because they must necessarily rely on highly questionable (e.g., non-verbal) indicators of pain” and thus “a person of ordinary skill would not in 1993, based on Akerman’s animal pain models, have believed that or been able to predict with any reasonable degree of success whether ropivacaine would have any effectiveness in pain treatment in humans” (Br. 61, 85-87). Appellant also points to Moore’s statement that establishing a maximum human dose based on extrapolating from animal data is “unfortunate” (id. at 88).

Regardless of the reliability of animal studies in isolation, however, the record indicates that ropivacaine and bupivacaine had both been used, and had been shown to be effective, for pain relief in humans. See FFs 1-4, 13, 21, 26.

Appellant also argues that McCrae does not state that it measured the concentration of the drugs used in its study in units of percent by weight, as recited in claim 1 (Br. 68). Appellant cites the deposition transcript of Dr. White as support for its position that a concentration stated simply as “0.5%” or “0.25%” could be in any of several units, including percentage “by weight, by volume, or upon the basis of some other metric, such as mole percent . . . and therefore McCrae does not necessarily disclose, and does not suggest, a percent by weight” (id.).

This argument does not persuade us that the rejection on appeal is not supported by the cited references. First, although McCrae does not state that
its concentrations are measured in units of percent by weight, “the meaning of a prior art reference requires analysis of the understanding of an artisan of ordinary skill.” *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008). In this case, Dr. White testified that “the most common way of describing it [percentage concentration] is in milligrams per milliliter” of solution (White Depo. Transcript 218:2-3 (Br., Evidence Appendix)). Similarly, Dr. Lubenow\(^\text{12}\) testified that an anesthesiologist would understand a concentration specified simply as a percentage to mean that the units are in milligrams per milliliter (Lubenow Depo. Transcript 134:24 to 135:13 (Br., Evidence Appendix)).

Appellant has calculated that “a range of 1.25 mg/ml to 15 mg/ml in an aqueous solution . . . corresponds to a range of 0.125% by weight to 1.5% by weight” (Br. 31). The Examiner has calculated that percentage in weight per volume (e.g., milligrams per milliliter) would be the same as percentage by weight if the solvent was pure water, but percentage by weight would be slightly lower than percentage by volume if the solvent contained solutes such as salts in addition to the active agent (Ans. 22). Because the evidence shows that those skilled in the art would have understood McCrae’s percentage concentrations to refer to percent weight per volume, and the Examiner has found that percent by weight, as recited in claim 1, is either the same as or lower than the same percentage expressed as percent weight per volume, Appellant’s argument that McCrae does not specify its

\(^{12}\) Appellant cites the deposition transcript of Timothy R. Lubenow, whom Appellant identifies as the expert of the third party that requested this reexamination (Br. 68).
concentrations in units of percent by weight is unpersuasive. In any event, the rejection is based on substituting ropivacaine for the bupivacaine used in Li’s method, which administered 0.0625% or 0.125% bupivacaine. Appellant has provided no basis on which to conclude that these concentrations are outside the scope required by claim 1.

Appellant also argues that the cited references would not have provided a skilled worker with a reasonable expectation of success (Br. 85-95). This argument, however, is based on others that have already been addressed in this opinion: that claim 1 does not encompass steps other than the recited one, that ropivacaine was known to be less potent than bupivacaine, and that animal studies are unreliable (see id.). The argument that the cited references do not support a reasonable expectation of success is therefore unpersuasive.

Finally, with respect to claim 1, Appellant argues that several secondary considerations demonstrate the nonobviousness of the claimed method. Appellant argues that the claimed method met a long-felt but unmet need in the art: “to replace conventionally used narcotics in pain treatment” (Br. 97). Appellant argues that this need was not met by drugs like bupivacaine “because of concerns relating to the side effects (e.g., significant motor block, cardiotoxicity)” caused by such drugs (id. at 98).

This argument is unpersuasive. The Specification of the patent being reexamined concedes that epidural administration of local anesthetics was a known alternative to using narcotics for pain relief (Spec. 1:18-32). In addition, ropivacaine was known to be less cardiotoxic than bupivacaine (FFs 9, 11), so that need was not solved by the present invention. And
claim 1 includes no limitation regarding the degree of motor block resulting from administration of ropivacaine, so that asserted benefit is not an aspect of the claimed method.

