United States Court of Appeals for the Federal Circuit

PERSION PHARMACEUTICALS LLC,
Plaintiff-Appellant

v.

ALVOGEN MALTA OPERATIONS LTD.,
Defendant-Appellee

2018-2361

Appeal from the United States District Court for the District of Delaware in No. 1:16-cv-00139-WCB, Circuit Judge William C. Bryson.

Decided: December 27, 2019

DOMINICK A. CONDE, Venable LLP, New York, NY, argued for plaintiff-appellant. Also represented by CHRISTOPHER P. BORELLO, JOSHUA DANIEL CALABRO, ZACHARY GARRETT.

CHAD A. LANDMON, Axinn Veltrop Harkrider, LLP, Hartford, CT, argued for defendant-appellee. Also represented by MATTHEW BECKER, THOMAS K. HEDEMANN, DAVID KEELER LUDWIG, EDWARD M. MATHIAS; CHRISTOPHER MICHAEL GALLO, Washington, DC.

Before O'MALLEY, REYNA, and CHEN, *Circuit Judges.*

REYNA, *Circuit Judge.*

Persion Pharmaceuticals LLC appeals from a decision of the U.S. District Court for the District of Delaware finding the asserted claims of U.S. Patent Nos. 9,265,760 and 9,339,499 invalid as obvious and lacking adequate written description. Because we find no reversible error in the district court's obviousness determination, we affirm on that basis and do not reach the written description issue.

BACKGROUND

I. The Asserted Patents

Persion Pharmaceuticals LLC ("Persion")[1] owns U.S. Patent Nos. 9,265,760 ("the '760 patent") and 9,339,499 ("the '499 patent"), both entitled "Treating Pain in Patients with Hepatic Impairment." Both patents share a common written description[2] and priority date and are directed to methods of treating pain in patients with mild or moderate hepatic impairment using extended-release hydrocodone-only formulations. Hepatic impairment is compromised liver functionality.

---

[1] Pernix Ireland Pain DAC and Pernix Therapeutics, LLC (collectively, "Pernix") were the named plaintiffs before the district court and the original appellants in this case. During the pendency of this appeal, Persion acquired the patents at issue from Pernix, and we granted leave for Persion to be substituted as a party. *See* Order, *Persion Pharm. LLC v. Alvogen Malta Operations LTD*, No. 2018-2361 (Fed. Cir. May 23, 2019), ECF No. 63. For convenience, we refer to Persion as the plaintiff and appellant in this opinion.

[2] For convenience, this opinion cites to the written description of the '760 patent.

Hydrocodone is an opioid that is widely used to treat pain and has been FDA approved since 1943. It is marketed in both extended-release and immediate-release formulations and is often combined with other active ingredients. Like many opioids, hydrocodone is primarily metabolized in the human liver. If liver function is impaired, metabolism of opioids is slowed. Thus, the same dose of hydrocodone may pose a higher risk of overdose in a patient with hepatic impairment than in a healthy patient due to potential build-up of the drug in the patient's bloodstream.

The '760 and '499 patents cover the formulation for Zohydro ER, Persion's extended-release hydrocodone-only drug product. When Zohydro ER's prior owner sought approval to market the drug from the U.S. Food and Drug Administration ("FDA"), the FDA required the owner to conduct a clinical study to determine the potential effect of the drug on patients with hepatic impairment. The study showed that use of Zohydro ER did not result in substantially higher concentrations of hydrocodone in the bloodstream of subjects with mild and moderate hepatic impairment than in subjects without hepatic impairment.

Following this study, the researchers filed patent applications directed to their discovery, which later issued as the '760 and '499 patents. Example 8 of the patents describes the Zohydro ER clinical study and its results. *Id.* col. 22 l. 52–col. 23 l. 48. However, the patent claims are not limited to the use of the Zohydro ER formulation but instead cover methods of using any extended-release formulation with "hydrocodone bitartrate as the only active ingredient" to treat pain in patients with mild or moderate

hepatic impairment.[3] '760 patent col. 24 ll. 1–5, col. 25 ll. 13–17, '499 patent col. 24 ll. 1–5, col. 26 ll. 9–13.

