Trials@uspto.gov
Tel.: 571-272-7822

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS XI LLC,
Petitioner,

v.

INSYS PHARMA, INC.,
Patent Owner.

Case IPR2015-01797
Patent 8,835,459 B2

Before DEBORAH KATZ, GRACE KARAFFA OBERMANN, and SUSAN L. C. MITCHELL, *Administrative Patent Judges.*

OBERMANN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Petitioner requests an *inter partes* review of claims 1–6 of U.S. Patent 8,835,459 B2 ("the '459 patent"). Paper 1 ("Pet."). Patent Owner filed a Preliminary Response. Paper 8 ("Prelim. Resp."). We have statutory authority under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted unless the Petition demonstrates "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Taking account of the information presented in the Preliminary Response, we conclude that the Petition fails to make that showing. On this record, we deny the Petition and decline to institute review.

A. Related Proceedings

Petitioner identifies no related district court proceedings. Pet. 2–3. With this decision, we issue decisions denying *inter partes* review in IPR2016-01799 and IPR2016-01800, which involve the same parties and related patents.

B. The '459 Patent

The '459 patent relates to a sublingual formulation of fentanyl, an opioid receptor agonist with analgesic potency up to 100 times that of morphine. Ex. 1001, 1:19–20. Sublingual delivery is achieved through the mucosal membranes lining the floor of the mouth. *Id.* at 10:22–23. The '459 patent describes a sublingual formulation of fentanyl useful for relieving "breakthrough pain" in cancer patients almost immediately after administration. *Id.* at 8:14–27.

The '459 patent distinguishes sublingual (floor of the mouth) administration from other routes of delivery, for example, buccal (lining of the cheeks) administration. *Id.* at 9:45–10:28. The specification recognizes solid (such as lozenge) and liquid (such as spray pump) forms of sublingual fentanyl. *Id.* at 2:1–3; 11:8–11. The '459 patent discloses a fentanyl formulation delivered "to the

sublingual mucosa via spray," which "results in a rapid onset of therapeutic effect of" the active agent. *Id*. at 11:41–43. The specification identifies embodiments that "provide a mean time to maximum plasma concentration (T_{max}) of fentanyl" within certain ranges after sublingual administration to humans. *Id.* at 11:45–50.

C. Illustrative Claim

Claims 1 is illustrative and reads as follows:

> 1. A sublingual formulation comprising from about 0.001% to about 15% by weight fentanyl, a free base, or a pharmaceutically acceptable salt thereof, from about 20% to about 60% by weight ethanol, and from about 4% to about 6% by weight propylene glycol, the formulation providing a mean T_{max} of about 1.28+/-0.60 hours when a dose is administered sublingually to humans.

Claims 1, 2, and 3 require "from about 4% to about 6% by weight of propylene glycol." Claims 1 and 3 specify a mean T_{max} range for the sublingual formulation. Claims 4, 5, and 6 do not require propylene glycol, or specify a mean T_{max} range; however, those claims specify pharmacokinetic properties of the formulation, as represented by an area-under-the-curve ("AUC") limitation.

D. The Asserted Prior Art

The Petition asserts the following references in the grounds of unpatentability:

1. UK Patent App. No. GB 2399286 A, pub. Sept. 15, 2004. (Ex. 1003) ("Ross GB").

2. US Patent Pub. No. 2006/0062812 A1, pub. Mar. 23, 2006 (Ex. 1005) ("Ross US").

3. US Patent No. 5,370,862, issued Dec. 6, 1994 (Ex. 1004) ("Klokkers-Bethke").

4. Susanne Bredenberg, *New Concepts in Administration of Drugs in Tablet Form: Formulation and Evaluation of a Sublingual Tablet for Rapid Absorption of an Individualised Dose Administration System*, Comprehensive Summaries of

Uppsala Dissertations from the Faculty of Pharmacy 287, 1–83 (2003) (Ex. 1006) ("Bredenberg").

5. Cephalon, Inc., *ACTIQ® (oral tansmucosal fentanyl citrate) Label NDA20-747/S-017*, 2–32 (2001) (Ex. 1008) ("the ACTIQ label").

E. Asserted Grounds of Unpatentability

The Petition asserts the following grounds of unpatentability:

References	Basis	Claim(s) Challenged
Ross GB, Ross US, and Klokkers-Bethke	§ 103	1
Ross GB, Ross US, Klokkers-Bethke, and Bredenberg	§ 103	2, 3
Ross US and Bredenberg	§ 103	4
Ross GB and the ACTIQ label	§ 103	4, 5
Ross GB, the ACTIQ label, and Bredenberg	§ 103	6

In addition to the asserted prior art references, the Petition advances declaration testimony of Dr. Kinam Park. Ex. 1002 ("Park Declaration").

