IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	§	
	§	
Plaintiffs,	§	
	§	
v.	§	Civil Action No. 16-139-WCB
	§	
ALVOGEN MALTA OPERATIONS LTD.,	§	
	§	
Defendant.	§	
	§	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

BACKGROUND

This is a Hatch-Waxman Act case. The plaintiffs, Pernix Ireland Pain DAC and Pernix Therapeutics, LLC, (collectively, "Pernix") have sued the defendant, Alvogen Malta Operations Ltd. ("Alvogen") for patent infringement under 35 U.S.C. § 271(e)(2). Pernix is the owner of U.S. Patent Nos. 9,265,760 ("the '760 patent") and 9,339,499 ("the '499 patent"), both of which are entitled "Treating Pain in Patients with Hepatic Impairment." The patents share an essentially identical specification, referred to here as the common specification. The two Pernix patents have a priority date of July 31, 2012.

1. The Hatch-Waxman Act is the name commonly used to refer to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360(cc), 35 U.S.C. §§ 156, 271, 282), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066. The Hatch-Waxman Act was intended to strike a balance between two competing policy interests: (1) to induce pioneering research and development of new drugs; and

(2) to enable competitors to bring low-cost generic copies of those drugs to market rapidly if those drugs are not entitled to patent protection. *See Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002). To promote those objectives, the Hatch-Waxman Act provides a means for pharmaceutical companies to resolve patent disputes relatively quickly. Ideally, it provides for a prompt determination of whether particular drugs made and sold by brand-name pharmaceutical companies are protected by valid patents. If the patents are held to be infringed and not invalid, the covered drugs cannot be made and sold by generic manufacturers until the patents expire. If the patents are held to be invalid or not infringed, the Act provides a mechanism for prompt approval of the generic versions of the drugs by the U.S. Food and Drug Administration ("FDA"), which regulates the sale of pharmaceutical drugs in this country.

In order to obtain the necessary FDA approval to market a new drug, a pharmaceutical company must file a New Drug Application ("NDA"). That application is designed to show the FDA, through rigorous testing procedures, that the drug is safe and effective for its proposed indications. After considering the application, and often after extended negotiations with the pharmaceutical company, the FDA may grant the application and authorize the company to market the drug for particular indications. The company is restricted to marketing the drug for those indications, as dictated by FDA regulations that govern both labeling and advertising for all prescription drugs. *See* 21 C.F.R. §§ 201.1–201.327 (labeling); *id.* § 202.1 (advertising).

In an effort to speed up the approval process for generic drugs, the Hatch-Waxman Act provides that a generic drug manufacturer may submit an Abbreviated New Drug Application ("ANDA") for approval by the FDA. If the generic company intends to market a drug that is equivalent to the first pharmaceutical company's approved drug, the ANDA may rely on the

safety and efficacy studies previously submitted as part of the first company's NDA. In order to take advantage of those studies, the ANDA applicant must demonstrate that the proposed generic drug is bioequivalent to the previously approved drug product. *See* 21 U.S.C. § 355(j)(2)(A); *Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1282 (Fed. Cir. 2008).

Under the Hatch-Waxman Act, NDA holders are required to notify the FDA of all patents that "claim[] the drug for which the [NDA] applicant submitted the application . . . and with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1), (c)(2). The FDA lists such patents in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," which is commonly referred to as the "Orange Book." *See Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1318 (Fed. Cir. 2012); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045 (Fed. Cir. 2010).

The Hatch-Waxman Act creates what is referred to as an "artificial" type of infringement that allows for the adjudication of the parties' rights in patents that would be infringed if the ANDA were issued and the generic product made, used, or sold. *See Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004). In particular, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of patent infringement to submit an ANDA for a drug claimed in a patent or the use of which is claimed in a patent if the purpose of the submission of the ANDA is to obtain approval to engage in the commercial manufacture, use, or sale of the drug claimed in the patent, or the use of which is claimed in the patent before the patent's expiration.

2. Zohydro ER, which the parties sometimes refer to as "HC-ER," is an extended-release hydrocodone product that contains no other active ingredients.[1] The formulation for Zohydro ER was set forth in a prior art U.S. patent application to Devane, U.S. Patent Appl. No. 2006/0240105 (JTX37), which was published on October 26, 2006. *See* Trial Tr. 210:20–211:7, 368:24–369:3. When Zogenix, Inc., the prior owner of Zohydro ER, sought FDA approval to market Zohydro ER, the FDA insisted that Zogenix conduct a "hepatic impairment study" to determine the potential effect of Zohydro ER on patients with hepatic impairment—i.e., compromised liver functionality—and to determine whether special restrictions should be imposed on the use of the drug in such patient populations. Trial Tr. 280:7–19, 359:10–360:21. The Zohydro ER hepatic impairment study produced results that surprised the Zogenix scientists who conducted the study. Contrary to their expectations, they discovered that the concentration of hydrocodone in the bloodstream of subjects with mild and moderate hepatic impairment was not dramatically higher than in patients without hepatic impairment. Trial Tr. 369:7–371:4, 379:16–380:5, 387:8–21, 391:21–393:13, 398:5–399:13, 412:23–413:12, 433:23–435:10, 440:18–25.

The FDA approved the NDA for Zohydro ER on October 25, 2013, in capsule dosage forms ranging from 10 to 50 milligrams that are administered twice daily. The FDA-approved label for Zohydro ER provided, in the Dosage and Administration section: "Patients with Severe Hepatic Impairment: Initiate dosing with 10 mg every 12 hours and titrate carefully, while monitoring for respiratory depression, sedation, and hypotension. No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment." JTX5,

[1] HC-ER was the internal name for the extended-release hydrocodone product before the adoption of the brand name Zohydro ER. Trial Tr. 368:6–14.

at 1. In a subsection entitled Dosage Modification in Patients with Severe Hepatic Impairment, the label advises that "[p]atients with severe hepatic impairment may have higher plasma concentrations of hydrocodone than those with normal function," but it adds that "[n]o adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment." JTX5, at 7. And in the section dedicated to the use of the drug in specific populations, the label repeats that "[n]o adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function . . . . Therefore a dosage reduction is recommended for patients with severe hepatic impairment . . . ." JTX5, at 17. In the section on clinical pharmacology, the label reported the results of the hepatic impairment study that was performed in connection with the filing of the NDA. JTX5, at 22.

Following the approval of Zohydro ER, Alvogen filed an ANDA seeking FDA authorization to market a generic form of that product. Alvogen proposed to market its hydrocodone extended-release capsules in strengths ranging from 10 to 50 milligrams. The proposed label for Alvogen's ANDA product, JTX6, is essentially identical to the label for Zohydro ER.[2]

3. Hydrocodone is an opioid that is widely prescribed to treat pain. It is marketed in both an extended-release form and an immediate-release form. It is often combined with another ingredient, and was found in several products before the priority date of Pernix's patents, including: Vicoprofen, which is hydrocodone combined with ibuprofen; Lortab and Vicodin,

[2] The '760 and '499 patents had not issued at the time Alvogen filed its ANDA with the FDA. At that time, however, there were other patents listed in the Orange Book as pertinent to Zohydro ER. Those patents are not at issue in this case.

which are hydrocodone combined with acetaminophen; and TussiCaps, which is hydrocodone combined with chlorpheniramine, an antihistamine, and is approved for coughs and upper respiratory symptoms. Vicoprofen, Lortab, and Vicodin were sold in immediate-release form, while TussiCaps was sold as an extended-release product.

Since the priority date of the Pernix patents, two other extended-release hydrocodone products were developed besides Zohydro ER—Hysingla ER and Vantrela. Neither of those products has an active ingredient other than hydrocodone. In addition, many other opioid products, both immediate-release and extended-release, have been on the market since before the priority date of the Pernix patents, including Percocet and OxyContin, which contain oxycodone; Dilaudid and Exalgo, which contain hydromorphone; Opana and Opana ER, which contain oxymorphone; Nucynta ER, which contains tapentadol; and Kadian and Avinza, which contain morphine.

For many opioids, including hydrocodone, the bulk of the metabolism of the drug occurs in the liver. For that reason, persons of skill in the art have frequently expressed the view that dosages of opioids need to be adjusted for persons suffering from hepatic impairment in order to avoid a dangerous build-up of the opioid in the patient's bloodstream. Such a build-up could occur if the patient's liver were unable to metabolize the opioid as quickly as would be the case for a patient with normal liver function and the patient continued to administer additional doses of the drug.

4. Following the hepatic impairment study that was conducted as part of the NDA process, the scientists who worked on the project filed applications for the patents-in-suit. Although the Zohydro ER study was the only clinical study supporting the patent, the inventors did not limit themselves to claiming the Zohydro ER formulation or a method of treatment using

the Zohydro ER formulation. Rather, the inventors claimed a method of treating pain in a patient having mild or moderate hepatic impairment in which the patient would be administered "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."[3]

The '760 patent issued to Pernix on February 23, 2016. Ten days later, Pernix brought this action, alleging that Alvogen's act of filing its ANDA infringed the '760 patent. Pernix sought injunctive and declaratory relief to prevent Alvogen from marketing its proposed product. After the '499 patent issued on May 17, 2016, Pernix filed an amended complaint adding claims of infringement of that patent.

5. Pernix's patents claim methods of treating pain in patients with mild or moderate hepatic impairment. The methods recited in the asserted claims entail using a formulation comprising hydrocodone in an extended-release form, in which hydrocodone is the only active ingredient and in which the formulation has effects on patients with mild or moderate hepatic impairment similar to its effects on patients without hepatic impairment. The common specification contains an embodiment described in Example 8, which is the formulation Pernix sells under the brand name Zohydro ER.

At trial, Pernix asserted a total of nine claims from the two patents, claims 1–4, 11, 12, 17, and 19 of the '760 patent, and claim 1 of the '499 patent. In addition to the formulation limitation set forth above, the various claims contain limitations seeking to capture the functional efficacy of the invention, either by reference to the absence of a need to reduce the dosage for

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[3] Hydrocodone bitartrate, a salt of hydrocodone, is used to deliver hydrocodone to the body. '760 patent, col. 13, ll. 13–15; *see Arnold Partnership v. Dudas*, 362 F.3d 1338, 1339 (Fed. Cir. 2004); U.S. Pat. No. 8,808,740, col. 19, ll. 3–4; JTX13, at 25.

patients with mild or moderate hepatic impairment relative to patients without hepatic impairment, or by reference to particular pharmacokinetic parameters that reflect the similarity in the results of administering the claimed formulations to persons with and without hepatic impairment.

The parties refer to the asserted claims as falling into two groups: the two-step (or "non-adjustment") claims and the one-step (or "pharmacokinetic-only") claims. The two-step non-adjustment claims (claims 1–4 and 11 of the '760 patent) include that "the starting dose [for a patient with mild or moderate hepatic impairment] is not adjusted relative to a patient without hepatic impairment." Those claims contain two steps: a physician prescribes a starting dose that is not adjusted, and a patient self-administers that starting dose. The one-step pharmacokinetic claims (claims 12, 17, and 19 of the '760 patent and claim 1 of the '499 patent) do not contain a "non-adjustment" limitation, but instead provide for a release profile of hydrocodone that either results in certain defined pharmacokinetic values in patients with mild or moderate hepatic impairment, or results in pharmacokinetic values that do not deviate by more than a certain percentage amount from the values that the same dosage unit would produce in a patient without hepatic impairment. The method recited in the one-step claims, as construed, requires only that a patient self-administer an oral dosage unit that meets those pharmacokinetic parameters.[4]

An example of the two-step claims is claim 1 of the '760 patent, which provides as follows:

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[4] Judge Sleet construed the term "administering" in each of the asserted claims to mean "delivering into the body" and not to include a physician's act of prescribing a drug to a patient. Dkt. No. 69, at 1–2 & n.1. That construction has been applied throughout the subsequent proceedings in this case.

> 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.

An example of the one-step claims is claim 1 of the '499 patent, which provides as follows:

> A method of treating pain in a patient having mild or moderate haptic 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:
>
> does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%; and
>
> does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%.

