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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte NAJIB BABUL

Appeal 2017-011082
Application 13/320,989
Technology Center 1600

Before JEFFREY N. FREDMAN, ULRIKE W. JENKS, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134(a) involving claims to a dosage form for orally administering levorphanol to a human. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellant identifies the Real Party in Interest as Relmada Therapeutics, Inc. (*see* App. Br. 1).

[2] We have considered and herein refer to the Specification of Nov. 17, 2011 ("Spec."); Final Office Action of July 5, 2016 ("Final Act."); Appeal Brief of May 5, 2017 ("App. Br."); Examiner's Answer of June 27, 2017 ("Ans."); and Reply Brief of Aug. 28, 2017 ("Reply Br.").

Statement of the Case

Background

"Extended release opioid formulations have now become the standard of care for the management of chronic pain" (Spec. ¶ 4). However, the Specification identifies "a need for new therapeutic alternatives for the management of pain, including alternative extended release opioids that are bioavailable, therapeutically effective and pharmacologically differentiated from existing extended release opioids" (*id.*).

"Levorphanol . . . is a potent opioid analgesic . . . levorphanol is purported to have a long half life and a long duration of analgesic action" (Spec. ¶¶ 5, 7). "[L]evorphanol has significant greater activity than morphine at the kappa and delta opioid receptor, and robust activity as an NMDA antagonist, the latter being important in modulating pain and opioid tolerance. Levorphanol has also been shown to substantially reverse analgesic tolerance to morphine" (Spec. ¶ 6).

The Claims

Claims 4–9 and 53–68 are on appeal. Claim 4 is representative and reads as follows:

> 4. A dosage form for orally administering levorphanol to a human patient, the dosage form comprising
>
> a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, combined with
>
> a controlled release material comprising
>
> a) at least one of a wax, a vegetable oil, a vegetable oil ester, and a combination of these;
>
> b) a cellulose-based release rate modifier; and
>
> c) a thixotrope and
>
> being formulated such that the in-vitro fractional release of levorphanol therefrom, when measured by the USP Paddle

Method at 100 rpm in 900 mL aqueous phosphate buffer at pH 6.8 and at 37 °C is:

not greater than 47.5% at 1 hour,
from 10% to 65% at 2 hours,
from 15% to 70% at 4 hours,
from 25% to 77.5% at 6 hours,
from 35% to 87.5% at 9 hours, and
greater than 65% at 12 hours.

The Issues

A. The Examiner rejected claims 4–9 and 53–67 under 35 U.S.C. § 103(a) as obvious over Chasin[3] and Anderson[4] (Final Act. 3–5).

B. The Examiner rejected claims 7 and 68 under 35 U.S.C. § 103(a) as obvious over Chasin, Anderson, and Katzung[5] (Final Act. 8–9).

A. 35 U.S.C. § 103(a) over Chasin and Anderson

The Examiner finds Chasin teaches "controlled-release oral dosage forms comprising a controlled-release matrix (col. 2, ll. 49-53) and levorphanol (col. 3, l. 4)" (Final Act. 3). The Examiner finds that Chasin further teaches that the controlled release "matrix includes vegetable oils or waxes (col. 10, l. 66 - col. 11, l. 2)" as well as "HPMC (col. 11, ll. 11-17)" (*id.*). The Examiner finds that Chasin teaches the "properties of the dosage form may be modified by including a gastrointestinal or time-release coating" (*id.*).

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[3] Chasin et al., US 6,103,261, issued Aug. 15, 2000.
[4] Anderson et al., US 2003/0125347 A1, published July 3, 2003.
[5] Katzung, Basic & Clinical Pharmacology, Appleton & Lange 513 (7th ed. 1998).

The Examiner acknowledges that Chasin does not teach inclusion of fumed silica as well as "the various functional (i.e., pharmacological) limitations" (Final Act. 4). The Examiner finds Anderson teaches the use of fumed silica (*see id.*).

The Examiner finds the functional limitations obvious because Chasin "discloses compositions that have similar (if not identical) release profiles as asserted by applicant . . . [so] a composition prepared according to the combined teachings of the cited references would meet the [pharmacokinetic parameter] limitations of the instant claims" (Final Act. 5).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that Chasin and Anderson render the claims obvious?

Findings of Fact

1. Chasin teaches "a solid controlled-release oral dosage form, the dosage form comprising a therapeutically effective amount of analgesic, preferably an opioid analgesic" (Chasin 2:49–53).