The relevant claims of the '760 and '499 patents can generally be grouped into two sets: the "non-adjustment" claims and the "pharmacokinetic" claims. The non-adjustment claims are directed to administering a starting dose of hydrocodone to a patient having mild or moderate hepatic impairment without adjusting the dose relative to a patient with a healthy liver. Independent claim 1 of the '760 patent is representative of the non-adjustment claims, and recites:

> 1. A method of treating pain in a patient having mild or moderate hepatic impairment, the method comprising:
>
> > administering to the patient having mild or moderate hepatic impairment a starting dose of an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate, and wherein the starting dose is not adjusted relative to a patient without hepatic impairment.

'760 patent col. 23 l. 66–col. 24 l. 7.

The pharmacokinetic claims recite pharmacokinetic parameters either as absolute values or in relation to values in a healthy patient. Independent claim 12 of the '760

---

[3] Hydrocodone bitartrate is a salt of hydrocodone used to deliver hydrocodone to the human body. *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F.Supp.3d 566, 575 (D. Del. 2018) (citing '760 patent col. 13 ll. 13–15).

patent is representative of the pharmacokinetic claims, and recites:

> 12. A method of treating pain in a patient having mild or moderate hepatic impairment, the method comprising:
>
> administering to the patient having mild or moderate hepatic impairment an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate,
>
> wherein the dosage unit provides a release profile of hydrocodone that:
>
> (1) does not increase average hydrocodone $AUC_{0–inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%;
>
> (2) does not increase average hydrocodone $AUC_{0–inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%;
>
> (3) does not increase average hydrocodone C_{max} in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 9%; and

> (4) does not increase average hydrocodone C_{max} in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%.

'760 patent col. 25 ll. 11–35.

II. Prior Art

A. Devane

U.S. Patent Publication No. 2006/0240105 ("Devane") is entitled "Multiparticulate Modified Release Composition" and was published on October 26, 2006. Devane is directed to a controlled-release composition that provides both immediate and extended release of one or more active ingredients. J.A. 3616 (Devane, ¶¶ 26–27). Devane teaches that one active ingredient that can be used with these compositions is hydrocodone. J.A. 3615 (Devane, ¶ 17); J.A. 3620 (Devane, ¶ 70). As an example, Devane discloses the Zohydro ER formulation and describes an in vivo study in which the formulation is used to treat pain. J.A. 3625–26 (Devane, ¶¶ 103–06); J.A. 6, 490; Appellee's Br. 4.

B. Jain

U.S. Patent Publication No. 2010/0010030 ("Jain") is entitled "Extended Release Hydrocodone Acetaminophen and Related Methods and Uses Thereof" and was published on January 14, 2010. Jain is directed to methods of treating pain using an extended-release formulation containing about 15 milligrams of hydrocodone and about 500 milligrams of acetaminophen. J.A. 3631 (Jain, Abstract). This formulation is known as Vicodin CR. J.A. 3647 (Jain, ¶ 34). Jain describes several clinical studies involving Vicodin CR, including a study conducted to determine the effects of hepatic insufficiency on the pharmacokinetics of Vicodin

CR. J.A. 3649 (Jain, ¶ 64). The results of the study demonstrated that pharmacokinetic parameters for hydrocodone "were similar in normal subjects and subjects with mild and moderate hepatic impairment." *Id.* The results further demonstrated that the pharmacokinetic parameters for acetaminophen "were similar in normal subjects and subjects with mild hepatic impairment, and 34 to 42% higher in subjects with moderate hepatic impairment." *Id.*

C. Vicodin and Lortab Labels

Vicodin and Lortab are both immediate-release formulations of hydrocodone and acetaminophen that are used to treat pain. J.A. 3121, 3230. The 2011 labels for these products provide safety information and instructions for use. J.A. 3121, 3230–33. Although both labels state that these drugs "should be used with caution in . . . those [patients] with severe impairment of hepatic . . . function," neither label includes any precautions or dosage restrictions for patients with mild or moderate hepatic impairment. J.A. 3121, 3231.