All nine claims recite a method of treating pain in a patient having mild or moderate hepatic impairment, and all nine recite a patient administering an oral dosage unit of hydrocodone bitartrate comprising an extended-release formulation. Broken out by claim, the functional limitations of each of the asserted claims provide as follows:

- Claim 1 of the '760 patent adds the limitation: "wherein the starting dose is not adjusted relative to a patient without hepatic impairment."
- Claims 2 and 3 of the '760 patent depend from claim 1 and add the limitation that the dosage unit provides a release profile that does not increase average hydrocodone $AUC_{0\text{-}inf}$ by more than certain percentage amounts in subjects suffering from mild or

moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment.[5]

- Claim 4 of the '760 patent depends from claim 1 and adds the limitation that the dosage unit provides a release profile that does not increase average hydrocodone C_{max} by more than certain percentage amounts in subjects suffering from mild or moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment.[6]
- Claim 11 of the '760 patent depends from claims 1 and 9 and adds limitations to claim 1 that the dosage unit provides a release profile of hydrocodone such that the average hydrocodone $AUC_{0\text{-}inf}$ per 20 milligrams of hydrocodone bitartrate falls in particular ranges for persons not suffering from renal or hepatic impairment, for persons suffering from mild hepatic impairment, and for persons suffering from moderate hepatic impairment.
- Claim 12 of the '760 patent contains the same limitations as claims 1, 3, and 4, except that it does not require that the "starting dose is not adjusted relative to a patient without hepatic impairment."
- Claims 17 and 19 of the '760 patent depend from claim 12 and add limitations that the dosage unit provides a release profile for hydrocodone such that the average

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[5] "$AUC_{0\text{-}inf}$" means "area under the curve," which is a way of measuring the total amount of the active drug in a subject's system over a period of time from administration ("0") to the time that the drug is no longer present in the subject's body ("infinity"). '760 patent, col. 11, ll. 12–23.

[6] "C_{max}" refers to the maximum observed concentration level of the active drug in the subject's system following administration of the drug. '760 patent, col. 11, line 63, to col. 12, line 5.

hydrocodone $AUC_{0\text{-}inf}$ per 20 milligrams of hydrocodone bitartrate falls in particular ranges for persons not suffering from renal or hepatic impairment, for persons suffering from mild hepatic impairment, and for persons suffering from moderate hepatic impairment.

- Claim 1 of the ’499 patent contains the same limitations that are common to all nine asserted claims and adds the limitations found in claims 2 and 3 of the ’760 patent regarding the dosage unit providing a release profile that does not increase average hydrocodone $AUC_{0\text{-}inf}$ by more than certain percentage amounts in subjects suffering from mild or moderate hepatic impairment, relative to subjects not suffering from renal or hepatic impairment.

6. At trial, Pernix sought to show that Alvogen induced infringement of the asserted claims. As to the two-step claims, Pernix’s theory was that by marketing its generic product, Alvogen would infringe because (1) patients would administer the drug to themselves when taking the oral dosage prescribed by their physicians; (2) physicians would not adjust the starting dose of the drug when prescribing it to patients with mild or moderate hepatic impairment; (3) physicians and patients would engage in joint direct infringement because the physicians would direct the patients to take the drug and would condition the patients’ continued treatment on their compliance with the physicians’ directions; and (4) Alvogen would be liable for induced infringement, because it would encourage physicians to direct patients with hepatic impairment to take the same dose that would be administered to patients without hepatic impairment. As to the one-step claims, Pernix’s theory was that by marketing its generic product, Alvogen would be liable for induced infringement, because it would induce patients to commit direct

infringement by administering the drug to themselves, thereby producing the pharmacokinetic results recited in the claims.

Alvogen disputed various aspects of Pernix's infringement theory, and raised three defenses and counterclaims at trial. First, it contended that the Devane patent application anticipated all the asserted claims. Second, it contended that the asserted claims were invalid for obviousness based on various references, including Devane; a 2010 published patent application to Jain; and various products that were on the market as of the priority date of the Pernix patents, as well as prior art publications that addressed the issue of treating hepatically impaired patients with opioids. Finally, Alvogen contended that the asserted claims of the two Pernix patents were much broader than the disclosures in the common specification, and thus the claims were invalid for lacking adequate written description support in the specification.

The following findings of fact and conclusions of law address each of those issues.

DISCUSSION

I. Infringement

Pernix argues that Alvogen is liable for infringement under section 271(e)(2)(A) based on Alvogen's submission of an ANDA to the FDA for a drug the use of which is claimed in the '760 and '499 patents. In the "artificial infringement" environment of the Hatch-Waxman Act, Pernix must show by a preponderance of the evidence that Alvogen would either directly or indirectly infringe the asserted patents if Alvogen's proposed product were marketed. *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018). At trial, Pernix did not attempt to show that Alvogen would directly infringe any of the asserted claims, all of which require at least one step to be performed by a patient or physician, and the Court

granted Alvogen's Rule 52 motion of no direct infringement at the conclusion of the trial. Trial Tr. 809:4–25. Instead, Pernix relies on a theory of indirect infringement.

In order to establish that Alvogen indirectly infringes the asserted claims, Pernix must first prove that all the steps of the claimed methods would be performed by or be attributable to a single entity. *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (en banc). For the one-step claims, Pernix's theory is that patients with mild or moderate hepatic impairment would directly infringe the asserted claims by taking Alvogen's product at a dosage level that would produce the pharmacokinetic results set forth in the claims.

For the two-step claims, in which no single actor performs all the steps of the claimed methods, Pernix must show that joint direct infringement would occur, which requires that "the acts of one are attributable to the other such that a single entity is responsible for the infringement." *Id.* To establish joint direct infringement, a plaintiff must show either that the parties will be engaged in a joint enterprise or that one party will direct and control the infringing activity of the other. *Id.; see also Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017) (*Lilly–Teva*). Pernix does not rely on the "joint enterprise" theory of liability to prove joint direct infringement. Instead, Pernix's theory is that physicians would direct and control their patients' administration of Alvogen's proposed product, thereby establishing joint direct infringement of the two-step claims.

For both the one- and two-step claims, Pernix must next show that Alvogen is liable for induced infringement. To do so, Pernix must show that Alvogen would induce a party or parties to directly infringe the asserted claims. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2117 (2014); *Vanda*, 887 F.3d at 1130. To make that showing, Pernix must establish that Alvogen specifically intends "to encourage another's infringement and not merely that

[Alvogen will have] knowledge of the acts alleged to constitute inducement." *Vanda*, 887 F.3d at 1129 (quoting *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc in relevant part)).

Based on the evidence at trial, as discussed in detail below, the Court finds (in part I.A) that patients with mild or moderate hepatic impairment taking Alvogen's product in accordance with the directions in Alvogen's proposed label would directly infringe the one-step claims: Physicians would prescribe a non-adjusted dose of Alvogen's product for patients with mild or moderate hepatic impairment, and the patients would self-administer the dosages as prescribed and directed by their physicians. The Court finds (in part I.B) that physicians and patients would jointly infringe the two-step claims, because the patients would self-administer the drugs pursuant to the physicians' direction and control. Finally, the Court finds (in part I.C) that Alvogen's label would induce infringement of both the one-step and two-step claims.

A. Direct Infringement: The Court's Findings

The Court makes the following findings with regard to the issue of direct infringement:

1. Alvogen's proposed label states that Alvogen's product is a hydrocodone bitartrate extended-release capsule that is indicated for the management of pain; the label specifies that the product contains hydrocodone bitartrate as the only active ingredient. JTX6, at 1, 4, 19; *see* Trial Tr. 24:10–17, 160:10–12, 160:18–23. It is undisputed that the pharmacokinetic parameters of Alvogen's proposed product exhibit the ranges recited in the asserted claims. JTX6, at 21; *see* Trial Tr. 34:12–37:14, 160:24–161:5. As such, Alvogen's proposed product satisfies both the pharmacokinetic limitations and the limitation that requires "an oral dosage unit having hydrocodone bitartrate as the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate."

2. Pernix's infringement expert, Dr. Jeffrey Gudin, testified that patients, including patients having mild or moderate hepatic impairment, would self-administer Alvogen's proposed product to treat their pain. Trial Tr. 14:10–15:1, 16:19–17:9, 24:18–26:22, 82:1–17. Alvogen's expert did not disagree. Trial Tr. 110:6–18, 160:10–17. The Court therefore finds that patients having mild or moderate hepatic impairment would self-administer a starting dose of Alvogen's proposed product, and that those patients would therefore infringe the one-step claims.

3. As for prescribing physicians, Dr. Gudin testified that at least some physicians—upon reading the statement in Alvogen's proposed label that "[n]o adjustment in starting dose with Hydrocodone Bitartrate Extended Release Capsules is required in patients with mild or moderate hepatic impairment," JTX6, at 1, 7, 17—would not adjust the starting dose for patients with mild or moderate hepatic impairment relative to a patient without hepatic impairment. Trial Tr. 21:24–23, 26:25–28:1, 31:20–32:8. Alvogen's expert did not dispute that physicians would directly infringe the "starting dose is not adjusted" step when prescribing a starting dose of Alvogen's product that was not adjusted for patients with mild or moderate hepatic impairment. *See* Trial Tr. 110:6–18.

Based on Dr. Gudin's testimony, the Court concludes that at least some physicians, upon reviewing Alvogen's proposed label, would prescribe a dose of Alvogen's product to a patient with mild or moderate hepatic impairment when initiating treatment that is not reduced due to that hepatic impairment relative to the dose that the physician would prescribe to a patient without hepatic impairment when initiating treatment. The Court also concludes, as described above, that some hepatically impaired patients would take a non-reduced dose of Alvogen's product, which satisfies those limitations of the two-step claims of the '760 and '499 patents.

B. Joint Infringement

1. Legal Standard

In order to prove direct infringement of the two-step claims, Pernix must show that a physician would prescribe an unadjusted starting dose of Alvogen's proposed product for a patient with mild or moderate hepatic impairment, and that the patient would self-administer that unadjusted dose. In addition, Pernix must show that patient and the physician jointly infringe, as that term is used in patent law. Joint infringement occurs when one entity "directs or controls" the other's performance, or when the actors "form a joint enterprise." *Lilly–Teva*, 845 F.3d at 1364 (quoting *Akamai*, 797 F.3d at 1022). Pernix did not pursue a joint enterprise theory, but instead seeks to prove that physicians would direct and control their patients' administration of Alvogen's proposed hydrocodone product. Direction and control can be shown where an actor "(1) '*conditions* participation in an activity or receipt of a benefit' upon others' performance of one or more steps of a patented method, and (2) '*establishes the manner or timing* of that performance.'" *Id.* at 1365 (quoting *Akamai*, 797 F.3d at 1023).

The parties disagree about the level of conditioning necessary to satisfy the *Akamai* test. Alvogen argues that "the alleged condition must be categorical to establish joint infringement." Dkt. No. 243, at 35. Pernix disagrees, arguing that the requirements of joint infringement can be satisfied even if the conditioning is not absolute. Dkt. No. 244, at 35.

The case law does not support Alvogen's strict categorical conditioning requirement. Alvogen relies on the Federal Circuit's opinions in *Akamai*, *Lilly–Teva*, and *Travel Sentry, Inc. v. Tropp*, 877 F.3d 1370 (Fed. Cir. 2017), but a close examination of those cases shows that they do not erect the rigid standard that Alvogen suggests.

In *Akamai*, Limelight was accused of infringing a patent on methods of hosting content and delivering it over the Internet. The evidence showed that Limelight performed several steps of the claimed methods, but that Limelight's customers performed at least one of the steps, in which the customers "tagged" and "served" the content to be hosted and delivered by Limelight's content delivery network. The en banc Federal Circuit held that substantial evidence supported the jury's determination that Limelight directed or controlled its customers' performance of the remaining method steps. The court observed that "if Limelight's customers wish to use Limelight's product, they must tag and serve content." *Akamai*, 797 F.3d at 1024. That statement was based on evidence that "Limelight requires all of its customers to sign a standard contract" that "delineates the steps customers must perform if they use the Limelight service." *Id.* The Federal Circuit did not recite any evidence that Limelight categorically enforced the contract, but found conditioning based only on the contractual promise of the user.

Lilly–Teva, which addressed joint infringement of a method of treatment claim in the Hatch-Waxman context, is even more directly applicable here. In *Lilly–Teva*, the issue of joint infringement was presented because the patient would self-administer folic acid, after which the physician would administer pemetrexed, a drug used to treat certain types of mesothelioma and lung cancer. The opinion quoted expert testimony that "taking folic acid was 'an absolute requirement' before pemetrexed treatment because 'it wouldn't be safe to take the drug without the vitamin supplementation. . . . [I]t must be done this way." 845 F.3d at 1366 (alterations in original). Another expert testified that it was "standard practice" that a patient "must have taken their required folic acid in order to have the pemetrexed administered." *Id.* Based on the facts of the *Lilly–Teva* case, Alvogen argues that categorical conditioning is required in order to find joint infringement. *See* Dkt. No. 243, at 35.