2. Chasin teaches that "[p]referred opioids include mu-agonist opioid analgesics such as . . . levorphanol" (Chasin 3:2–4).

3. Chasin teaches "a controlled-release matrix that affords in-vitro dissolution rates of the opioid within the narrow ranges required and that releases the opioid in a pH-independent manner. Suitable materials for inclusion in a controlled-release matrix are . . . vegetable oils and waxes" (Chasin 10:54 to 11:2).

4. Chasin teaches a "suitable matrix comprises at least one water soluble hydroxyalkyl cellulose . . . The at least one hydroxyalkyl cellulose is preferably . . . hydroxypropylmethylcellulose" (Chasin 11:11–17). Chasin

further teaches that "a controlled-release matrix may also contain suitable quantities of other materials, e.g., . . . glidants that are conventional in the pharmaceutical art" (Chasin 11:53–57).

5. Chasin teaches a

> dissolution rate in-vitro of the dosage form, when measured by the USP Paddle or Basket Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is from about 12.5 to about 42.5% (by wt) opioid released after 1 hour, from about 25 to about 65% (by wt) opioid released after 2 hours, from about 45 to about 85% (by wt) opioid released after 4 hours, and greater than about 60% (by wt) opioid released after 8 hours, the in-vitro release rate being substantially independent of pH, such that the peak plasma level of opioid obtained in-vivo occurs from about 2 to about 8 hours after administration of the dosage form. The oral dosage forms of the present invention provide pain relief for about 24 hours, and therefore may be administered on a once-a-day basis.

(Chasin 2:54–67).

6. Anderson teaches a "composition comprises as the analgesic only one or more opiates" (Anderson ¶ 15) where the opiate may include levorphanol (*id.* ¶ 13).

7. Anderson teaches "[e]xamples of suitable glidants (or anti-adherents) include . . . fumed silica" (Anderson ¶ 38).

8. Anderson also teaches inclusion of excipients including hydroxypropylmethyl cellulose (Anderson ¶ 35), hydrogenated vegetable oils (*id.* ¶ 37) and waxes (*id.* ¶ 37).

9. Anderson teaches "an absorption profile which is capable of providing in the user a sustained release of opiate, for example, at least about 1 hour up to about 30 hours . . . the coating is designed to achieve optimal release" (Anderson ¶ 46).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Analysis

We adopt the Examiner's findings of fact and conclusions of law (*see* Final Act. 3–5; FF 1–9) and agree that the combination of Chasin and Anderson renders the claims obvious.

In particular, we agree that Chasin teaches controlled release oral dosage opioid compositions (FF 1) and specifically identifies levorphanol as a preferred opioid (FF 2). Chasin teaches to include in the formulation materials to provide for controlled release including waxes and vegetable oils (FF 3) as well as celluloses such as HPMC (FF 4). Anderson teaches a sustained release composition (FF 9) that may include levorphanol (FF 6) as well as excipients such as the thixotrope fumed silica (FF 7) along with HPMC, vegetable oils and waxes (FF 8). Finally, Chasin teaches desirable delayed release profiles that provide pain relief for up to 24 hours (FF 5). Thus, we agree with the Examiner that Chasin and Anderson reasonably support a prima facie case of obviousness because the references use known opioids with known excipients to obtain known controlled release profiles (FF 1–9). An "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982) (citation omitted). Moreover, the flexible analysis set out by the Supreme Court in *KSR* recognizes the obviousness of pursuing known options within the technical grasp of the skilled artisan, e.g., known equivalents. *See KSR*, 550 U.S. at 421.

We address Appellant's arguments below.

Appellant contends

> A POSA reading CHASIN and ANDERSON would conclude that CHASIN and ANDERSON simply failed to appreciate the unsuitability of LEV in ER dosage forms – not that CHASIN or ANDERSON had discovered any way of overcoming that unsuitability. The Applicant's specification is the first disclosure of compositions that overcome the accepted unsuitability of LEV for ER dosage forms.

(App. Br. 10). Appellant states they "provided three references (Argoff,[6] [Du Pen],[7] and Zichterman[8]) to the Examiner which demonstrate that a POSA considered LEV unsuitable for use in ER dosage forms and also explained to the Examiner what a POSA would infer from those references" (*id.* at 11; original citations replaced).