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, we construe claim terms of an unexpired patent according to their broadest reasonable interpretation in light of the patent specification. 37 C.F.R. § 42.100(b). Under that standard, we assign terms their ordinary and customary meaning as understood by one of ordinary skill in the art in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set

forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). We construe only those terms necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

No claim term requires express construction for the purposes of this decision. The prior art, itself, demonstrates the appropriate level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect the level of skill in the art).

B. A Problem Common to All Grounds Asserted in the Petition

A problem common to all grounds asserted in the Petition is a failure to identify a persuasive reason why a person of ordinary skill in the art would have been prompted to combine the various elements of the prior art in the precise fashion required by the challenged claims. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). "If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Obviousness can be established when the prior art, itself, would have suggested the claimed subject matter. *In re Rinehart*, 531 F.2d 1048, 1051 (CCPA 1976). But the Petition identifies no persuasive reason why the prior art would have recommended the combination of elements upon which the challenges depend. In that regard, the Petition strives to identify each element of the claims, from among disparate disclosures in the art, but neglects to explain adequately why one would have selected and combined those particular features to arrive at the sublingual fentanyl formulation required by the challenged claims. The Petition is

replete with examples of that deficiency. We focus our analysis on three examples, which together are dispositive and require denial of review.

C. The Propylene Glycol Limitation of Claims 1, 2, and 3

Claims 1, 2, and 3 are directed to a sublingual fentanyl formulation comprising fentanyl (or fentanyl active forms), ethanol, and propylene glycol in specified weight-percent amounts. The Petition relies on the combined disclosures of Ross GB and Klokkers-Bethke to establish the obviousness of the limitation that requires "from about 4% to about 6% by weight" of propylene glycol.

The Petition relies on a modification to Example 1 in Ross GB, which discloses a formulation that includes fentanyl base, saccharin, ethanol, menthol, and citrate buffer—but no propylene glycol. Pet. 27–30 (citing Ex. 1003, 11:1–9 (Ross GB's Example 1)). For the teaching of the propylene glycol limitation, Petitioner directs us to two disclosures in Ross GB that mention that ingredient; first, as a suitable solubility enhancer for fentanyl (Ex. 1003, 5:1–4), and second, as a suitable moisturizing agent (*id.* at 7:11–14). Pet. 27–28. The Petition does not identify in Ross GB any disclosure or suggestion of a weight-percent range of propylene glycol that would be useful in Ross GB's Example 1 formulation. *Id.*

Instead, the Petition directs us to Klokkers-Bethke's disclosure of propylene glycol in a nitroglycerin formulation for treating angina. Pet. 28; Ex. 1004, Title, 1:16–18. The Petition identifies no disclosure in Klokkers-Bethke that mentions fentanyl or pain management. Pet. 27–30. The Petition ignores that Ross GB's fentanyl formulation is "preferably free of any propellant," whereas Klokkers-Bethke's nitroglycerin formulation is delivered via a closed and charged aerosol canister and, thus, includes propellant. Ex. 1003, 4:1; *see* Ex. 1004, Abstract, 3:20–23, 4:2, 6:10; Prelim Resp. 14 (discussing that distinction between the applied references) (citations omitted).

The Petition identifies Klokkers-Bethke's disclosure of a "broad range of 2% to 30% by weight" for propylene glycol in the aerosol nitroglycerin formulation, and then argues, without adequate analysis, that an ordinary artisan, by routine experimentation, would have modified that range in the nitroglycerin formulation to reach an optimal range "of about 4% to about 6%" by weight. Pet. 28–30. The Petition does not direct us to a disclosed purpose for propylene glycol in Klokkers-Bethke's nitroglycerin formulation—for example, a purpose comparable to one described for the fentanyl formulation of Example 1 in Ross GB. *Id.* at 27–29. The closest the Petition comes to identifying some reason that would have prompted one to import the optimized weight-percent of propylene glycol from the propellant-containing nitroglycerin formulation of Klokkers-Bethke, into the propellant-free fentanyl formulation of Ross GB, is in the argument that both formulations are "used in emergencies when the medication should be fast acting." *Id.* at 29 (quoting Ex. 1002 ¶ 24).

Critically lacking is any objective evidence—for example, a suggestion in the prior art—that a person of ordinary skill in the art would have understood that the amount of propylene glycol, optimized for use in an aerosol nitroglycerin formulation, would match the optimal amount of propylene glycol, useful in a propellant-free fentanyl formulation. *Id.* at 28–30. The Petition fails to address adequately how the compositional differences between the disparate formulations of Ross GB and Klokkers-Bethke would have informed that understanding. *Compare* Ex. 1003, 11:1–9 (Example 1 of Ross GB includes fentanyl, saccharin, ethanol, menthol, and citrate buffer), *with* Ex. 1004, 3:65–4:8 (Klokkers-Bethke's formulation includes nitroglycerin, ethanol, propylene glycol, and propellant).