Alvogen reads the *Lilly–Teva* opinion too restrictively. As the Federal Circuit explained in that case, the legal standard requires that a physician "cross the line from merely guiding or instructing patients . . . to conditioning." 845 F.3d at 1366. After reciting the evidence, the court concluded that "a physician, *in his or her discretion, need not provide* pemetrexed treatment based on the patient's failure to perform the step of folic acid administration." *Id.* (emphasis added). The defendants in that case argued that the proof of joint infringement was insufficient because the record lacked evidence that physicians "'verify compliance' with their instructions" or "'threaten' denial of pemetrexed treatment." *Id.* The court, however, rejected those arguments. Instead, the court stated that conditioning "does not necessarily require double-checking another's performance or making threats." *Id.* The court also rejected the defendants' argument that conditioning requires a legal obligation or unavoidable technological prerequisites to participation, which were the facts at issue in *Akamai*. *Id.* at 1366–67. The court explained that the contract in *Akamai* "was not significant for imposing potential civil liability but for 'delineat[ing] the steps' that customers would have to perform 'if [they] wish[ed] to use [the defendant's] product.' And we did not focus on whether a customer's failure to perform certain steps might have made it technologically impossible for other steps to occur." *Id.* at 1367 n.5 (alterations in original) (citation omitted) (quoting *Akamai*, 797 F.3d at 1024).

Finally, Alvogen relies on *Travel Sentry*, which involved a claim of joint infringement of a patent directed to an improvement in airline luggage inspection systems. The evidence showed that the accused infringer, Travel Sentry, performed certain steps of the patented method, and that agents of the federal Transportation Security Administration ("TSA") performed the final two steps. The Federal Circuit held that the evidence was sufficient for a reasonable jury to conclude that the TSA agents' performance of the final two claim steps was attributable to

Travel Sentry. The Court explained that "whatever benefits flow to TSA . . . can only be realized if TSA performs the final two claim steps." 877 F.3d at 1382–83. The court, moreover, reaffirmed the conditioning standard articulated in *Lilly–Teva*, stating that conditioning does not require the imposition of a "legal obligation" or a "technological prerequisite," nor does it require verification of compliance or a threat of denial of treatment. 877 F.3d at 1380 (quoting *Lilly–Teva*, 845 F.3d at 1366–67).

Based on the applicable Federal Circuit precedent, the Court holds that double-checking and threat-making are not required to establish that a benefit has been conditioned upon performance of a method step. Direction or control can be shown where an actor crosses the line from merely guiding or instructing to conditioning, even if the conditioning is not categorical in nature.

2. The Court's Findings

1. Pernix argues, and Alvogen does not dispute, that a physician would establish the dosage and frequency of a patient's administration of a drug such as Alvogen's proposed opioid product. *See* Trial Tr. 118:24–120:14. The undisputed evidence shows that (1) Alvogen's label instructs physicians to dose the product on a particular schedule, JTX6, at 4–8; Trial Tr. 52:7–18; (2) physicians would give dosing instructions to their patients that establish the frequency of administration and dosage amounts, Trial Tr. 148:10–149:17; and (3) Alvogen's label directs patients to use the product exactly as prescribed, JTX6, at 25; Trial Tr. 41:5–12. Nothing more is required to show the manner or timing of performance, *see Lilly–Teva*, 845 F.3d at 1367–68, and the Court therefore finds that physicians would establish the manner or timing of their patients' administration of Alvogen's proposed product.

2. The dispute between the parties concerns the extent to which physicians would condition treatment on the patient's self-administering Alvogen's proposed product. The Court finds that Pernix has proved by a preponderance of the evidence that physicians would condition a benefit—that is, the prescription of a starting dose or subsequent prescriptions for Alvogen's proposed product—upon their patients' self-administration of the drug in accordance with the physicians' instructions.

3. Pernix's expert Dr. Gudin is a palliative care physician with extensive experience in treating patients with chronic pain. Trial Tr. 7:19–24, 9:12–24. At trial, he explained that hydrocodone, as a Schedule II drug, is subject to strict prescribing requirements, including a prohibition on automatic refills. Trial Tr. 38:10–40:11; PTX30, at 23. As a result, according to Dr. Gudin, each individual prescription must be written by the clinician and must include specific instructions for use. Trial Tr. 40:1–11. Alvogen's expert, Dr. William Schmidt, agreed that it is important for a physician, when prescribing an opioid, to counsel the patient to follow the physician's instructions. Trial Tr. 150:6–12.

4. Dr. Gudin explained that the standard of care in pain management practice requires physicians who prescribe opioids to take steps to monitor their patients to ensure they are taking the drugs as directed. He testified, for example, that a doctor can confirm compliance with the patient's family or caregiver and can check the state's prescription drug monitoring database to confirm that the patient is filling the prescriptions as directed. Trial Tr. 51:2–13. In addition, Dr. Gudin explained that it has become the standard of care to do toxicology testing both before the physician writes a patient's first prescription and then at random intervals during treatment. Trial Tr. 51:14–23.

5. Dr. Gudin also testified about the use of physician-patient agreements, which are signed by both the physician and the patient and which "lay out the roles, rules and responsibilities of patients and physicians when it comes to prescribing the controlled substances." Trial Tr. 42:2–4. Such physician-patient agreements often require the patients to agree to keep the medication in a secure location, to take the medication exactly as prescribed, and not to alter the dose or frequency of administration. Trial Tr. 42:5–11. Dr. Gudin explained that the physician-patient agreements often state that the patient's continued treatment is conditioned on the patient's following the agreement. Trial Tr. 42:11–15. According to Dr. Gudin, "most, if not all, state medical boards mandate that clinicians use" such agreements, and some states, including New Jersey and Florida, require them. Trial Tr. 41:18–24, 44:16–22, 131:1–132:9; PTX81.

6. A number of sample agreements were introduced into evidence. All of them condition continued receipt of an opioid on compliance with the physician's administration instructions. For example, Dr. Gudin introduced the agreement that he uses in his medical practice, which includes the statement: "I agree to take this medication as prescribed, and not to change the amount or frequency of the medication without discussing it with the prescribing doctor. Running out early, needing early refills, escalating doses without permission, and losing prescriptions may be signs of misuse of the medication, and may be reasons for the doctor to discontinue prescribing to me." JTX22, at 1; Trial Tr. 45:10–13, 121:15–19.

7. Pernix introduced a template for controlled substances therapy for chronic pain treatment developed by the American Academy of Pain Medicine. The template states that "[b]ecause these medications have the potential for abuse or diversion . . . , strict accountability is necessary for both medical safety and legal reasons." The template requires the patient to

"take all medications exactly as prescribed" and states that "failure to adhere to these policies will be considered noncompliance and may result in cessation of opioid prescribing by your physician and possible dismissal from this clinic." PTX37, at 1–3; *see also* PTX82, at 1–2.

8. Pernix also submitted into evidence two template agreements distributed by the National Institute of Health's National Institute on Drug Abuse. The first requires that the patient agree to "take my medication as instructed and not change the way I take it without first talking to the doctor or other member of the treatment team," and that the patient acknowledge that "I may lose my right to treatment in this office if I break any part of this agreement." PTX39, at 2–3. The other requires that the patient agree to "not increase my medicine until I speak with my doctor or nurse," and acknowledge that "[i]f I break any of the rules, or if my doctor decides that this medicine is hurting me more than helping me, this medicine may be stopped by my doctor in a safe way." PTX39, at 4–5.

9. The Court finds that Dr. Gudin's testimony and the prevalence of physician-patient agreements governing the use of opioids establishes that physicians frequently establish strict conditions for initial prescriptions and continued opioid treatments, and that many physicians would do so with respect to Alvogen's proposed product. *See, e.g.*, Trial Tr. 40:12–16 (Dr. Gudin testifying that the patient's agreement to take the drug as prescribed is "[a]bsolutely" a requirement for the patient to receive treatment), 48:16–49:7 (Dr. Gudin explaining that he has discontinued treatment for non-compliant patients "[t]housands of times"). The evidence thus shows that physicians do not merely "guid[e] or instruct[]" their patients to follow the prescribed dosing regimen for such opioids, but that they condition both the prescription of the starting dose and any continued treatment on the patient's agreement to follow the physician's dosage plan. As the Federal Circuit has explained, a physician need not verify compliance or issue threats to

satisfy the "conditioning" requirement, *Lilly–Teva*, 845 F.3d at 1366, although the evidence at trial shows that physicians would frequently do both when prescribing an opioid such as Alvogen's proposed product.

10. The Court finds Alvogen's arguments to the contrary to be unpersuasive. First, Alvogen argues that Dr. Gudin's testimony proved only that physicians condition treatment on the patients' promise to abide by the prescribing directions. Dkt. No. 243, at 34. The Court disagrees with that characterization of both the evidence and the applicable legal standard. *Lilly–Teva* made clear that conditioning "does not necessarily require double-checking another's performance or making threats." 845 F.3d at 1366. As long as the conduct goes beyond merely "guiding or instructing," the conditioning requirement is satisfied. The evidence at trial shows that the governing standard is satisfied here.

11. Alvogen argues that Pernix's evidence that physicians "may" sometimes discontinue treatment is insufficient to satisfy the "conditions" test for joint infringement. Dkt. No. 243, at 34–37. Alvogen expert Dr. Keith Allen Candiotti testified that patients do not always follow their physicians' dosing instructions precisely. Trial Tr. 118:24–122:9. He explained that "patients often deviate from prescribing instructions for, often for very good reason[s]." Trial Tr. 119:14–17; *see also* Trial Tr. 120:1–25 (Dr. Candiotti testifying that patients may, for example, underdose, and "[t]here are a lot of reasons and some medical reasons as well why people vary [from] their pattern of medicine administration."). He emphasized that the physician-patient agreements referred to by Dr. Gudin state that evidence of misuse "may" lead to the termination of their treatment, but do not categorically require it. Trial Tr. 121:23–122:9.

That argument relies on Alvogen's position regarding the proper legal standard for "conditioning," which, as discussed above, is incorrect. Dr. Gudin explained that the agreements

include the word "may" because "there are circumstances . . . where patients have a valid excuse . . . for being non-compliant," such as when a patient loses his medicine, so there are instances in which a physician may elect to excuse non-compliance. Trial Tr. 47:18–48:15. But providing for such exceptions does not alter the fact that, in the absence of a valid excuse, physicians will typically discontinue treatment if the patient fails to properly self-administer the drug. Trial Tr. 65:5–9 (Dr. Gudin testifying that "we redirect them to be compliant, or we discontinue their therapy.").

12. Finally, Alvogen argues that Pernix's "conditions" theory was "uniformly presented as physicians conditioning treatment on the patient's administering the drug 'as prescribed' or 'exactly as prescribed.'" Dkt. No. 248, at 15 (quoting Dkt. No. 219, ex. 13 ¶ 59). Alvogen argues that Pernix has improperly raised a "new and previously undisclosed theory that physicians will condition treatment upon the patient's self-administering Alvogen's proposed product *in any manner*, regardless of whether that administration is compliant with the physician's prescribing instructions." Dkt. No. 248, at 16. The Court disagrees. Dr. Gudin credibly testified that a physician would condition a prescription for Alvogen's proposed product upon proper administration in accordance with the physician's instructions. *See*, *e.g.*, Trial Tr. 41:17–42:15. And to the extent that Alvogen argues that the conditioning must be categorical—that is, that a physician must require perfect compliance with the dosing instructions—Alvogen's position has been rejected by the Federal Circuit.

Based on the findings set forth above, the Court concludes that Pernix has proved by a preponderance of the evidence that physicians would condition receipt of a benefit—the initial or subsequent prescription of Alvogen's proposed product—upon the patient's performance of the self-administration limitation, and that the physician establishes the manner and timing of that

administration. The Court therefore concludes that Pernix has proved by a preponderance of the evidence that the use of an unadjusted starting dose of Alvogen's proposed product for persons with mild or moderate hepatic impairment would result in joint infringement by physicians and their patients of the two-step claims of '760 patent.

B. Inducement

Having found that patients would directly infringe the one-step claims, and that physicians and patients would jointly infringe the two-step claims, the Court now turns to the question whether Alvogen's label would induce that infringement. The Court finds that it would.

1. Legal Standard

Pernix must show "specific intent and action to induce infringement." *Lilly–Teva*, 845 F.3d at 1368 (quoting *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015)). In the context of patent infringement litigation involving pharmaceuticals, the Federal Circuit has held that "the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent." *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011).

In a Hatch-Waxman Act case in which the act of infringement under section 271(e)(2)(A) consists of the filing of an ANDA for a method of treatment protected by a patent, "[t]he pertinent question is whether the proposed label [of the ANDA product] instructs users to perform the patented method." *AstraZeneca*, 633 F.3d at 1060. In that setting, the Federal Circuit has explained, "[t]he label must encourage, recommend, or promote infringement." *Takeda*, 785 F.3d at 631. Evidence that a proposed label would "inevitably lead some consumers to practice the claimed method" can suffice to support a finding of specific intent to induce infringement. *AstraZeneca*, 633 F.3d at 1060; *Novartis Pharm. Corp. v. Breckenridge Pharm.*,

Inc., 248 F. Supp. 3d 578, 585 (D. Del. 2017). Put another way, the question is whether the instructions in the label "teach an infringing use . . . such that we are willing to infer from those instructions an affirmative intent to infringe the patent." *Takeda*, 785 F.3d at 631 (emphasis omitted) (quoting *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009)); *Rhodes Pharm. L.P. v. Indivior, Inc.*, No. 16-cv-1308, 2018 WL 326405, at *7 (D. Del. Jan. 8, 2018).