Appellant also argues that the commercial success of its drug Naropin™ demonstrates the nonobviousness of its claimed method (Br. 99-101). The only “evidence” that Appellant cites to show the alleged commercial success, however, is the opinion of a Federal district court judge in related litigation and the unsupported opinion of its expert witness Paul F. White (id. at 99, 100). While those individuals are certainly well-qualified to draw conclusions based on the evidence that they have been presented, our role is to draw our own conclusions based on the evidence that has been made of record in this reexamination proceeding. Because Appellant has presented no actual evidence that Naropin™ is commercially successful, its argument for nonobviousness on this basis is unpersuasive.

Appellant also argues that “the discovery that ropivacaine, a known pain-preventing drug commonly used prior to surgery, provided treatment of pain, and could do so with minimal motor blockade when administered at concentrations less than 0.25%, was completely unexpected and surprising to a person of ordinary skill in 1993” (Br. 101-102, citing ¶¶ 122 and 123 of the White Declaration\(^\text{13}\)). Dr. White testified that it was unexpected that “compositions containing a low concentration (e.g., less than 0.25% by weight) of ropivacaine can be used for treating or managing pain, and can do so with a minimal effect on motor function” (White Declaration, ¶ 123).

\(^{13}\) Declaration under 37 C.F.R. § 1.132 of Paul F. White, filed Jan. 4, 2011.
This argument is also unpersuasive. First, the allegedly unexpected results are not commensurate in scope with claim 1, which includes no limitation regarding motor blockade and does not exclude steps other than the recited one (including, for example, a preliminary step of administering a higher concentration of ropivacaine). Second, Dr. White makes no attempt to address why the claimed method provides unexpected results when the prior art discloses that 0.25% ropivacaine and 0.125% bupivacaine were known to be used in effective methods of relieving labor pain (FFs 1-3, 21; see also Li 268, right col. (“A continuous infusion of 0.125% bupivacaine 10 ml h⁻¹ resulted in 69% of these primigravid mothers requiring no or only one top-up.”)).

The final secondary consideration that Appellant asserts in support of its position is copying, because “many generic drug manufacturing companies have tried to copy the idea by filing ANDA applications with the FDA to introduce generic versions of Naropin™” (Br. 102). The only specific example that Appellant cites, however, is the submission by Navinta (the third party that requested this reexamination) to the FDA of an ANDA for approval to market ropivacaine products at, apparently, concentrations of 0.2%, 0.5%, and 1.0% (id.). Appellant cites the opinion of a Federal district court judge in related litigation as stating that the products would be marketed for use in treating pain (id.). Appellant argues that “[t]his copying by Navinta and other generic drug manufacturing companies of the inventions described and claimed in the ‘524 patent also supports the non-obviousness of the claimed inventions” (id. at 103).
As with its argument based on commercial success, however, Appellant has pointed to no actual evidence that has been made of record in this reexamination to support its position that Navinta “copied” the method defined by claim 1. While we respect the opinions of Federal district court judges, those opinions are not themselves evidence of the facts underlying them. Appellant has pointed to no actual evidence presented during this reexamination proceeding that demonstrates copying of the claimed method by anyone, and its argument that such copying shows the nonobviousness of claim 1 is therefore unpersuasive.

With regard to claims 7 and 42, Appellant argues that these claims require treatment of post-surgical pain and, contrary to the Examiner’s finding, Moore does not teach treatment of post-surgical pain with ropivacaine (Br. 85).

This argument is unpersuasive. As the Examiner found (Ans. 7, 25), Moore teaches that bupivacaine was known to provide “both surgical anesthesia and postoperative analgesia” (FF 24), and that it was the “drug of choice . . . for relief of postoperative or chronic pain” (Moore 52, left col.). This teaching, viewed in combination with Li’s method of administering bupivacaine at either 0.0625% or 0.125% as part of a pain-relief procedure, and the disclosures of Brockway, Thuresson, and McCrae that ropivacaine was comparable or superior to bupivacaine in effectiveness, would have provided a person of ordinary skill in the art with a reason to use ropivacaine for treating post-surgical pain with a reasonable expectation of success.

With regard to claims 38-44, Appellant argues that the Examiner has not shown that the cited references meet the claim limitation of
administering ropivacaine at a concentration of less than 0.25% by weight in an amount effective to treat pain, as recited in those claims (Br. 64-65). This argument is unpersuasive because, as the Examiner noted (Ans. 6-7, 28), the methods disclosed by Li (using bupivacaine) and McCrae (using either bupivacaine or ropivacaine) were described as providing effective pain relief; thus, a skilled worker would reasonably expect that substituting ropivacaine for the bupivacaine in Li’s method would also result in administering an amount of ropivacaine that is effective to treat pain.