III. District Court Proceedings

On March 4, 2016, Persion sued Alvogen Malta Operations Ltd. ("Alvogen") for infringement of claims 1–4, 11–12, 17, and 19 of the '760 patent. After the '499 patent issued, Persion filed an amended complaint additionally asserting infringement of claim 1 of that patent. Persion alleged that Alvogen infringed these claims by filing an Abbreviated New Drug Application ("ANDA") seeking to market a generic version of Zohydro ER.[4]

---

[4] Alvogen filed its ANDA with the FDA prior to the issuance of the '760 and '499 patents. Other patents at issue in this case, however, were listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations"

After a bench trial, the district court concluded that Alvogen would indirectly infringe the asserted claims because its product label would induce doctors and patients to administer Alvogen's product in an infringing manner. *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 579 (D. Del. 2018). The district court also concluded that the asserted claims are not invalid as anticipated by Devane. *Id.* at 594. These rulings are not at issue on appeal.

The district court next determined that the asserted claims are invalid as obvious over Devane in view of Jain, the state of the prior art at the time of invention, and the Vicodin and Lortab labels. *Id.* at 595–96, 610. Specifically, the district court found that in light of the teachings of Jain and the Vicodin and Lortab labels, a person of ordinary skill in the art would have been motivated to administer the extended-release hydrocodone bitartrate formulation disclosed in Devane to patients with mild or moderate hepatic impairment at an unadjusted dose and would have had a reasonable expectation of success in so doing. *Id.* at 609–10, 615. The district court further found that the pharmacokinetic limitations in the pharmacokinetic claims are "inherent in any obviousness combination that contains the Devane formulation" because the recited pharmacokinetic parameters were "necessarily present" in the Zohydro ER formulation described in both Devane and the asserted patents. *Id.* at 607. Finally, the district court found that the objective factors of unexpected results, long-felt but unmet need, and failure of others did not weigh in favor of finding nonobviousness.

In addition, the district court determined that the asserted claims of the '760 and '499 patents are invalid under 35 U.S.C. § 112(a) for lack of adequate written description

---

publication, otherwise known as the "Orange Book," for Zohydro ER at the time Alvogen filed its ANDA.

support. *Id.* at 624–25. The district court found that the written description discloses only the formulation described in Example 8, which is the same as both the Zohydro ER and the Devane formulations. *Id.* at 575, 619. The district court explained that, by contrast, the claims of the '760 and '499 patents "are broadly cast in generic form," and "are not limited to that single disclosed formulation." *Id.* at 618–19. The district court concluded that because "[t]he pharmacokinetic data and dissolution profile for the Devane formulation provide no guidance as to whether other formulations would satisfy the functional limitations of the claims," the asserted claims of the '760 and '499 patents were not supported by the written description as required by § 112(a). *Id.* at 623, 625.

Persion timely appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Obviousness is a question of law with underlying factual findings relating to the scope and content of the prior art; differences between the prior art and the claims at issue; the level of ordinary skill in the pertinent art; the presence or absence of a motivation to combine or modify with a reasonable expectation of success; and any objective indicia of non-obviousness. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1328 (Fed. Cir. 2018) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)); *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1364 (Fed. Cir. 2015). "The inherent teaching of a prior art reference is a question of fact." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014) (quoting *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995)) (internal quotation marks omitted).

In an appeal from a bench trial, we review the district court's factual findings for clear error and the district court's legal conclusion on obviousness de novo. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346,

1354 (Fed. Cir. 2013). Under the clearly erroneous standard of review, we defer to the district court's factual findings unless, considering the totality of the evidence, we are "left with the definite and firm conviction that a mistake has been committed." *Zenith Radio Corp. v. Hazeltine Research, Inc.*, 395 U.S. 100, 123 (1969) (quoting *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948)).

Persion raises four primary challenges to the district court's obviousness conclusion. First, Persion contends that the district court improperly relied on inherency to conclude that Devane discloses the pharmacokinetic limitations of the asserted claims. Second, Persion argues that the district court improperly relied on pharmacokinetic profiles from drugs other than extended-release single-active-ingredient hydrocodone formulations and from patients other than those with hepatic impairment in reaching its obviousness conclusion.[5] Third, Persion contends that the district court erred by finding the asserted claims obvious before considering the objective indicia factors. Fourth, Persion argues that the district court's factual findings concerning obviousness are inconsistent with its findings concerning the lack of written description support. We address each argument in turn.