2. The Court's Findings: The One-Step Claims

As discussed above, it is undisputed that Alvogen's draft label directs the use of the product for the treatment of pain and that Alvogen's proposed product satisfies the pharmacokinetic limitations of the one-step claims. The only remaining question bearing on inducement is whether Alvogen's proposed label would encourage a patient with mild or moderate hepatic impairment to use Alvogen's proposed product to inhibit pain. The Court makes the following findings directed to that issue:

1. The evidence at trial established that a physician, when prescribing an opioid to treat pain in a patient with hepatic impairment, would prefer a drug that does not require a dose adjustment relative to the dose for a normal patient. Dr. Gudin explained that a physician would be cautious in prescribing an opioid for a patient with hepatic impairment, and that a physician would therefore rely on dosing recommendations and pharmacokinetic data included in the product's label. Trial Tr. 12:22–14:9, 24:18–26:22.

2. Alvogen's draft label contains dosing instructions and clinical data that support the use of the product in patients with mild or moderate hepatic impairment. JTX6, at 1 (summary of treatment of patients with mild, moderate, and severe hepatic impairment); JTX6, at 17 ("Hepatic Impairment" section); JTX6, at 21 ("Pharmacokinetics" section).

3. Dr. Gudin testified that a physician would look to the pharmacokinetics section of a drug's label to understand "how the product behaves . . . inside the patient's body," and that "it's an important section that physicians often reference." Trial Tr. 26:6–13. Dr. Gudin also explained that physicians generally follow the instructions provided on a drug's label because "it's important to understand where to use the product and how to appropriately use the product." Trial Tr. 22:12–21. For those reasons, Dr. Gudin concluded that Alvogen's label would encourage a physician to use Alvogen's product in treating patients with mild or moderate hepatic impairment. Trial Tr. 26:14–22.

4. Alvogen's expert Dr. Schmidt agreed that a physician would be encouraged to prescribe Alvogen's proposed product to patients with mild or moderate hepatic impairment. He testified that "if I were selecting or recommending to a physician who [was] treating a patient with mild or moderate hepatic insufficiency, dysfunction, I would recommend one of the products where you don't need to make dose adjustments." Trial Tr. 253:10–14. That evidence undercuts the testimony of Alvogen's infringement expert, Dr. Candiotti, who characterized the statements in Alvogen's draft label as merely "data statements" and said that he does not "find it as an endorsement at all or promoting use. It's simply stating data without commentary as it were." Trial Tr. 123:17–24. The Court does not find Dr. Candiotti's conclusory testimony on that point to be credible. To the contrary, the Court finds that the several references to patients with mild or moderate hepatic impairment in Alvogen's draft label would be understood by a physician as a recommendation that the product can be prescribed to such patients and that Alvogen's product would allow a patient with mild or moderate hepatic impairment to obtain the analgesic benefits of a full dose of hydrocodone without running the risk of overdosing that some opioid formulations might present for hepatically impaired patients.

5. Alvogen's label also instructs patients, including patients who suffer from mild or moderate hepatic impairment, to administer Alvogen's product for the treatment of pain, and to do so as prescribed by their physicians. Alvogen's draft label includes a Medication Guide, directed at patients, that describes using Alvogen's product to treat pain and instructs patients to take the product "exactly as prescribed by your healthcare provider," which includes taking the starting dose as prescribed. JTX6, at 27.

6. Based on the foregoing findings, the Court finds that Alvogen's draft label would induce physicians to prescribe Alvogen's product to patients with mild or moderate hepatic impairment and would induce those patients to self-administer Alvogen's proposed product as directed. The Court therefore finds that Alvogen induces infringement of the one-step claims.

3. The Court's Findings: The Two-Step Claims

The two-step claims contain the additional limitation that "the starting dose is not adjusted relative to a patient without hepatic impairment." The Court makes the following findings directed to those claims:

1. Alvogen's draft label states, three times, that "No adjustment in starting dose . . . is required in patients with mild or moderate hepatic impairment." JTX6, at 1, 7, 17. It also provides pharmacokinetic data as to the effect of the drug on patients with hepatic impairment. JTX6, at 21. Dr. Gudin explained that the pharmacokinetic information "gives the detailed information of the performance of this drug in patients with mild to moderate hepatic impairment," Trial Tr. 25:22–24, and Dr. Candiotti admitted that the pharmacokinetic data is "useful information that a physician would consider when prescribing medication," Trial Tr. 145:8–9.

2. The evidence at trial showed that dosing instructions in labels can be crucial information to a prescribing physician. Dr. Gudin testified that "[o]ne of the challenges we face as clinicians is finding the right dose of the medicine, of an effective medicine as quickly as possible." Trial Tr. 725:1–3. Dr. Gudin explained that both overdosing and underdosing can be a problem, Trial Tr. 724:19–725:22, and that particularly in special populations such as patients with hepatic impairment, "[t]he dosage selection is as important as anything else," Trial Tr. 747:16–21. A dosing instruction that suggests that a starting dose adjustment is "not required" would therefore be significant to the physician. Trial Tr. 798:24–799:9. Similarly, Dr. Schmidt testified that "if you don't have to make dose adjustments, it makes life easier for a physician," Trial Tr. 236:23–237:5, and that he would recommend that a physician treating a patient with hepatic impairment use an opioid product for which a dose adjustment is not required, Trial Tr. 253:10–14. Dr. Candiotti's statement that the information in Alvogen's draft label is useful information but does not constitute an endorsement or promotion of unadjusted doses for patients with hepatic impairment, Trial Tr. 123:17–24, is unpersuasive in light of the other evidence at trial, including the proposed label itself and the testimony of Drs. Gudin and Schmidt.

3. In response to Alvogen's suggestion that the language "is not required" in Alvogen's draft label does not "encourage, recommend, or promote infringement," *see* Dkt. No. 243, at 39–40, Dr. Gudin explained that a categorical instruction on a product label—e.g., "do not adjust the starting dose"—would be ill-advised because a physician should retain some discretion to modify the dose in his or her judgment: "[I]f it says do not adjust the starting dose, clinicians would not adjust the starting dose. And there are many scenarios in this patient population where you want to adjust the starting dose." Trial Tr. 27:20–24. The Federal Circuit has made clear that all that is required is that "the product labeling . . . would inevitably lead *some*

physicians to infringe." *Lilly–Teva*, 845 F.3d at 1369 (emphasis added). Alvogen's argument is unavailing, as it demands that *all* physicians would *never* adjust the dose to find inducement, a standard that is too restrictive.

Based on the findings set forth above, viewed in light of the governing case law, the Court concludes that the language in Alvogen's draft label is sufficient to establish inducement. In *AstraZeneca LP v. Apotex, Inc.*, the proposed label "implicitly instructed users to administer the generic drug once daily," by including statements such as "[i]n all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved," and "[o]nce the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose." 633 F.3d at 1057 (alterations in original). Similarly here, the trial testimony from Dr. Gudin and Dr. Schmidt shows that a physician would be encouraged not to adjust a starting dose for a patient with mild or moderate hepatic impairment unless instructed otherwise, and an instruction that "no adjustment in starting dose . . . is required" would promote the infringing use. This is not a case in which the label provides only "'vague' instructions that require one to 'look outside the label to understand the alleged implicit encouragement," which, without more, would not be sufficient to induce infringement." *Lilly–Teva*, 845 F.3d at 1369 (quoting *Takeda*, 785 F.3d at 632, 634).

Alvogen relies heavily on two District of New Jersey cases in which inducement was not found. In *Acorda Therapeutics Inc. v. Apotex Inc.*, No. 07-4937, 2011 WL 4074116 (D.N.J. Sept. 6, 2011), *aff'd* 476 F. App'x 746 (Fed. Cir. 2012), an asserted method patent concerned the administration of a particular drug with food. The proposed label directed physicians to "the pharmacokinetics section of the label for information on the *differences* between the fed and fasted states with capsules and tablets," and stated that physicians should be "thoroughly familiar

with the complex effects of food" on the drug. *Id.* at *17. However, the court explained that none of the label's statements "direct any action on the part of any physician, but merely call attention to the pharmacokinetics section." *Id.* In addition, the label did not state "a preference of one over the other or a direction to use the capsule form in the fed state." *Id.* For that reason, the court found that the label did not induce infringement. Similarly, in *Shire LLC v. Amneal Pharm., LLC*, No. 11-3781, 2014 WL 2861430 (D.N.J. June 23, 2014), some of the asserted claims recited a method of treatment that comprised administering a drug to patients "with intake of food by said subject." *Id.* at *4. The proposed label stated that the ANDA product may be taken "with or without food." The district court concluded that such a neutral formulation "cannot be reasonably understood to be an instruction to engage in an infringing use" because "it is indifferent to which option is selected." *Id.* at *5.

Unlike the labels at issue in *Acorda* and *Shire*, Alvogen's label goes beyond merely providing pharmacokinetic data or neutral information. Rather, the label provides both data and instructions on how to prescribe a starting dose in patients with mild or moderate hepatic impairment. Based on the evidence at trial, the Court finds that the contents of that label would encourage a physician to prescribe to patients with mild or moderate hepatic impairment a starting dose of Alvogen's proposed product that is not adjusted relative to a starting dose prescribed to a patient without hepatic impairment.

Accordingly, the Court finds that Pernix has proved by a preponderance of the evidence that Alvogen's draft label would induce physicians to directly infringe the non-adjustment limitation of the two-step claims of the '760 patent.

II. Anticipation

To anticipate a patent claim, a single prior art reference must contain all the limitations of the asserted claim, either explicitly or inherently. *See In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007). In order to establish inherent anticipation, any missing limitations must necessarily be present in the prior art reference, not merely probably or possibly present. *See Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002); *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268–69 (Fed. Cir. 1991). If the prior art reference "necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (quoting *In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986)). In general, "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Id.* Anticipation is a question of fact, subject to the court's application of the proper legal standards in making that factual determination. *See Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1067–68 (Fed. Cir. 2017); *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

Alvogen argues that all of the asserted claims are anticipated by the Devane reference. Devane is a published patent application entitled "Multiparticulate Modified Release Composition." It is directed to a controlled-release composition that provides both immediate and delayed release of the active ingredient or ingredients. JTX37 ¶ 26. Devane teaches that its "modified release composition" can be used with hydrocodone to provide continuous analgesia for up to 24 hours. JTX37 ¶ 70. It provides an example of a hydrocodone bitartrate modified-release composition with six possible immediate-release components and seven possible modified-release components. JTX37 ¶¶ 99–102.

Devane also describes the results of an in vivo study on patients immediately following bunionectomy surgery, in which one of those hydrocodone bitartrate formulations was used to treat the patients' post-operative pain.[7] The study was conducted to evaluate the safety, efficacy, and pharmacokinetic parameters of the hydrocodone formulation, and the Devane reference summarizes the results from that study. JTX37 ¶¶ 104–06. The study was conducted with 115 subjects, who were administered one of six products: an extended-release hydrocodone bitartrate formulation with 10, 20, 30 or 40 milligrams of active ingredient, a "matching active comparator," or a placebo. *Id.* The active comparator was described as containing 10 milligrams of hydrocodone and acetaminophen, and the trial testimony indicates that the comparator was Vicodin. Trial Tr. 256:12–14.

The Court finds (in part II.A) that Devane anticipates administering an oral dosage unit of extended-release hydrocodone bitartrate, and (in part II.B) that Devane inherently anticipates the pharmacokinetic limitations. However, the Court finds that Alvogen has failed to show by clear and convincing evidence that Devane discloses the limitations that recite treating patients with mild or moderate hepatic impairment (in part II.C) or administering a starting dose to such patients that is not adjusted relative to the starting dose prescribed to patients without hepatic impairment (in part II.D).

[7] Bunionectomy surgery, which involves realignment and reshaping of the large toe, can be very painful and frequently requires the use of powerful analgesia, such as provided by opioids, for three to five days following the surgery. Trial Tr. 187:12–17.