Even if we set aside those shortcomings, the Petition is still deficient. As Patent Owner points out, the Petition is silent on "how the percentage by weight of

propylene glycol in a closed and charged aerosol canister would change upon dispensation, prior to sublingual delivery." Prelim. Resp. 14. The Petition also fails to take into account how the addition of propylene glycol would upset the weight-percent amounts of fentanyl or ethanol in Ross GB's Example 1 formulation, upon which the Petition relies for disclosure of the other weight-percent limitations of the challenged claims. Pet. 26–30.

Ross GB discloses that propylene glycol is useful in fentanyl formulations that are "free of [] alcohol." Prelim. Resp. 16 (quoting Ex. 1003, 5:14–15). Ross GB's Example 1 formulation comprises "40% by weight of ethanol." Pet. 27; Ex. 1003, 11:1–9 (Example 1). Petitioner does not explain adequately why one would have imported Klokkers-Bethke's optimized amount of propylene glycol into the ethanol-containing formulation of Ross GB's Example 1.

In sum, the information presented does not show sufficiently that an ordinary artisan would have modified the formulation of Ross GB's Example 1 to include propylene glycol in a weight-percent amount that satisfies claim 1, 2, or 3. Each asserted challenge to those claims depends upon that modification. Pet. 28, 38. On this record, the Petition fails to establish a reasonable likelihood of prevailing with respect to claim 1, 2, or 3.

D. The mean T_{max} Limitation of Claims 1 and 3

The challenge to claims 1 and 3 is deficient for a second reason. Those claims require a fentanyl formulation that provides a mean T_{max} value that, by Petitioner's own calculation, falls within the range of 40.8 to 112.8 minutes. Pet. 31. The Petition directs us to T_{max} values reported in Table 2 of Ross US, relating to a fentanyl preparation designated as Formulation 2. Pet. 31–32. Petitioner then argues that one would have modified a different fentanyl

formulation—the one disclosed in Example 1 of Ross GB—to attain the same T_{max} values. *Id.* at 31–34.

The crux of Petitioner's argument is that Ross US's Formulation 2 exhibits "a mean T*max* of 29 minutes for 12 patients," and that 29 minutes "is within the claimed range of 'about 40.8 minutes to about 112.8 minutes.'" Pet. 31–32 (quoting Ex. 1002 ¶ 27). Petitioner relies on the Park Declaration for evidence that 29 minutes is "about 40.8" minutes as claimed. *Id.* Dr. Park testifies that 29 minutes is within the claimed range "because the adjective 'about' preceding 40.8 minutes indicates that the lower bound is approximate and because a mean time of 29 minutes is close to the approximate lower bound." Ex. 1002 ¶ 27. Dr. Park's opinion is conclusory and unpersuasive because it is not keyed to objective proof, regarding the understanding of a person of ordinary skill in the art. *See* 37 C.F.R. § 42.65(a) (opinion testimony that does not disclose underlying facts "is entitled to little or no weight"); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (lack of objective support for opinion testimony "may render the testimony of little probative value in a validity determination").

We find insufficient Petitioner's further argument, and Dr. Park's testimony, that "a subgroup" of two patients—plucked from among the larger group of twelve patients for which data is reported in Table 2 of Ross US—makes obvious a mean T_{max} of 45 minutes in a fentanyl formulation. Pet. 32 (focusing on patients 11 and 12); *see* Ex. 1005, Table 2 (reporting data for patients 1 through 12); *see also* Ex. 1002, ¶ 27. Petitioner arrives at a mean T_{max} of 45 minutes by averaging data reported for patients 11 and 12, to the exclusion of other data reported for patients 1 through 10. *Id.* We discern no reason for Petitioner's focus on those two particular patients, except that the exercise produces a result that falls within the mean T*max* range of claim 1. That exercise is fraught with hindsight bias.

Petitioner also argues generally that one would have combined the disclosures of Ross GB and Ross US "to achieve a T*max* in the range of 40.8 minutes to about 112.8 minutes . . . so that the patient would more quickly experience the effects of the drug." Pet. 33–34 (quoting Ex. 1002 ¶ 30). That argument depends on an opinion that runs counter to objective evidence advanced elsewhere in the Petition. *Id.* By Petitioner's own calculation, the prior art suggests a mean T*max* value of 29 minutes, when all twelve patients in Table 2 of Ross US are considered in the mean calculation. *Id.* at 31; *see* Ex. 1005, Table 2. It is unclear on this record, and Petitioner does not explain adequately, why one would have adjusted upward (from 29 to 40.8 minutes) the mean T_{max} value suggested in the art, if the goal was to allow the patient to "more quickly experience the effects of the drug." Pet. 33–34 (quoting Ex. 1002 ¶ 30).