A. Inherency

"[I]nherency may supply a missing claim limitation in an obviousness analysis." *PAR*, 773 F.3d at 1194–95; *see also Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018) ("An inherent characteristic of a formulation can be part of the prior art in an obviousness

---

[5] Persion characterizes several of its arguments as challenging the district court's legal errors. *See, e.g.*, Appellant's Br. 24, 26, 29. It is clear, however, that Persion's arguments are directed to the district court's factual findings, which we review for clear error.

analysis even if the inherent characteristic was unrecognized or unappreciated by a skilled artisan."). It is long settled that in the context of obviousness, the "mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art." *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981). The Supreme Court explained long ago that "[i]t is not invention to perceive that the product which others had discovered had qualities they failed to detect." *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249 (1945).

We too have previously explained that "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations," because "[t]o hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). In *In re Kao*, we found that the claimed controlled-release oxymorphone formulation was obvious because an inherent pharmacokinetic property of oxymorphone that was present in controlled-release oxymorphone "add[ed] nothing of patentable consequence." 639 F.3d 1057, 1070 (Fed. Cir. 2011). In *In re Kubin*, we found an inherent property obvious, explaining that "[e]ven if no prior art of record explicitly discusses the [limitation], the . . . application itself instructs that [the limitation] is not an additional requirement imposed by the claims on the [claimed protein], but rather a property necessarily present in [the claimed protein]." 561 F.3d 1351, 1357 (Fed. Cir. 2009). Our predecessor court similarly concluded that it "is not the law" that "a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable . . . because it also possesses an [i]nherent, but hitherto unknown, function which [the patentees] claim to have discovered." *In re Wiseman*, 596 F.2d 1019, 1023 (C.C.P.A. 1979).

Inherency, however, is a "high standard," that is "carefully circumscribed in the context of obviousness." *PAR*, 773 F.3d at 1195. Inherency "may not be established by probabilities or possibilities," and "[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Oelrich*, 666 F.2d at 581 (emphasis added) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939); *see also In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993). Rather, inherency renders a claimed limitation obvious only if the limitation is "necessarily present," or is "the natural result of the combination of elements explicitly disclosed by the prior art." *PAR*, 773 F.3d at 1195–96; *see also Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (relying on inherency where the claims recited "a property that is necessarily present" in the prior art). "If . . . the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient" to render the function inherent. *Oelrich*, 666 F.2d at 581 (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939)).

On appeal, Persion contends that the district court erred in applying the inherency doctrine in its obviousness analysis because Devane does not teach administering its hydrocodone-only formulation to patients with mild or moderate hepatic impairment. Thus, Persion asserts, "'the natural result flowing from the operation as taught' in Devane cannot be the claimed [pharmacokinetic] values for [hepatically impaired] patients." Appellant's Br. 37 (quoting *Oelrich*, 666 F.2d at 581); Reply Br. 19.

To the extent Persion contends that inherency can only satisfy a claim limitation when all other limitations are taught in a single reference, that position is contrary to our prior recognition that "inherency may supply a missing claim limitation in an obviousness analysis" where the limitation at issue is "the natural result of the *combination of*

prior art elements." *PAR*, 773 F.3d at 1194-95 (emphasis added, internal quotations omitted). Here, the district court specifically found that Devane, together with Jain, the state of the prior art at the time of invention, and the Vicodin and Lortab labels, taught the combination of elements that inherently result in the claimed pharmacokinetic parameters. The district court found that a person of ordinary skill in the art would have been motivated, with reasonable expectation of success, to administer an unadjusted dose of the Devane formulation to hepatically impaired patients. There was also no dispute that the Devane formulation, which was identical to the Zohydro ER formulation described in the patents in suit, necessarily exhibited the claimed parameters under these conditions. *Pernix*, 323 F. Supp. 3d at 607, 610. In this context, the district court did not err by finding that the pharmacokinetic limitations of the asserted claims were inherent and added no patentable weight to the pharmacokinetic claims.