A. "Administering . . . [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"

The formulation disclosed in Devane's bunionectomy study is identical to the formulation disclosed in the asserted patents and contained in the product that has been commercialized by Pernix under the name Zohydro ER. Trial Tr. 368:2–369:6; '706 patent, col. 22, ll. 50–58. Devane claims a method for the treatment of pain comprising administering a therapeutically effective amount of a composition, such as hydrocodone, in a multiparticulate modified-release form. *See* JTX37, cl. 81. As such, there is no dispute that Devane discloses a method of treating pain by administering an extended-release hydrocodone bitartrate as the only active ingredient. Trial Tr. 184:13–186:25, 193:19–195:16; *see also* Trial Tr. 679:7–689:16 (Dr. Gudin's anticipation testimony, not disputing that Devane discloses administering an extended-release form of hydrocodone bitartrate, unaccompanied by any other active component).

B. Pharmacokinetic Limitations

Devane inherently anticipates the pharmacokinetic limitations of the asserted claims. The pharmacokinetic character of a particular compound is an inherent, necessarily present property of that compound that "adds nothing of patentable consequence" when claimed as a limitation. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011); *see also In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002) ("Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates."); *In re Omeprazole Patent Litig.*, 483 F.3d at 1373; *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963); *Cubist Pharm., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 659–60 (D. Del. 2014), *aff'd*, 805 F.3d 1112 (Fed. Cir. 2015).

Pernix's arguments to the contrary are unavailing. Dr. Gudin's conclusory testimony that "Devane does not disclose any of those [pharmacokinetic] limitations," Trial Tr. 688:25, addresses only express anticipation, not inherency, and is therefore unhelpful on the issue. Nor did Pernix argue in its post-trial brief or responsive brief that the pharmacokinetic limitations were not anticipated. *See* Dkt. No. 244, at 14–25; Dkt. No. 248, at 6–11.

When asked during closing argument whether Pernix conceded that the pharmacokinetic limitations are inherently anticipated, Pernix's counsel argued that Pernix was not making such a concession. Counsel then raised for the first time the argument that the claims recited pharmacokinetic parameters in relative terms, rather than in absolute numbers; that is, the claims recited that particular pharmacokinetic parameters are not increased more than a certain percentage in patients with mild or moderate hepatic impairment as compared to patients without hepatic impairment. Dkt. No. 254, at 92:17–93:4. The Court sees no reason why a pharmacokinetic parameter stated in relative numbers is any less inherent and necessarily present than such a parameter stated in absolute numbers, and Pernix's belated argument is not supported by any case law or trial testimony. The Court therefore finds that Devane inherently anticipates the pharmacokinetic limitations.

C. "Administering to the patient having mild or moderate hepatic impairment"

There is no dispute that Devane is silent as to the treatment of patients with hepatic impairment. The question, therefore, is whether Alvogen has shown by clear and convincing evidence that Devane inherently discloses the treatment of hepatically impaired patients. The Court finds that Alvogen has not met its burden on that issue.

In order to prove inherency, the patent challenger normally must show that the anticipating reference "necessarily functions in accordance with, or includes, the claimed

limitations." *In re Cruciferous Sprout Litig.*, 301 F.3d at 1349 (quoting *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999)). Because Devane is silent about treating patients with hepatic impairment, it cannot be said that treating patients with hepatic impairment "must necessarily" occur. *King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1274 (Fed. Cir. 2010). The evidence at trial that patients with hepatic impairment are also often treated for pain with opioids is not sufficient to establish that the treatment of patients with hepatic impairment was *necessarily* contemplated for Devane's formulation. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." (quoting *Cont'l Can Co. USA, Inc.*, 948 F.2d at 1269)); *see also Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376–79 (Fed. Cir. 2005) (narrow application of applying lotion to sunburned skin not inherently anticipated by broad application of applying lotion topically). Because Devane does not necessarily disclose treating patients with hepatic impairment, Alvogen fails to show inherent anticipation under its proposed legal framework.

An alternative method of showing inherent anticipation is to use the genus-species approach. Under that approach, "the issue of anticipation turns on whether the genus was of such a defined and limited class that one of ordinary skill in the art could 'at once envisage' each member of the genus." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012) (quoting *Lilly–Zenith*, 471 F.3d at 1376).[8]

[8] Citing Judge Schall's separate opinion in *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1352 (Fed. Cir. 2016) (Schall, J., dissenting-in-part), Alvogen argues that the genus-species framework is not the proper approach to the issue of anticipation by inherency for a

In order to find that a generic disclosure anticipates a species within a particular genus, the generic reference must identify the claimed species with "sufficient specificity"; that is, the reference must express "specific preferences" for one or more particular species or must disclose a genus that is sufficiently small that the disclosure of the genus effectively describes the species. *See AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1379 (Fed. Cir. 2014); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001); *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006); *In re Petering*, 301 F.2d 676, 682–83 (C.C.P.A. 1976). The standard for finding that a prior art genus anticipates an incorporated species is significantly more restrictive than the standard for determining whether a prior art genus renders obvious a species that is incorporated within it. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083–84 (Fed. Cir. 2008).

As applied to this case, the genus-species approach requires Alvogen to show that the Devane reference discloses a sufficiently small genus that a person of skill in the art would "at once envisage" each member of the genus. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092 (Fed. Cir. 2015); *AbbVie Inc.*, 764 F.3d at 1379; *Wm. Wrigley Jr. Co.*, 683 F.3d at 1361.

Prometheus addressed the issue of inherency in a patent on the treatment of one of four types of irritable bowel syndrome, in light of a prior art reference that disclosed the same treatment for irritable bowel syndrome generally. 805 F.3d at 1098. Although the court found

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claim directed to a subset of patients. *See* Dkt. No. 243, at 13 n.4. In the Court's view, Judge Schall did not adopt a different legal approach to the issue of inherent anticipation, but simply disagreed with the majority that inherency had been shown in that case. *See Blue Calypso*, 815 F.3d at 1356.

the claims in that case obvious, it noted that the genus-species framework "may have particular relevance in the field of personalized medicine" where "[s]ingling out a particular subset of patients for treatment (for example, patients with a particular gene) may reflect a new and useful invention that is patent eligible despite the existence of prior art or a prior art patent disclosing the treatment method to patients generally." *Id.*

Similarly, in *AbbVie*, the patent was directed to the treatment of patients with "active disease," which the patentee argued was a narrow species of a broader genus. The Federal Circuit analyzed the issue of obviousness under that framework. *See* 764 F.3d at 1378–80. Although both of those cases addressed the question in the context of obviousness, there is no reason why that approach is not equally applicable to the issue of inherency in the setting in which the asserted claims recite treating a subset of patients, and a prior art reference recites treating patients generally.

Alvogen argues that all opioid drug labels identify a small group of "specific populations"—such as pregnant women, patients with hepatic impairment, patients with renal impairment, elderly patients, and so forth. For that reason, Alvogen argues, the group of patients with hepatic impairment is one of a small number of species within the genus of all patients disclosed by Devane. Dkt. No. 243, at 13–14 (citing JTX5, JTX65, JTX66, DTX66, DTX27, DTX67, DTX91).

The Court disagrees with Alvogen's characterization of the size of the genus in this case. Regardless of the fact that opioids frequently contain instructions for the treatment of certain populations, Devane's genus is very broad. It covers the treatment of any patient, including any number of special populations that are not regularly described on opioid drug labels. *See* Trial Tr. 274:42–25 (Dr. Schmidt testifying that "Devane covers a large population of patients.").

The Federal Circuit and its predecessor court have found anticipation of a species by a genus in this context only when the genus itself is narrowly defined. In *VirnetX Inc. v. Apple Inc.*, 665 F. App'x 880 (Fed. Cir. 2016), the court affirmed a finding of anticipation where the prior art disclosed a "computer," which a person of skill would have understood to refer to either a desktop or a notebook computer. *Id.* at 888. In *In re Petering*, 301 F.2d 676 (C.C.P.A. 1962), the Federal Circuit's predecessor court held that a genus that disclosed a "limited class" of 20 compounds rendered unpatentable a patent that recited one of those 20. *Id.* at 682. And in *In re Schaumann*, 572 F.2d 312 (C.C.P.A. 1978), the court found anticipation where the genus of the prior art reference contained only 14 compounds, which "led inevitably to the conclusion that the reference provides a description of those compounds just as surely as if they were identified in the reference by name." *Id.* at 314–17. In contrast, the Federal Circuit affirmed a finding of no anticipation in *Lilly–Zenith*, where the genus included millions of possible substituents. 471 F.3d 1377.

Devane's genus includes the treatment of patients with any possible medical condition and any possible combination of conditions. As such, Alvogen has not established by clear and convincing evidence that Devane's disclosed genus is so small that a person of skill would immediately recognize the "defined and limited class" of the pertinent species of patients with mild or moderate hepatic impairment as falling within Devane's genus and thus being anticipated by Devane's disclosure.

The parties dispute whether the underlying data from the bunionectomy study described in Devane supports or undercuts Alvogen's position. Dr. Gudin testified that he reviewed the data from the bunionectomy study and found that the study protocol stated that the patients were in generally good health and that there was no indication that any of the subjects suffered from

hepatic impairment. Trial Tr. 684:23–687:1. Alvogen argues that Dr. Gudin is incorrect and that, properly viewed, the bunionectomy study must be regarded as having disclosed the treatment of patients with hepatic impairment. Dkt. No. 243, at 15–17.

Alvogen's argument is based on one of the parties' stipulated claim constructions, which provided that "mild hepatic impairment" means "the level of hepatic impairment characterized by Child-Pugh Scores of 5–6 and classified as Child-Pugh Class A." Dkt. No. 71, at 2. The Child-Pugh classification system has five different criteria, each scored one through three, with a score of one indicating the least impaired. Because the lowest possible score on the Child-Pugh scale is 5, Trial Tr. 85:8–86:7, Alvogen argues that even a completely healthy individual, with no symptoms of hepatic impairment, would be classified as having mild hepatic impairment under the Child-Pugh scale. Thus, Alvogen contends that Devane treats hepatically impaired patients because *everyone* is hepatically impaired under the Child-Pugh classification system, and thus under the parties' construction.

Dr. Gudin's testimony provides a complete answer to that argument. Dr. Gudin credibly testified that Child-Pugh scores do not apply to persons with no hepatic impairment because a physician would not apply the Child-Pugh classification to a person not suffering from some degree of liver dysfunction. Trial Tr. 676:24–678:4. As Dr. Gudin explained, "it's illogical to offer a normal patient a disease category score." Trial Tr. 677:23–24. Therefore, it is inaccurate to say that Devane inherently discloses treating patients with mild or moderate hepatic

impairment on the ground that every one of the patients in the Devane study necessarily had some degree of hepatic impairment.[9]

Finally, to the extent that Devane's description of the bunionectomy study suggests anything about the treatment of hepatically impaired patients, it is that the Devane hydrocodone formulation was not administered to such patients in the course of that study. As Dr. Schmidt testified, hepatic impairment is a "critical consideration" in clinical study design, "just as if they were testing elderly patients or they were testing pediatric patients." As a result, "[t]hat would have been a special population that they would have called out" in a summary of the study. Trial Tr. 278:22–279:16. For that reason as well, the Court finds that a person of skill would not have read Devane as teaching anything about the administration of hydrocodone to patients with hepatic impairment.

In sum, this is not a case in which "the disclosure of a small genus may anticipate the species of that genus." *Bristol-Myers Squibb Co.*, 246 F.3d at 1380. In reciting a "method of treating pain comprising administering a therapeutically effective amount of" hydrocodone, Devane recites a genus that includes any and every category of patient, which makes it much more akin to *Lilly–Zenith* than to *VirnetX*, *In re Petering*, and *In re Schaumann*. In addition, if a general method-of-treatment claim were deemed to inherently disclose the treatment of all possible special populations, no subsequent patent claiming the treatment of a special population

[9] As for Pernix's assertion that none of the patients in the bunionectomy study suffered from hepatic impairment, the Court observes that the report of the study noted that one subject exhibited abnormal liver function that was categorized as "mild." PTX43, at 149. Without relevant trial testimony, however, that data point is all but meaningless, and it is insufficient to affect the scope of Devane's disclosure. *See generally Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1346 (Fed. Cir. 2018); *Ciba-Geigy Corp. v. Alza Corp.*, 68 F.3d 487 (Table), 1995 WL 598380, at *2 (Fed. Cir. 1995).

would ever be valid. A finding of inherency is appropriate only where the claimed invention is the "natural result flowing from" the prior art. *Cont'l Can Co. USA, Inc.*, 948 F.2d at 1269 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). Because Devane neither "necessarily" discloses administration of hydrocodone bitartrate to patients with mild or moderate hepatic impairment nor identifies such patients with sufficient specificity as a species within its broad genus, Devane does not anticipate the asserted claims.

D. "Wherein the starting dose is not adjusted relative to a patient without hepatic impairment"

In addition to the "administering" step, the two-step claims recite a second method step directed to the level of dosing for patients with mild or moderate hepatic impairment. Because Devane does not anticipate administering hydrocodone bitartrate to such patients, it also cannot anticipate a physician administering an unadjusted dose of hydrocodone to such patients.