With regard to claim 39, Appellant argues that none of the cited references “suggests that ropivacaine can be administered to treat already existing pain with minimal motor blockade. Rather, in every reference discussing motor blockade at all, the methods resulted in substantial, not minimal motor blockade.” (Br. 56.) Appellant argues that the Specification of the patent under reexamination “teaches that minimal motor blockade is achieved, for example, when patients can ‘leave [their] bed without assistance’” (id. at 72).

This argument is also unpersuasive. “[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification.” In re Hyatt, 211 F.3d 1367, 1372 (Fed. Cir. 2000). The Specification here does not expressly define what degree of motor blockade is “minimal,” as that term is used in claim 39. However, it does provide some examples that shed light on what the term means.

The Specification states that one drawback of epidural administration of a local anesthetic is motor blockade of the legs (Spec. 1:31-41). “Among other effects, the motor blockade means that the patient cannot leave his bed
without assistance as the legs will not bear” (id. at 1:42-44). The Specification provides working examples in which the effects of administering either 0.3% or 0.2% ropivacaine was assessed in a group of volunteers (id. at 2:46-67). The example using 0.3% ropivacaine states that it caused “motorblock [that] was somewhat less profound compared to bupivacaine. 5 out of 7 volunteers could not stand at any occasion during the infusion.” (Id. at 2:53-55.) The example using 0.2% ropivacaine states that the “motorblock was less profound. . . . 25% (2/8) of the volunteers could not at any occasion stand up.” (Id. at 2:62-65.)

The Specification concludes that “[a]t the dosages 0.3% and 0.2% ropivacaine gives about the same motor blockade” (id. at 3:10-11) and that low dosage ropivacaine provides “good balance between sufficient sensoric block and a desirable minimal degree of motor block” (id. at 3:16-18).

Thus, as used in the Specification, “minimal motor block” includes administration of ropivacaine at dosages that result in 5/7 (71%) of patients being unable to stand during the infusion. Appellant has not pointed to evidence showing that substituting ropivacaine for the bupivacaine used in Li’s procedure, as would have been obvious based on the cited references, would have resulted in a procedure causing more than “minimal motor block,” as the phrase is used in the Specification; specifically, that it would have resulted in more than 71% of patients being unable to stand at any point during the infusion. We note that “[i]t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.” In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir.
1990).\textsuperscript{14} Since Appellant has not shown that the method made obvious by the cited references differs in any manipulative step from methods encompassed by claim 39, we agree with the Examiner (Ans. 25-26) that it is reasonable to conclude that they would result in the same effects.

Conclusion of Law

We conclude that the references cited by the Examiner support a conclusion of obviousness with respect to claims 1, 7, 38, and 39. We therefore affirm the rejection based on 35 U.S.C. § 103(a) with respect to those claims. Claims 2–6, 8, and 18 have not been argued separately and therefore fall with claim 1; claim 42 falls with claim 7; and claims 40, 41, 43, and 44 fall with claim 38. 37 C.F.R. § 41.37(c)(1)(vii).

SUMMARY

We affirm the rejection of claims 45–55 under 35 U.S.C. § 112, second paragraph, as indefinite.

We affirm the rejection of claims 9 and 10 under 35 U.S.C. § 102(b) as anticipated by Åkerman.

We reverse the rejection of claims 9 and 10 under 35 U.S.C. § 102(b) as anticipated by Sandberg.

\textsuperscript{14} Although the Woodruff court referred to “an old process,” the rejection under discussion was based on obviousness, not anticipation. \textit{See id.} (“While the processes encompassed by the claims are not entirely \textit{old}, the rule is applicable here to the extent that the claims and the prior art overlap.”).
We reverse the rejection of claims 45–55 under 35 U.S.C. § 102(b) as anticipated by, or alternatively under 35 U.S.C. § 103(a) as obvious based on, Åkerman with evidence provided by Soni and Lim.

We affirm the rejection of claims 1–8, 18, and 38–44 under 35 U.S.C. § 103(a) as obvious based on Li, Brockway, Thuresson, McCrae, Åkerman, and Moore.

TIME PERIOD FOR RESPONSE

Requests for extensions of time in this ex parte reexamination proceeding are governed by 37 C.F.R. § 1.550(c). See 37 C.F.R. § 41.50(f).

AFFIRMED

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