B. Evidence of Obviousness

Persion also argues that the district court clearly erred in its obviousness findings by relying on pharmacokinetic data from formulations and patient groups not covered by the asserted claims. Persion asserts that pharmacokinetic data for drug products with more than one active ingredient, for immediate-release hydrocodone products, or for hydrocodone-only products administered to unimpaired patients is irrelevant to the obviousness inquiry in this case because that data would not allow a person of ordinary skill in the art to predict the correct dose of its claimed hydrocodone-only extended-release formulation for hepatically impaired patients. Appellant's Br. 24–28, 30–36. On this basis, Persion argues that Jain would not have provided a person of ordinary skill in the art "with any reasonable expectation that a hydrocodone-only dosage form could be dosed the same way in patients with and without [hepatic impairment]." Appellant's Br. 35; Reply Br. 7–14. Also on this basis, Persion contends that Devane's

pharmacokinetic data is "irrelevant to Jain's formulation" because "none of the data in Devane is for [hepatically impaired] patients." Appellant's Br. 31; Reply Br. 16. We do not find these arguments persuasive because we find no clear error in the district court's analysis.

The district court provided several reasons for its conclusion that a person of ordinary skill in the art would have considered other types of drug products in developing a hydrocodone-only extended-release formulation. *Pernix*, 323 F. Supp. 3d at 608–09. In particular, the district court found that in light of acetaminophen's hepatotoxicity, a person of skill in the art would have expected that an acetaminophen-free hydrocodone formulation, such as the one disclosed in Devane, would have been even safer for patients with hepatic impairment than the combination formulations disclosed in Jain and other references. *Id.* at 608. While Persion asserts that Jain "extols the 'significantly greater benefits' of acetaminophen-containing combination products," and thus undermines the district court's finding of a motivation to remove acetaminophen from Jain's formulation, Appellant's Br. 30, Jain only discusses these benefits in comparison to a *placebo* used in its clinical study, not to hydrocodone alone, J.A. 3652, ¶ 89 (emphasis added). Thus, nothing in the text of Jain leads us to conclude that the district court clearly erred in combining the teachings of Jain with the Devane formulation.

Persion also asserts that the district court improperly relied on the FDA's acceptance of safety data for Vicoprofen, an immediate-release combination hydrocodone and ibuprofen drug, as part of the New Drug Application ("NDA") for Zohydro ER. Appellant's Br. 24–25. The district court found that the FDA's willingness to accept such data supports the view that a combination product containing hydrocodone would have been relevant to a person of ordinary skill evaluating the appropriate administration of the Devane formulation. *Pernix*, 323 F. Supp. 3d at 608–09. Persion argues this finding was clearly erroneous

because the FDA did not find the Vicoprofen data sufficient to establish the proper dosing of Zohydro ER for hepatically impaired patients and had previously refused to rely on such "combination products" data in evaluating another hydrocodone-only product. Appellant's Br. 25. However, as the district court explained, "[t]he standard to find a motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA," and therefore, "[t]he fact that the FDA found the comparison [between Vicoprofen and Zohydro ER] insufficient to satisfy its safety and efficacy standards does not speak to the issue of obviousness." *Pernix*, 323 F. Supp. 3d at 611. We find no clear error in the district court's conclusion that the FDA's approval requirements do not undermine the force of the evidence as to obviousness. *Id.* In light of the record as a whole, we find no clear error in the district court's findings on the relevance of combination product data to a person of ordinary skill considering the administration of a hydrocodone-only product.

Persion also challenges the district court's reliance on Jain's description of the pharmacokinetic parameters of hydrocodone in healthy subjects and in subjects with mild or moderate hepatic impairment as "similar." Persion argues that Jain does not define "similar" and the district court erred by "presuming" that "similar" meant "less than 34 to 42%" because a presumption is not evidence. Appellant's Br. 32–34. Jain, however, expressly distinguishes "similar" pharmacokinetic results from those that are "34 to 42% higher." J.A. 3649; *see also Pernix*, 323 F. Supp. 3d at 613. Thus, the district court did not merely presume to know what Jain meant by "similar," contrary to Persion's argument. We find no clear error in the district court's interpretation of Jain or in its conclusion that because Jain discloses "similar" pharmacokinetic values for both hepatically impaired and unimpaired patients, a person of ordinary skill in the art would understand that no dose

adjustment would be necessary in administering hydrocodone to hepatically impaired patients.