Alvogen argues that the non-adjustment limitation is an inherent property of Devane's extended-release hydrocodone formulation. Dkt. No. 243, at 18. A property such as the pharmacokinetic profile of a drug in a patient with mild hepatic impairment compared to the profile in a patient without hepatic impairment may be an inherent property, even if it was not previously recognized. *See Trintec Indus., Inc.*, 295 F.3d at 1295. However, the non-adjustment limitation, as construed, is a separate method step that must be performed by the physician. Dkt. No. 69, at 2 & n.2. A modification of a method of treatment is not a "necessarily present" property. *See, e.g.*, *AstraZeneca*, 633 F.3d at 1055. Devane does not disclose the pharmacokinetic parameters of the hydrocodone formulation in patients with hepatic impairment, and it does not, as Dr. Schmidt admitted, disclose a recommended, unadjusted starting dose. Trial Tr. 273:6–19.

Alvogen further argues that there can "never be a dosage reduction with Devane's HC-ER 'due to' a patient's [hepatic impairment]" because the Devane formulation "inherently provides similar PK [i.e., pharmacokinetic] profiles in patients with and without mild or moderate [hepatic impairment]." Dkt. No. 248, at 9–10. Alvogen's argument confuses what is "medically necessary" with what is "necessarily present," which is what is required for inherent anticipation. Even though the pharmacokinetic parameters of the hydrocodone formulation are inherent, and therefore a dose adjustment due to hepatic impairment would not be medically necessary to achieve the desired pharmacokinetic profile, there is nothing in Devane that would suggest not adjusting the proper dose for hepatically impaired patients if the pharmacokinetic profile of the drug in such patients is unknown.

Finally, Alvogen's anticipation arguments that are based on prior art other than Devane, *see* Dkt. No. 248, at 10–11, are appropriate for an obviousness analysis, but not for anticipation, as they are directed to what other prior art references disclose and teach rather than illuminating what Devane itself teaches. *See Monsanto Tech. LLC*, 878 F.3d at 1346. Accordingly, the Court finds that the step of not adjusting the starting dose is not inherently disclosed in Devane. The Devane reference thus does not anticipate either the one-step or the two-step claims of the patents-in-suit.

III. Obviousness

Obviousness under 35 U.S.C. § 103 is a question of law based on underlying findings of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The underlying factual considerations "include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations" of nonobviousness, such as the commercial success of the patented product or

method, a long-felt but unmet need for the functionality of the patented invention, unexpected results, industry praise for the patented invention, and the failure of others who have unsuccessfully attempted to accomplish what the patentee has achieved. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1052–53 (Fed. Cir. 2016) (en banc); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736 (Fed. Cir. 2013) (citing *Graham*, 383 U.S. at 17–18, and *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)). The obviousness analysis should not be conducted "in a narrow, rigid manner," but should instead focus on whether a claimed invention is merely "the result[] of ordinary innovation," which is not entitled to patent protection. *KSR Int'l*, 550 U.S. at 427–28.

"A party seeking to invalidate a patent as obvious must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.'" *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014) (quoting *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)). Although the patent owner bears the burden of production as to secondary considerations of nonobviousness, the party challenging the patent bears the ultimate burden of proving obviousness. *Galderma*, 737 F.3d at 738.

At trial, Alvogen contended that the asserted claims would have been obvious over Devane in view of one or more of U.S. Patent Publ. No. 2010/0010030 ("Jain") (JTX38), the 2011 Vicodin label (JTX20), and/or the 2011 Lortab label (JTX15). Jain, a patent application published in 2010, describes an opioid formulation referred to as Vicodin CR, which was a controlled-release analgesic that contained 15 milligrams of hydrocodone bitartrate and 500 milligrams of acetaminophen. JTX38 ¶ 34; *see* Trial Tr. 196:13–21. The Jain application

describes more than a dozen clinical studies that were conducted using Vicodin CR. *See* JTX38 ¶¶ 88–288.[10] As relevant to this case, Jain describes a hepatic impairment pharmacokinetic study conducted with Vicodin CR. Jain summarizes those results, reporting that the pharmacokinetic parameters for hydrocodone in that formulation were "similar" in normal subjects and subjects with mild or moderate hepatic impairment. JTX38 ¶ 64.

The 2011 Vicodin and Lortab labels describe the safety and dosing instructions for those drugs, both of which contain hydrocodone and acetaminophen in an immediate-release formulation. Although both labels state that the product should be "used with caution" in patients with severe hepatic impairment, the labels are silent about dosing levels for patients with mild or moderate hepatic impairment. JTX15, at 1; JTX20, at 2. From that silence, Alvogen argues that a person of ordinary skill would assume that no dose adjustment is required in prescribing Vicodin, Lortab, or other hydrocodone-containing products, to patients with mild or moderate hepatic impairment.

Based on the evidence at trial, the Court finds that all of the asserted claims would have been obvious over the combination of Devane and Jain, particularly in light of the state of the art that would have been known to a person of ordinary skill, including the Vicodin and Lortab labels. The Court first addresses (in part III.A) the parties' submissions regarding the levels of education and experience that would be expected of a person of ordinary skill in the field. Next, the Court describes (in part III.B) the state of the art at the time of the patented invention, as shown by the trial testimony, various contemporaneous journal articles, and the 15 prior art drug labels that were introduced into evidence. The Court then (in part III.C) addresses the four

[10] The FDA did not ultimately approve Vicodin CR for commercial distribution. *See* Trial Tr. 297:6–8.

categories of limitations that cover all of the asserted claims, and finds that each, both separately and in combination, would have been obvious in light of Devane and Jain. Finally, the Court addresses (in part III.D) the secondary considerations of nonobviousness raised by the parties and finds that they do not weigh in favor of finding the asserted claims nonobvious.

A. Person of Ordinary Skill in the Art

The parties largely agree on the education and experience that would characterize a person of ordinary skill in the art, and the differences between their definitions are not material.

For Pernix, Dr. Gudin testified that he believed a person of ordinary skill in the art would be

> a person or more likely a team of people with either a medical degree or Ph.D. degree in pharmacy, pharmaceutics, pharmacology, chemistry, or biology, who is familiar with the literature on hydrocodone and its metabolism as well as hepatic impairment, having at least two years of practical experience in drug development, including drug product formulation, or four years of experience if education is limited to a bachelor's or Master's degree.

Trial Tr. 18:16–25.

For Alvogen, Dr. Candiotti testified that a person of ordinary skill would be

> a chemist, biochemist, physician, pharmaceutical scientist, physical chemist, or medicinal chemist involved in the research and development of pharmaceutical formulations and dosage forms, including but not limited to extended release delivery systems. A [person of ordinary skill] may also work in consultation with an M.D. to understand clinical aspects of treating patients with hepatic impairment.
>
> A person of ordinary skill in the art would have one of the following combinations of education and experience:
>
> One, a Ph.D. or Pharm.D. in a field related to pharmaceutical formulations and at least one year of experience in pharmaceutical formulation development.
>
> Two, a similar Master's degree and at least two to three years of experience in pharmaceutical formulation development.
>
> Three, a similar undergraduate degree and at least five years of experience in pharmaceutical formulation development.
>
> Or, four, an M.D. with several years of experience in the treatment of pain in patients, and the clinical effects of utilizing opioids such as hydrocodone, particularly in the treatment of pain in hepatically impaired and healthy patients.

Trial Tr. 112:18–113:18.

The parties' proposals do not differ in any meaningful way. Moreover, the experts at trial all testified that the substantive analysis in this case is not affected by the differences between the two definitions. Trial Tr. 115:3–16 (Dr. Candiotti testifying that "the time [of work experience] is actually kind of arbitrary" and agreeing that the differences between the two are largely inconsequential); Trial Tr. 114:10–13 (Dr. Candiotti testifying that applying Dr. Gudin's definition of a person of ordinary skill would not have changed his opinion in this case); Trial Tr. 175:8–11 (Dr. Schmidt testifying to the same effect); Trial Tr. 457:11–13 (Alvogen expert Dr. Michael Laurence Weinberger testifying to the same effect); Trial Tr. 557:7–10 (Alvogen expert Dr. Michael Mayersohn testifying to the same effect); Trial Tr. 606:14–16 (Pernix expert Dr. John J. Koleng testifying to the same effect).

The Court finds that the parties' definitions of a person of skill in the art agree in all material respects. Based on the parties' presentations, the Court finds that a person of ordinary skill in the art would be a person or team of persons with a degree or degrees in the relevant fields such as chemistry, biology, pharmaceutics, or medicine, and work experience in formulating or administering pharmaceuticals, as follows: at least one to two years of experience for a person holding a Ph.D. or M.D.; at least two to four years of experience for a person holding a master's degree; and at least four to five years of experience for a person holding a bachelor's degree. The most important point here is that under both sides' proposals, the level of skill in the art is quite high; a person of skill in the art for purposes of the obviousness analysis is a person having a high degree of sophistication in the field.

B. State of the Art

Much of the evidence at trial related to articles and other background references that describe the proper dosing of opioids in patients suffering from hepatic impairment. Those references indicate how a person of ordinary skill, who would be familiar with the references, would have understood the teachings of Devane in combination with Jain, the Vicodin label, and the Lortab label. For that reason, the Court makes the following detailed findings regarding the references and the trial testimony from the parties' experts regarding what a person of ordinary skill would have understood from those references about the state of the art as of July 2012.

The pertinent references can be divided into four groups. First, there are four background articles that describe the metabolism of opioids and liver impairment generally. Second, there are three articles that the parties focused on during the trial that relate to the dosing of hydrocodone in patients with hepatic impairment. Third, there are seven labels for hydrocodone-containing drugs, four of which are prior art and three of which post-date the priority date for the patents-in-suit and thus do not qualify as prior art. And fourth, there are nine opioid analgesics that do not contain hydrocodone, all of which are prior art. The Court describes each in turn.

1. Background Articles

The parties presented a series of articles that provide background information regarding the metabolism of opioids, such as hydrocodone. The articles demonstrate that a person of ordinary skill would have understood that opioids are primarily metabolized by certain enzymes in the liver, and that hepatic impairment may result in a reduced rate of drug clearance from the body. The Court makes the following findings with regard to the four articles in the record that shed light on that issue:

1. The first is an article by Natasha Chandok, M.D., and Kymberly D. S. Watt, M.D., entitled "Pain Management in the Cirrhotic Patient: The Clinical Challenge," published in the *Mayo Clinic Proceedings* in 2010. PTX14. The article, which addresses dosing concerns for patients with hepatic and renal impairment, explains that "[t]he liver is the main site of metabolism for most opioids" and cautions that patients with liver problems "have decreased drug clearance and/or increased oral bioavailability, leading to drug accumulation in the body, especially with repeated administration." PTX14, at 4–5. The article also notes that "[i]neffective drug metabolism in this patient population can also lead to decreased analgesic action" of hydrocodone and oxycodone. PTX14, at 5. The article recommends a reduction of dose amount and frequency in patients with liver impairment for both oxycodone and tramadol, but does not make any recommendation for hydrocodone, although it notes that an active metabolite of hydrocodone is hydromorphone, for which the article recommends that physicians "[c]onsider dose reduction in patients with liver impairment." PTX14, at 5 tbl. 2; *see also* Trial Tr. 12:30–13:3, 697:3–6.

2. The second article, written by Roger K. Verbeeck and published in the *European Journal of Clinical Pharmacology* in 2008, is entitled "Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction." PTX33. The Verbeeck article explains that "[t]he liver plays a central role in the absorption, distribution, and elimination kinetics of most drugs" and that "[d]osage adjustment in patients with liver dysfunction is therefore essential for many drugs to avoid excessive accumulation of the drug, and possibly of active drug metabolite(s), which may lead to serious adverse reactions." PTX33, at 1–2. The article mentions opioids only in passing and does not provide specifics about how to dose opioids in hepatically impaired patients.

3. The third background article, by Reem H. Elbekai, et al., is entitled "The Effect of Liver Cirrhosis on the Regulation and Expression of Drug Metabolizing Enzymes" and was published in 2004 in *Current Drug Metabolism*. PTX51. Although the article does not discuss opioids, it includes a table of 22 other drugs and provides a summary of the effects of liver impairment on the pharmacokinetic parameters of those drugs. It recommends a dose adjustment for patients with mild or moderate hepatic impairment for approximately half of those 22 drugs. PTX51, at 8 tbl.2.