Appellant concludes that Argoff "illustrates the crucial interplay between DoE[9] (leading to 'good;' *i.e.,* the beneficial effects of the drug) and pHL[10] (leading to 'bad;' *i.e.,* the adverse effects of the drug) for assessing the suitability of a drug for multiple-sequential or extended release administration" (App. Br. 13). Appellant contends that Argoff demonstrates "it was recognized that opioid analgesics having DoE>pHL (like HYD[,

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[6] Argoff et al., *A Comparison of Long- and Short-Acting Opioids for the Treatment of Chronic Noncancer Pain: Tailoring Therapy to Meet Patient Needs*, 84 MAYO CLIN. PROC. 602–12 (2009).
[7] Du Pen et al., US 2003/0178031 A1, published Sept. 25, 2003.
[8] Zichterman, *Opioid Pharmacology and Considerations in Pain Management*, U.S. Pharmacist (2007); http://www.uspharmacist.com/continuing_education/ceviewtest/lessonid/105473 (accessed Mar. 27, 2014).
[9] DoE stands for duration of effect. (App. Br. 13.)
[10] pHL stands for plasma half-life. (App. Br. 13.)

hydromorphone,] and MOR[, morphine,]) could be effectively used in ER formulations, while opioid analgesics having DoE<pHL (like LEV) were unsuitable for use in ER formulations" (*id.*).

The Examiner responds "[w]hile the examiner agrees that [Argoff] classifies some opioids as long- or short-acting (see, e.g., Table 1 at p. 603), the reference does not stand for the conclusion that 'opioid analgesics having DoE<pHL (like LEV) were unsuitable for use in ER formulations'" (Ans. 6). The Examiner contends that Appellant's argument "does not point to any specific page, paragraph, figure, table, or other disclosure in Argoff" and that "[a]t best, [A]ppellant's suggestion that Argoff et al. teaches away from extended-release formulations of levorphanol is a matter of opinion" (*id.* at 7).

We agree with the Examiner because Argoff never teaches or suggests that levorphanol or long acting opioids [LAOs] in general are unsuitable for a controlled release composition. Argoff states "[s]ome LAOs ([e.g.,] methadone, levorphanol) are inherently pharmacologically long acting. . . . The analgesic effects of LAOs generally last 8 to 72 hours, making them appropriate for patients with persistent CNCP [chronic noncancer pain] that requires stable, around-the-clock (ATC) dosing" (Argoff 603, col. 1–2). Argoff states that "evidence suggests that longer-acting agents provide more consistent blood plasma levels and may prevent end-of-dose failure" (*id.* at 603, col. 2). Argoff suggests

> treatment goals are tailored to the needs of each patient. For some patients, controlling constant pain with LAOs may be best, if less frequent dosing and sufficient pain relief allow them to resume at least some, if not all, normal activities; other patients may find that an SAO[, short acting opiod,] provides

> them with the same outcome and is more effective than an LAO.

(Argoff 607, col. 1).

Thus, the evidence in Argoff does not support Appellant's position that controlled release of opioids such as levorphanol would be unsuitable. Rather, Argoff suggests that levorphanol is suitable for some patients who prefer less frequent, more stable, and longer acting doses (*see* Argoff 603, col. 1–2). *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (A "given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine.")

Appellant contends that

> DuPen discloses that MOR is suitable for use in ER dosage forms and has a pHL/DoE of about 0.25-0.33 and that LEV has a pHL/DoE of about 1.8-2.7. DuPen neither discloses nor suggests that LEV is suitable for use in ER dosage forms. Zichterman also discloses that MOR is suitable for use in ER dosage forms and that LEV has a pHL/DoE of about 2-2.5.

(App. Br. 15; citations omitted).

We also find this argument unpersuasive because Du Pen teaches "[o]ne of many valuable 'go to' opioids in the list of sequential trial options, levorphanol is listed as a long acting opioid but is considered by most clinicians more as a medium duration opioid due to it's six hour dosing interval" (Du Pen ¶ 240). Similarly, Zichterman simply states that

> levorphanol has a long half-life (usually 12-15 hours), and accumulation may result in delayed sedation and respiratory depression. Duration of analgesia is usually four to six hours, with typical dosages scheduled at six-hour intervals. Levorphanol also exhibits NMDA receptor antagonism and

> may provide benefit for the treatment of neuropathic pain. Levorphanol is available for parenteral and oral administration. The oral formulation is available only as a 2-mg tablet, which makes titration difficult.