Persion next challenges the district court's reliance on Devane's study of healthy patients in finding that the presence of acetaminophen had no appreciable effect on the pharmacokinetic profile for hydrocodone. *See Pernix*, 323 F. Supp. 3d at 610. The district court credited the testimony of Alvogen's expert that the relevant pharmacokinetic parameter values disclosed in Devane's study for a hydrocodone-only product and a hydrocodone-acetaminophen product are "virtually identical values." *Id.* Relying on Devane's study, the district court found that a person of ordinary skill in the art would have appreciated that hydrocodone and acetaminophen are metabolized differently, and accordingly, would not have been deterred from relying on combination products containing acetaminophen for guidance about the dosing of the Devane formulation. *Id.* Persion asserts that pharmacokinetic data for hepatically unimpaired patients is irrelevant to motivation or expectation of success for administration of a drug to patients with hepatic impairment. Appellant's Br. 31. We disagree. Persion provides no support for its assertion, and we find no clear error in the district court's crediting of expert testimony that relied on the Devane data in discussing how a person of ordinary skill in the art would have understood the effect of acetaminophen on the metabolism of hydrocodone in a combination product. *See Pernix*, 323 F. Supp. 3d at 609 (citing J.A. 552, Trial Tr. 257:1–8); *see also* J.A. 551:21-25.

Persion also contends that the district court erred by taking judicial notice of the FDA's recommendation to "limit the strength of acetaminophen in prescription drug products." Specifically, Persion asserts that Alvogen had expressly dropped an obviousness combination that included the FDA's statement and thus Persion was deprived of an adequate opportunity to respond to the statement during trial. Appellant's Br. 29 (citing *Pernix*, 323 F. Supp.

3d at 609). However, the district court relied on the FDA's statements not as part of a prior art combination, but only in rebutting Pernix's assertion that there was no motivation to combine the teachings of Devane with the hydrocodone-acetaminophen formulations described in Jain and the Vicodin and Lortab labels. In rejecting Persion's argument, the district court relied on three additional bases for finding a motivation to combine that were independently supported by other evidence presented at trial. *Pernix*, 323 F. Supp. 3d at 609–10. Thus, regardless of whether the district court's consideration of the FDA's statement was proper, we find no clear error in the court's finding that there was a motivation to combine in light of the evidence as a whole.

In sum, after reviewing the entire evidentiary record, we are not left with any conviction that the district court has made a mistake. *See Zenith*, 395 U.S. at 123. We therefore reject Persion's challenge to the district court's factual findings, which are not clearly erroneous.

C. Objective Indicia

Persion argues that the district court erred by finding the asserted claims obvious before considering the asserted objective indicia of nonobviousness, which Persion contends clouded the district court's analysis of the objective indicia. Appellant's Br. 38–43. Relying on *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, Persion argues that the district court's finding of obviousness was premature. 676 F.3d 1063, 1075 (Fed. Cir. 2012). We disagree. Unlike the trial court in *Cyclobenzaprine*, the district court here considered Persion's evidence of objective indicia together with the other evidence presented at trial on the issue of obviousness. *See, e.g.*, *Pernix*, 323 F. Supp. 3d at 615–16 (considering whether Persion's objective indicia arguments were "supported by other evidence adduced at trial"); *id.* at 616–17 (considering the inventors' testimony directed to the unexpected

results factor in the context of "all the evidence at trial"). While the district court's discussion of objective indicia follows its discussion of the asserted prior art, the substance of the court's analysis makes clear that it properly considered the totality of the obviousness evidence in reaching its conclusion and did not treat the objective indicia as a mere "afterthought" relegated to "rebut[ting]" a prima facie case. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357–58 (Fed. Cir. 2013); *Cyclobenzaprine*, 676 F.3d at 1075.

The remainder of Persion's arguments amount to challenges against the district court's weighing of the objective indicia. For example, Persion argues that in addressing the failure of others, the district court did not give any weight to evidence of Cephalon, Inc.'s failure to develop its Vantrela drug in a manner that would not require a dose adjustment for hepatically impaired patients. Appellant's Br. 39–40. The district court, however, expressly considered this evidence and determined that it did not warrant a finding of nonobviousness. The district court found that Cephalon, Inc.'s failure was not persuasive in light of evidence demonstrating that others had succeeded in making a hydrocodone drug that did not require a dose adjustment. *Pernix*, 323 F. Supp. 3d at 617. In addition, the district court heard trial testimony that the FDA would not have required a dose adjustment for administering Vantrela to patients with hepatic impairment. *See* J.A. 596–97 (Trial Tr. 301:21–302:4). Persion additionally argues that the district court improperly dismissed the testimony of the inventors regarding unexpected results. Appellant's Br. 40–42. However, the district court considered this testimony, and we see no clear error in the court's discounting of the evidence in light of the inventors' failure to account for the teachings in Jain. *Pernix*, 323 F. Supp. 3d at 616–17. Overall, we find no clear error with the district court's assessment of the objective indicia evidence.