4. Pernix introduced two articles by its expert Dr. Gudin. The first article, entitled "Opioid Therapies and Cytochrome P450 Interactions" ("Gudin I"), was published in the *Journal of Pain and Symptom Management* in December 2012. JTX11. Although the publication date is after the priority date of the asserted patents, Dr. Gudin testified that he wrote the article in 2011 or early 2012 and "[i]t's a review article, so there's no new work in here, and the majority of the references from this article were from 2011 and before." Trial Tr. 697:19–698:1. As such, the information in the article would have been known to a person of ordinary skill as of the July 31, 2012, priority date for the two patents-in-suit. Trial Tr. 698:2–5. The article explains that because the liver is responsible for most opioid metabolism, "hepatic impairment can significantly alter the bioavailability of an opioid and its metabolites." JTX11, at 8. The article adds that "[d]ose reductions for most opioids may be necessary for patients with hepatic impairment" and that "[e]xtreme caution is warranted when using any opioid in individuals with liver disease." JTX11, at 8. The article recommends that the starting dose of an opioid should always be the lowest dose, "with appropriate interval titration, especially in the opioid-naïve patient." JTX11, at 9.

5. The Court finds that these articles are representative of some of the knowledge that a person of ordinary skill would possess as of July 2012. In particular, a person of ordinary skill would have understood that opioids are metabolized through systems in the liver that can be impaired in patients with liver dysfunction. If those systems are underperforming and the patient is given the same dose of an opioid as would be given to a patient without hepatic impairment, the opioid may not be metabolized quickly enough, which could lead to an overdose of the opioid. The risk of overdosing would be particularly significant for patients with severe chronic pain who take opioids with regularity. As such, a person of ordinary skill would be cautious in dosing opioids for patients with hepatic impairment. In addition, given the potency of opioids as a class of drugs, a person of skill in the art would have been cautious in recommending anything more than the lowest effective dose to any patient, regardless of hepatic impairment, but especially to opioid-naïve patients. *See also* Trial Tr. 479:13–17.

6. A person of ordinary skill would also appreciate that dosing recommendations are drug-specific. For example, the table in the Elbekai article lists 10 drugs that are metabolized by a particular liver enzyme; for half of those drugs, the table recommends a dose adjustment or titration, and for the other half the table does not recommend a dose adjustment. PTX51, at 8 tbl. 2. The Elbekai table lists two other drugs that are metabolized by another liver enzyme; for one, the table recommends a dose adjustment for persons with moderate and severe hepatic impairment; for the other, the table does not recommend a dose adjustment for such patients. *Id.*

2. Significant Articles Directed to Opioid Dosing

The parties place special emphasis on three articles that were introduced at trial. The Court makes the following findings regarding these articles:

1. The first is a second article by Pernix's expert, Dr. Gudin. That article is entitled "Risk Evaluation and Mitigation Strategies (REMS) for Extended-Release and Long-Acting Opioid Analgesics: Considerations for Palliative Care Practice" and was published in the *Journal of Pain and Palliative Care Pharmacotherapy* in 2012. PTX55. The article does not discuss hepatic impairment, but discusses the risks associated with extended-release opioids more generally. In particular, the article states: "Although improper use of any opioid can cause oversedation and respiratory depression, this risk is magnified for [extended-release] opioids due to the large amount of active ingredient contained within one dose, and the extended time to elimination." PTX55, at 3. Dr. Gudin, at trial, and Pernix, in its papers, repeatedly emphasized that sentence from Dr. Gudin's article. When asked at trial whether the literature supports the idea that immediate-release products do not have the same risk of overexposure as extended-release products, Dr. Gudin referred to that passage of his article and explained that a patient could be exposed to a greater amount of hydrocodone from an extended-release product, so "there's a greater risk associated with extended release products." Trial Tr. 699:14–700:7. In its post-trial briefing, Pernix relies on Dr. Gudin's article and testimony in support of its contention that the dosing of immediate-release products "would not inform dosing with" extended-release products. Dkt. No. 246, at 13.

2. The Court finds that a person of ordinary skill would not draw the same conclusions from Dr. Gudin's article that Pernix draws. The sentence from Dr. Gudin's article on which Pernix relies states that the risk *of abuse* of extended-release opioid products is greater than the risk of abuse of immediate-release products, because extended-release dosage units contain a larger amount of the opioid than immediate-release dosage units. Dr. Gudin's article and his corresponding testimony, however, do not support the conclusion that an extended-release opioid

product would present any greater risk of overdose when administered properly. Because Dr. Gudin's article addresses opioid abuse, and not the risks of opioids when administered properly, the Court does not find Pernix's argument on that point persuasive.

3. The second significant article, entitled "Opioid Metabolism," by Howard S. Smith, M.D., was published in the *Mayo Clinic Proceedings* in July 2009. JTX34. The Smith article discusses metabolic pathways and dosing instructions for various opioids, including hydrocodone. In a table, the Smith article summarizes the "Demographic/Medical Factors Influencing Opioid Metabolism," including hepatic impairment. JTX34, at 8 tbl.5. The chart lists nine opioids, including hydrocodone. For four of the nine opioids—morphine, codeine, oxycodone, and hydromorphone—Smith states that a dose adjustment is recommended for hepatically impaired patients. *Id.* For two of the nine—methadone and tramadol—Smith states that a dose adjustment is recommended, or that the pharmacokinetic parameters are significantly altered, in patients with severe hepatic impairment, but it does not mention mild or moderate hepatic impairment. *Id.* For hydrocodone, Smith states that it is "[m]ost frequently administered in combination with acetaminophen; liver function monitoring is advised during treatment in patients with hepatic impairment." *Id.* Smith does not state whether a dose adjustment is required or recommended for hydrocodone. Smith concludes by stating that the "liver is the major site of biotransformation for most opioids" and that it is "therefore not surprising that the prescribing information for most frequently prescribed opioids recommends caution in patients with hepatic impairment." JTX34, at 8.

4. The parties' experts disagreed about what a person of ordinary skill would draw from the Smith article about dosing hydrocodone in patients with mild or moderate hepatic impairment. Dr. Gudin testified that Smith "could not have" taught anything about how to dose

an extended-release hydrocodone product to hepatically impaired patients because, at the time the article was published "there were no extended release single entity hydrocodone products, and there was no data on dosing in mild to moderate hepatic impairment." Trial Tr. 711:21–1. Alvogen's experts disagreed. Dr. Schmidt noted that Smith "describes a variety of narcotic related analgesic substances where hepatic dysfunction could influence their action in the body and provides recommendations for reducing dosing where indicated." He pointed out, however, that Smith has no recommendation for reducing doses of hydrocodone based upon mild or moderate hepatic impairment. Trial Tr. 217:21–218:2. Dr. Weinberger agreed, noting that "there's no statement here that any adjustment in dosing needs to be performed in patients with hepatic impairment." Trial Tr. 481:20–482:2. Moreover, Dr. Weinberger suggested that Smith's caution about monitoring liver function may be due to the toxicity of the acetaminophen in those combination products, rather than the effect of the hydrocodone on the liver, Trial Tr. 493:24–495:24.

5. The final significant article, entitled "Opioid Safety in Patients with Renal or Hepatic Dysfunction," by Sarah J. Johnson, Pharm.D., was published in the journal *Pain Treatment Topics* in 2007. JTX32. The Johnson article is a review article that, among other things, briefly summarizes dosing recommendations for various opioids. Johnson explains that "[i]n general, patients with severe liver disease should be prescribed lower doses of opioids, with extended dosing intervals when multiple daily doses of opioids are needed." JTX32, at 6 (emphasis omitted).

6. In a table, Johnson summarizes the "Recommended Use of Opioids in Hepatic Dysfunction." JTX32, at 7. For "Hydromorphone/Hydrocodone," the table recommends: "*Use cautiously* and monitor patient carefully for symptoms of opioid overdose." *Id.* For patients

with severe hepatic impairment, the table states that "the parent drug may not be readily converted to inactive metabolites," and it recommends "[d]ecrease initial dose by 50% of the usual amount." *Id.* The article's conclusion states that opioids "should be used cautiously in this patient population due to possible accumulation of the parent drug and/or metabolites. Usual or adjusted doses may be appropriate for certain opioids (eg, morphine, hydromorphone, hydrocodone)." *Id.*

7. The common specification of the patents-in-suit references the Johnson article, but misstates what Johnson expressly teaches. After describing the pharmacokinetic parameters of Devane's hydrocodone formulation, the specification states that "[a]ny difference due to level of hepatic impairment is not found to be clinically significant. This is quite surprising and non-obvious, especially given recommendations in the literature to dose patient with hepatic impairment at 50% of the normal dose [citing Johnson's article]." '760 patent, col. 16, ll. 8–14; '499 patent, col. 16, ll. 8–14. In fact, however, Johnson recommends a 50 percent dose reduction only for patients with severe hepatic impairment; the article is silent as to the proper dosing of hydrocodone for patients with mild or moderate hepatic impairment. *See* JTX32, at 6–8; Trial Tr. 209:21–212:13. Dr. Schmidt correctly characterized the discussion of Johnson in the specifications as "a misinterpretation of Johnson's recommendation." Trial Tr. 212:8–13.

8. The parties' experts disagree about what Johnson reflects as to the state of the art. Dr. Gudin testified that Johnson did not refer to extended-release hydrocodone products because in 2007 there were no extended-release hydrocodone products on the market. Trial Tr. 707:19–23. Therefore, Dr. Gudin concluded, Johnson would not have taught anything about how to dose extended-release hydrocodone-only formulations in patients with mild or moderate hepatic impairment. Trial Tr. 708:6–11. Dr. Gudin further testified that although the Johnson article

focused on severe hepatic impairment, a person of ordinary skill in the art would conclude from the article "that a dose adjustment would be necessary for any patient with hepatic impairment." Trial Tr. 710:10–14.

9. Alvogen's experts disagreed. Dr. Schmidt noted that Johnson offers "some warnings for some of the other drugs in patients with varying degrees of renal or hepatic impairment," but does not recommend a dose adjustment for patients with mild or moderate hepatic impairment, from which it could be inferred "that these products could be used safely in that population." Trial Tr. 209:15–20; *see also* Trial Tr. 217:21–218:2. Dr. Schmidt admitted, however, that the Johnson article did not explicitly state how to dose any of the listed products for mild or moderately hepatically impaired patients. Trial Tr. 291:21–292:1.

10. Dr. Weinberger interpreted Johnson to mean that "dose adjustments [are] only necessary in severe hepatic impairment" and are not required for a patient with mild or moderate hepatic impairment when using an extended-release hydrocodone product. Trial Tr. 483:1–5, 486:10–13. However, Dr. Weinberger admitted that Johnson is "painting with broad brush stroke[s] talking about all opioids." Trial Tr. 509:4–13.

11. The Court finds that the Smith and Johnson articles demonstrate that a person of ordinary skill in the art in July 2012 would appreciate that opioids are typically metabolized in the liver, and that dose adjustments are often required when dosing certain opioids in patients with hepatic impairment. A person of ordinary skill would have understood that dosing hydrocodone in patients with hepatic impairment requires caution, and that a dose adjustment would be required in patients with severe hepatic impairment. Because hydrocodone is often administered in combination with acetaminophen, which is hepatotoxic, *see* Trial. Tr. 493:8–

495:23, a person of ordinary skill would have been particularly cautious in prescribing combination products containing acetaminophen to hepatically impaired patients.

12. Given the descriptions in Smith and Johnson, the Court finds that a skilled artisan would not have been able to say with confidence in July 2012 what the proper dosage of hydrocodone would be for patients suffering from mild or moderate hepatic impairment, or whether a dose adjustment would be necessary for such patients. Neither Smith nor Johnson suggests that a physician must always adjust the dose of hydrocodone for patients with mild or moderate hepatic impairment. In particular, neither Johnson nor Smith criticizes, discredits, or discourages investigation into whether a dose adjustment would be necessary in administering hydrocodone to patients with mild or moderate hepatic impairment.

3. Hydrocodone Labels

The parties introduced into evidence the labels from seven hydrocodone-containing drugs, including four that are in the prior art. The Court makes the following findings regarding those labels:

1. The four prior art labels are for Vicoprofen (DTX60), an immediate-release combination product that contains hydrocodone and ibuprofen; for Vicodin (JTX20), an immediate-release combination product that contains hydrocodone and acetaminophen; for Lortab (JTX15), an immediate-release combination product that contains hydrocodone and ibuprofen; and for TussiCaps (DTX65), an extended-release combination product that contains hydrocodone and chlorpheniramine. The trial evidence shows that the use of hydrocodone as an analgesic was not a recent development. Vicodin, the most popular of these products, has been in use for decades, Trial Tr. 181:15–19, and has been the most prescribed opioid and one of the most frequently prescribed medications in this country, Trial Tr. 444:7–12, 487:23–24.