(Zichterman 3; citations omitted). Thus, neither Du Pen nor Zichterman teach away from formulating levorphanol as an extended release drug, and never criticizes, discredits, or discourages the use of levorphanol in an extended release formulation. *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.").

Appellant contends "like CHASIN, ANDERSON includes no pharmacokinetic or other information about LEV that would cause a POSA to doubt or reconsider the known unsuitability of LEV for ER administration (regardless of which excipients might be formulated with LEV)" (App. Br. 16).

We are not persuaded because Appellant has failed to demonstrate that levorphanol was unsuitable for use in extended release compositions. Chasin "is presumptively enabling barring any showing to the contrary by a patent applicant." *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012). Appellant does not identify a specific statement in the prior art of Argoff, Du Pen, Zichterman, or other evidence that supports the asserted unsuitability of levorphanol in extended release compositions. In contrast, the Examiner relies upon an issued patent that claims a controlled release formulation of opioids (*see* Chasin, claim 1) which may be levorphanol (*see* Chasin, claim 2) (*see also* FF 1–5). Moreover, Anderson also teaches

controlled release compositions that may include levorphanol (FF 6–9). Therefore, we conclude that the balance of the evidence supports the Examiner's position that the prior art renders the use of levorphanol in an extended release composition obvious.

> Appellant contends
>
> neither of CHASIN and ANDERSON discloses any reason to select a glidant that is a thixotrope, as required by CRM[11]_C. The Examiner appears to have selected ANDERSON to combine with CHASIN merely because ANDERSON discloses that one of the glidants disclosed therein, fumed silica, coincidentally acts as a thixotrope. ANDERSON, however, does not disclose that fumed silica is a thixotrope; that disclosure is found in the Applicant's specification. Thus neither of CHASIN and ANDERSON provides a POSA any reason to select as CRM_C a compound that is a thixotrope.

(App. Br. 18; citations omitted).

We find the arguments regarding reason to combine unpersuasive because, as the Examiner points out, Chasin suggests the use of glidants in controlled release compositions (FF 4) and Anderson teaches that fumed silica is a suitable glidant (FF 8), and fumed silica inherently is a thixotropic agent (*see* Spec. ¶ 503). *Wrigley* found a "strong case of obviousness based on the prior art references of record. [The claim] recites a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known . . . agent for another." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012). We conclude the same is true here.

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[11] CRM stands for controlled release material. (App. Br. 3.)

To the extent that Anderson suggests the use of fumed silica for a different reason than that of Appellant, simply because the prior art has a different reason or motivation to combine the components of Chasin and Anderson than Appellant is of no moment as long as there is a sufficient reason to make the combination. *See In re Kemps*, 97 F.3d 1427, 1430 (Fed. Cir. 1996) ("[T]he motivation in the prior art to combine the references does not have to be identical to that of the applicant to establish obviousness." (citation omitted)).

Appellant contends that

> even if one were to accept the Examiner's contention that a POSA might select the combination LEV+ CRM_A+ CRM_B + CRM_C from among the multitudinous combinations of potential ingredients and opioids disclosed in CHASIN and ANDERSON, there is no information in CHASIN, in ANDERSON, or in any other known prior art reference that would indicate to a POSA that the combination would be useable as an ER dosage form of LEV. The Examiner's positing of this combination is mere hindsight reconstruction of the Applicant's invention and should be reversed as such.

(App. Br. 22).

We find these arguments unpersuasive. While we are fully aware that hindsight bias may plague determinations of obviousness, *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966), we are also mindful that the Supreme Court has clearly stated that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

As to the issue of selecting known compounds from prior art lists, *Perricone* rejected "the notion that [a compound] cannot anticipate because it appears without special emphasis in a longer list." *Perricone v. Medicis*

Pharm. Corp., 432 F.3d 1368, 1376 (Fed. Cir. 2005). Here, where the rejection is for obviousness, not anticipation, we note that "picking and choosing may be entirely proper in the making of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness." *In re Arkley*, 455 F.2d 586, 588 (CCPA 1972).

The instant situation is close to that in *Perricone* with limited genus sizes because there are only eleven different opioids claimed by Chasin (*see* Chasin, claim 2), only five different hydrocarbons with waxes and vegetable oils being two of the five (*see* Chasin, claim 10), and only five different matrix components including alkylcellulose (*see* Chasin, claim 8). As to the glidants generically disclosed by Chasin (FF 5), Anderson teaches only eight different glidants including fumed silica (*see* Anderson ¶ 38). Consequently, in the absence of evidence of secondary considerations, the Examiner reasonably finds selection of known elements of controlled release compositions from relatively short detailed lists obvious.