D. Internal Inconsistency

Lastly, Persion argues that the district court's obviousness decision must be reversed because its obviousness findings are at odds with its findings concerning the written description issue. Persion states that, for example, in finding a lack of written description support for the asserted claims, the district court "found [that] 'nothing in the state of the art as of July 2012 . . . would have provided guidance as to which [ER hydrocodone-only] formulations would [achieve the claimed PK profile] and which would not[.]'" Appellant's Br. 22 (quoting *Pernix*, 323 F. Supp. 3d at 627) (emphasis omitted). Persion asserts this statement contradicts the district court's finding that a person of ordinary skill in the art "would 'look to Jain and to the Vicodin and Lortab labels for [] guidance as to the appropriate dosing levels of Devane's formulation for patients with mild or moderate [hepatic impairment].'" *Id.* (quoting *Pernix*, 323 F. Supp. 3d at 612) (emphasis omitted). We reject this argument as we see no inconsistency in the district court's findings.

Persion's entire argument with respect to this issue is based on incomplete quotations from the district court's opinion. For example, a complete reading of the district court's statement above belies Persion's assertion that the district court's findings are inconsistent. The district court stated that "there was nothing in the state of the art as of July 2012 that would have provided guidance as to which of the broadly claimed formulations would work and which would not, *with the exception of the single embodiment described in Example 8*." *Pernix*, 323 F. Supp. 3d at 627 (emphasis added). The embodiment described in Example 8 of the common written description of the '760 and '499 patents is the Devane formulation, which formed the basis for the district court's obviousness findings. *Id.* at 575, 619. In contrast to the "essentially limitless number of formulation species" covered by the claims of the '760 and '499 patents, the district court found that the prior art provided

adequate guidance with respect to the sole formulation described in Example 8: the Devane formulation. *Id.* at 618–19, 622–23. Thus, there is no inconsistency between the statement Persion quotes and the district court's conclusion that a person of ordinary skill in the art would have been motivated to combine Devane with Jain and the Vicodin and Lortab labels to arrive at the claimed invention.

For the same reason, we reject Persion's argument that the district court's findings with respect to reasonable expectation of success are inconsistent with its findings concerning the lack of written description. Persion asserts that the district court "found that there was no 'way of predicting which formulations would work and which would not[,]' stating that 'testing results would be fundamental to determining which formulations would satisfy the asserted claims[.]'" Appellant's Br. 20 (quoting *Pernix*, 323 F. Supp. 3d at 624, 628). According to Persion, this necessity for experimentation contradicts the district court's finding that a person of ordinary skill would have had a reasonable expectation of success in combining Devane with Jain and the Vicodin and Lortab labels. *Id.* at 20–21. Once again, however, Persion omits critical context from its quote that demonstrates the district court was addressing formulations other than the one described in Example 8. *See Pernix*, 323 F. Supp. 3d at 623 (declining to credit expert testimony that "the specification would provide guidance to a person of skill in the art regarding how to make a formulation that would satisfy the limitations of the asserted claims, *except for the Devane formulation set forth in Example 8 or compositions closely similar to that one*") (emphasis added). In context, there is no inconsistency between the district court's findings underlying its obviousness and lack of written description determinations, and we will not reverse the district court on this basis.

CONCLUSION

We have considered Persion's remaining arguments and find them unpersuasive. We conclude that the district court correctly applied inherency to find that the claimed pharmacokinetic limitations of the asserted claims added no patentable weight over the combination of Devane and other prior art references. We further conclude that the district court's factual findings concerning obviousness are not clearly erroneous. We therefore affirm the district court's decision that the asserted claims of the '760 and '499 patents are invalid as obvious under 35 U.S.C. § 103. We do not reach the district court's decision concerning the lack of written description support.

AFFIRMED

COSTS

Each party will bear its own costs.