The Petition fails to provide a logical explanation of why or how one would have modified the prior art formulations to attain a mean T_{max} range of 40.8 to 112.8 hours as required by claims 1 and 3. On this record, Petitioner does not show a reasonable likelihood of prevailing at trial with respect to claims 1 or 3.

E. The AUC Limitations of Claims 4, 5, and 6

Petitioner challenges claims 4, 5, and 6 on the basis of references that include Bredenberg and the ACTIQ label. Pet. 46, 49, 55. Bredenberg relates to the administration of drugs in tablet form, and mentions "a lollipop containing fentanyl citrate (Actiq™)," which is "designed to allow rapid absorption of the drug from the oral cavity." Ex. 1006, 56. Similarly, the ACTIQ label is directed to "a solid formulation of fentanyl citrate" that is "intended for oral transmucosal administration." Ex. 1008, 2. The ACTIQ label describes a "solid drug matrix on a handle" that "is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption." *Id.* "[T]he handle allows the Actiq unit to be

removed from the mouth if signs of excessive opioid effects appear during administration." *Id.*

Patent Owner challenges the prior art status of both Bredenberg and the ACTIQ label. Prelim. Resp. 44–49. Patent Owner, however, acknowledges that the pharmacokinetic properties of Actiq® were before the Examiner during prosecution of the '459 patent; in fact, the specification places them side-by-side for contrast with those of the claimed liquid formulations. Prelim. Resp. 34 (citing Ex. 1001, Tables 51–54). For the following reasons, even if we accept Petitioner's view that Bredenberg and the ACTIQ label qualify as prior art, we are not persuaded that the asserted combination of references supports a decision to institute *inter partes* review of claim 4, 5, or 6.

Claims 4, 5, and 6 include an AUC limitation that relates to pharmacokinetic properties of the specified sublingual spray formulation of fentanyl. The nub of Petitioner's argument is that one would have combined the liquid spray formulations of Ross GB or Ross US with the AUC data reported for the tablet or lollipop forms of fentanyl citrate, as disclosed in Bredenberg or the ACTIQ label. Pet. 46–59. Petitioner does not address why or how one would have replicated the AUC data reported in Bredenberg or the ACTIQ label in the compositionally dissimilar formulations of Ross GB or Ross US. *Id.*

The Petition is essentially silent regarding the compositional differences between the solid transmucosal and liquid sublingual formulations disclosed in the various asserted references. *Id.* Bredenberg discloses solid-form tablets that include granulated quality mannitol, cross-linked polyvinylpyrrolidone, silicified microcrystalline cellulose, and magnesium stearate. Prelim. Resp. 27 (and citations therein to Ex. 1006). The ACTIQ label discloses lollipops or lozenges that include hydrated dextrates, citric acid, dibasic sodium phosphate, artificial

berry flavor, magnesium stearate, modified food starch, and confectioner's sugar. *Id.* at 33 (and citations therein to Ex. 1008). The Petition identifies no comparable compositional elements in the liquid sublingual formulations of Ross GB or Ross US. Pet. 46–59.

Nor does the Petition address how the different delivery routes of the solid transmucosal and liquid sublingual formulations would have informed the understanding of an ordinary artisan. *Id.*; *see* Ex. 1001, 1:41–211 (the '459 patent specification, discussing the Actiq® lollipop, and distinguishing its "oral transmucosal administration" from the liquid sublingual administration of the invention); Pet. 12–13 (recognizing the distinctions between local, buccal, and sublingual administrations of active agents). The specification of the '459 patent explains that those delivery routes are quite different, because the active agent in Actiq® "must first be released and dispersed prior to being available for resorption in dissolved form." Ex. 1001, 2:3–6. On this record, the Petition fails to identify a persuasive reason why the asserted references would have led one, at the time of the invention, to modify a liquid sublingual formulation of fentanyl to exhibit the pharmacokinetic properties of a solid tablet or lozenge. *Id.* In sum, the Petition does not explain adequately how or why an ordinary artisan would have been led to the invention of claims 4, 5, and 6. Prelim. Resp. 32.

III. CONCLUSION

Taking account of the information in the Petition and Preliminary Response, we decline to institute review because the information presented does not demonstrate a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. 35 U.S.C. § 314(a).

IV. ORDER

For the reasons given, it is

ORDERED that the Petition is *denied*.

FOR PETITIONER:

Gregory J. Gonsalves
gonsalves@gonsalveslawfirm.com

Christopher Casieri
MCNEELY, HARE & WAR LLP
chris@miplaw.com

FOR PATENT OWNER:

Gerald J. Flattmann
Naveen Modi
PAUL HASTINGS LLP
CFAD-Insys@paulhastings.com