Appellant cites *In re Stepan Co.*, 868 F.3d 1342 (Fed. Cir. 2017) and contends that

> the Examiner merely alleges that he considers CHASIN and ANDERSON to be analogous to "recipes." This is insufficient, as a matter of law, to support an obviousness rejection – no more so than if the Examiner had cited "intuition" or "common sense" to select the claimed ingredients recited in the Applicant's claims (and, indeed, no more so than if the Examiner had merely alleged that the selections were "obvious").

(Reply Br. 3).

We find this argument unpersuasive because the instant facts differ from those in *Stepan*. *Stepan* found that the Board failed to "articulate why a person of ordinary skill in the art would have had a reasonable expectation of success to formulate the claimed surfactant system with a cloud point above at least 70°C." *Stepan*, 868 F.3d at 1347. However, in the instant case, Chasin provides specific reasons to select controlled release compositions that result in "from about 45 to about 85% (by wt) opioid released after 4 hours, and greater than about 60% (by wt) opioid released after 8 hours" in order to "provide pain relief for about 24 hours" (FF 5). Chasin's disclosed release rate ranges directly overlap the rate of "15% to 70% at 4 hours" and "25% to 77.5% at 6 hours" recited by claim 4. Moreover, Anderson teaches to obtain "optimum release" for the sustained release opiate composition (FF 9), demonstrating that release rate was a known results-effective variable.

Therefore, unlike *Stepan*, where the prior art lacked both disclosure and enablement of the functional limitation at issue, here the prior art discloses overlapping ranges for release rates and expressly identifies release as an optimizable variable.

Claims 5, 6, and 9

Appellant contends "that the Examiner's obviousness rejection is improper because each of dependent claims 5, 6, and 9 recites that the FR of LEV from the claimed dosage form is less than 60% after 8 hours and the cited references include no teaching or suggesting to reduce the FR to that level or lower" (App. Br. 24).

We find this argument unpersuasive for several reasons. First, none of claims 5, 6, and 9 recite a statement that the fractional release is less than

"60% after 8 hours" as argued by Appellant. Instead, claim 5 states a release "from about 20% to about 60% at 9 hours", claim 6 states a release of "from about 10% to about 60% at 9 hours", and claim 9 states a release of "from about 5% to about 50% at 8 hours." Second, to the extent that Appellant is contending that selection of a particular release rate is unobvious, we note that Chasin teaches a release rate of "greater than about 60% (by wt) opioid released after 8 hours" (FF 5). The "about 60%" release in Chasin reasonably overlaps within the "about 60%" recited by claims 5 and 6, and adjacent to the "about 50%" recited in claim 9.

> 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 . . . The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.

In re Peterson, 315 F.3d 1325, 1329, 1330 (Fed. Cir. 2003). "We have also held that a *prima facie* case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." *Id.* Here, Chasin teaches values overlapping claims 5 and 6, and a value close enough to that in claim 9 that, in the absence of evidence to the contrary, the ordinary artisan would expect the controlled release opioid compositions of claim 9 and of Chasin to function in longer term treatment of pain.

Third, Anderson teaches to obtain "optimum release" for the sustained release opiate composition (FF 9), demonstrating that release rate was a known results-effective variable, and "where 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). Appellant provides no evidence of any secondary consideration demonstrating that the particular values selected were something other than routinely optimized.

Conclusion of Law

A preponderance of the evidence of record supports the Examiner's conclusion that Chasin and Anderson render the claims obvious.

B. 35 U.S.C. § 103(a) over Chasin, Anderson, and Katzung

Appellant does not separately argue this rejection (*see* App. Br. 5). The Examiner provides sound fact-based reasoning combining Katzung with Chasin and Anderson (*see* Final Act. 8–9). We, therefore, also conclude that claims 7 and 68 would have been obvious for the reasons given by the Examiner.

SUMMARY

In summary, we affirm the rejection of claims 4–6 and 9 under 35 U.S.C. § 103(a) as obvious over Chasin and Anderson. Claims 7, 8, and 53–67 fall with claims 4–6 and 9.

We affirm the rejection of claims 7 and 68 under 35 U.S.C. § 103(a) as obvious over Chasin, Anderson, and Katzung.

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