2. Each of the four labels contains a precaution against administering the drug to patients with severe hepatic impairment, and the precautionary language in each label is almost identical. Each label contains the statement, in a section entitled "Special Risk Patients" that, as with any narcotic agent or opioid analgesic, the drug "should be used with caution in . . . [patients] with severe impairment of hepatic or renal function . . . . The usual precautions should be observed and the possibility of respiratory depression should be kept in mind." DTX65, at 3; JTX15, at 1; JTX20, at 2; DTX60, at 5. None of the labels contains a precaution or dosing adjustment recommendation for patients with mild or moderate hepatic impairment.

3. Dr. Schmidt testified that the fact that there was no mention of mild or moderate hepatic impairment in any of those four labels "would give you some confidence you could use the product safely in the same dose with patients with mild or moderate hepatic impairment as you would use with patients with normal function." Trial Tr. 205:3–10 (regarding Vicoprofen); *see also* Trial Tr. 206:10–17 (regarding TussiCaps), 203:24–204:5 (regarding Lortab), 202:9–21 (regarding Vicodin). Dr. Weinberger agreed: "[T]here's no indication that any changes in dosing need to be made for a patient who has mild or moderate hepatic impairment," and so a physician would not have adjusted the dose for a patient with mild or moderate hepatic impairment. Trial Tr. 459:2–23.

4. Dr. Schmidt and Dr. Weinberger acknowledged that none of the four labels contain pharmacokinetic data indicating how the drug is processed in a patient with hepatic impairment. *See* Trial Tr. 268:23–269:4, 487:2–19. Dr. Weinberger explained, however, that the absence of pharmacokinetic information did not affect his opinion on obviousness, because these drugs were very popular and Dr. Weinberger knew "of no reports of problems relating to hydrocodone use in mild or moderately impaired patients. The concern actually about these product[s] was the

acetaminophen, but not the hydrocodone." Trial Tr. 487:16–488:3. He concluded, "being the most commonly prescribed products, I would suspect there would have been information available if there were [problems] using these substances, these chemicals in patients with mild or moderate hepatic impairment." Trial Tr. 488:4–8.

5. Dr. Gudin drew the opposite conclusion regarding the four prior art opioid drugs. He testified that a person of ordinary skill would have understood that even though the labels of the four drugs advised physicians to use caution only with reference to patients with severe hepatic impairment, "we wouldn't just dose these full dose to . . . patients with mild or moderate hepatic impairment." Trial Tr. 694:14–21. Rather, Dr. Gudin testified that in the absence of pharmacokinetic data a person of ordinary skill would have exercised extreme caution and would have expected that a dose adjustment would be necessary for patients with mild or moderate hepatic impairment. Trial Tr. 694:21–696:2.

6. The Court finds that the state of the art in July 2012 was somewhere between the parties' two positions. A person of ordinary skill reading the four prior art labels would have appreciated that a physician could prescribe a hydrocodone-containing product to a patient with hepatic impairment, and that caution would be necessary, particularly if the patient's dysfunction were severe. Given that the labels do not mention patients with mild or moderate hepatic impairment, however, a physician might reasonably have concluded that it would be safe to prescribe the same starting dose for such patients as for patients without hepatic impairment.

7. Finally, the parties introduced three labels that are not in the prior art. Those labels are the 2017 label for Vicodin (PTX74), and the labels for two extended-release hydrocodone-only products, Hysingla ER (JTX13), which is dated December 2016, and Vantrela (JTX19), which is dated January 2017. The Vantrela label instructs physicians to initiate therapy at one-

half the recommended initial dose in patients with mild or moderate hepatic impairment, JTX19, at 1,7, 21; the Hysingla ER label recommends initiating therapy for patients with severe hepatic impairment at one-half the initial dose but states that a dose adjustment in starting dose for patients with mild or moderate hepatic impairment is not required, JTX13, at 7, 19; and the Vicodin label recommends that physicians "[u]se a low initial dose of hydrocodone bitartrate and acetaminophen tablets in patients with hepatic impairment and follow closely for adverse events such as respiratory depression and sedation." JTX74, at 16. Because all of those three labels were released years after the priority date for the '760 and '499 patents, the Court accords those references little weight in its obviousness analysis.

4. Non-Hydrocodone Opioid Labels

At trial, the parties introduced evidence relating to nine non-hydrocodone opioid drug labels, including six unique opioids. Three of the drugs were immediate-release formulations and six were extended-release formulations. All are in the prior art. The Court makes the following findings regarding those labels:

1. The immediate-release drugs are Percocet (PTX92), which contains oxycodone and acetaminophen; Dilaudid (PTX98), which contains hydromorphone as the only active ingredient; and Opana (PTX103), which contains oxymorphone as the only active ingredient. The Percocet label states that "[p]recaution should be taken in patients with liver disease." PTX92, at 1. The Dilaudid label instructs that "patients with moderate hepatic impairment should be started at a lower dose and closely monitored during dose titration," and it advises that "[s]ince the pharmacokinetics of hydromorphone are affected in hepatic and renal impairment with a consequent increase in exposure, patients with hepatic and renal impairment should be started on a lower starting dose." PTX98, at 4, 13. The Opana label recommends use of the drug "with

caution and at lower doses" in patients with mild hepatic impairment and states that the drug is contraindicated in patients with moderate or severe hepatic impairment. PTX103, at 1, 3.

2. The six extended-release drugs are Opana ER, Kadian, Avinza, Exalgo, Nucynta ER, and OxyContin. The Opana ER label provides the same caution for mild hepatic impairment and contraindication for moderate hepatic impairment that are found in the immediate-release Opana label, JTX65, at 1, 5. The labels for Kadian and Avinza, which contain morphine as the only active ingredient, do not mention mild or moderate hepatic impairment, but state that the drug should be administered with caution and in reduced dosages in patients with severe hepatic impairment. DTX67, at 18; DTX27, at 7. The label for Exalgo, which contains hydromorphone as the only active ingredient, contains data showing a four-fold increase in C_{max} and $AUC_{0\text{-}inf}$ in patients with moderate hepatic impairment, DTX91, at 9, and advises physicians to start patients suffering from moderate and severe hepatic impairment on a reduced dose and to closely monitor their progress during dose titration, DTX91, at 1, 5. The Exalgo label does not mention mild hepatic impairment. The 2011 and 2012 labels for Nucynta, which contains tapentadol as the only active ingredient, both state that no dose adjustment is required for patients with mild hepatic impairment, DTX66, at 9; JTX17, at 6, but that for patients with moderate hepatic impairment, treatment should be started at a low dose and the drug should be administered no more frequently than once every 24 hours, DTX66, at 9; JTX17, at 6. The labels state that total serum drug concentrations ($AUC_{0\text{-}inf}$) were increased 1.7-fold and 4.2-fold for patients with mild and moderate hepatic impairment, respectively, and that measurements of the maximum drug concentration level (C_{max}) were increased 1.4-fold and 2.5-fold, respectively. DTX66, at 22; JTX17, at 26. The 2010 and 2012 labels for OxyContin, which contains oxycodone as the only active ingredient, describe a hepatic impairment pharmacokinetic study that found AUC levels

for oxycodone to be 95% higher in hepatically impaired patients as compared with healthy patients. JTX66, at 26; JTX18, at 26. In light of that information, the labels state that "in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration." JTX66, at 17–18; JTX18, at 17.

3. In sum, of the six non-hydrocodone extended-release opioids in evidence, four are either silent on the dosage for mild hepatic impairment or explicitly state that no adjustment is required in such patients, while four of the six recommend reducing the starting dose for patients with moderate hepatic impairment.

C. Obviousness of the Asserted Claims

Alvogen argues that the asserted claims would have been obvious based on Devane in view of one or more of Jain, the 2011 Vicodin label, and the 2011 Lortab label. The Court agrees with Alvogen that all of the asserted claims would have been obvious in light of those prior art references. For convenience, the Court analyzes the obviousness arguments on a limitation-by-limitation basis. The Court's conclusion as to obviousness, however, applies to the claims as a whole and not simply to particular limitations.

1. "Administering . . . [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"

Devane discloses the hydrocodone extended-release formulation that was used in the asserted patents and describes the use of that formulation to treat pain in patients. Devane thus satisfies the limitation that recites a formulation comprising extended-release hydrocodone bitartrate in which hydrocodone bitartrate is the only active ingredient. Trial Tr. 195:3–16, 224:18–225:8. Pernix does not dispute that Devane teaches that limitation, which is common to all of the asserted claims.

2. Pharmacokinetic Limitations

As discussed above, Devane inherently anticipates the pharmacokinetic limitations claimed in the patents-in-suit because those pharmacokinetic properties are necessary features of the Devane formulation. Given the differing legal standards for inherency in the anticipation and obviousness contexts, however, the question is whether Devane renders the pharmacokinetic limitations of the asserted claims obvious. The Court concludes that it does.

Alvogen cites *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012), for the proposition that an "obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting" concentrations if those properties were inherent properties of the formulation. *See* Dkt. No. 243, at 22. Pernix responds that the pharmacokinetic limitations would not have been obvious, even if inherently anticipated, because "obviousness cannot be predicated on what is unknown" and "[w]hat is important regarding properties that may be inherent, but unknown, is whether they are unexpected." Dkt. No. 246, at 16 (quoting *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993), and *Honeywell Int'l Inc. v. Mexichem Amanco Holding, S.A.*, 865 F.3d at 1348, 1355 (Fed. Cir. 2017)).

On a number of occasions, the Federal Circuit has addressed the very issue presented here: i.e., whether an inherent property can add patentable weight in the obviousness context. The Federal Circuit's cases demonstrate that necessarily present properties, such as the pharmacokinetic parameters of previously known compositions, do not add patentable weight when they are claimed as limitations.

In *Par Pharmaceutical, Inc. v. TWI Pharmaceuticals, Inc.*, 773 F.3d 1186 (Fed. Cir. 2014), the patent at issue claimed methods of using megestrol acetate nanoparticles to "increas[e] the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass." *Id.*

at 1188 (alteration in original). The claims included limitations about specific food effects, such as "wherein after a single administration in a human subject of the formulation there is no substantial difference in the C_{max} of megestrol when the formulation is administered to the subject in a fed versus a fasted state." *Id.* at 1194. The district court found, and the Federal Circuit agreed, that the food effect was not known in the prior art, even though megestrol itself was well known. *Id.* The Federal Circuit stated that "the concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the 'natural result' of the combination of prior art elements." *Id.* at 1195 (quoting *In re Oelrich*, 666 F.2d at 581). Because the district court had not made factual findings that the claimed food limitation was necessarily present in the prior art combination, the circuit court reversed with instructions that "the district court [should] determine if TWI has presented clear and convincing evidence that demonstrates the food effect as *claimed* is *necessarily present* in the prior art combination." *Id.* at 1196 (emphasis in original).

As *Par Pharmaceutical* makes clear, a property such as a food effect or a pharmacokinetic parameter, when claimed as a limitation, is inherent if it is necessarily present in the prior art combination. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (inherency appropriate in obviousness context where it concerns a "property that is necessarily present"); *In re Kao*, 639 F.3d at 1070 (food effect pharmacokinetic limitation is inherent in obviousness analysis because it is "an inherent property of oxymorphone itself" and the prior art's "express teachings render the claimed controlled release oxymorphone formulation obvious" because "the claimed 'food effect' adds nothing of patentable consequence"); *Santarus*, 694 F.3d at 1354 ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. To hold otherwise

would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property."); *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) ("Even 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 invention], but rather a property necessarily present in the [claimed invention]."); *see also Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249 (1945) ("It is not invention to perceive that the product which others had discovered had qualities they failed to detect."); *In re Oelrich*, 666 F.2d at 581 ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. . . . If, however, 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." (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939))); *Application of Wiseman*, 596 F.2d 1019, 1023 (C.C.P.A. 1979) ("They are, in effect, arguing that a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable to them because it also possesses an inherent, but hitherto unknown, function which they claim to have discovered. This is not the law.").

Pernix's reliance on *In re Rijckaert* is not well founded, as that case does not involve a claim limitation that recites a necessarily present property. In *Rijckaert*, the Federal Circuit reversed an obviousness rejection based on inherency because the allegedly inherent property was based on the optimization of the product, not on a necessarily present property that was found in the prior art. 9 F.3d at 1533–34 ("To support the Board's affirmance of the rejection, the Commissioner points out that in the recording art, the exact matching of signal time to

recording time is an optimal condition, and that this condition would be met by fulfilling the claimed relationship. While the condition described may be an optimal one, it is not 'inherent' in [the prior art reference]. Nor are the means to achieve this optimal condition disclosed by [that reference], explicitly or implicitly.").

Honeywell is similarly inapposite, because that case involved using an unknown but inherent property as a teaching in an obviousness analysis; it did not involve a limitation that recites an inherent property. The patent in *Honeywell* recited a heat transfer composition that contained at least about 50% by weight of a particular compound and at least one specified lubricant. 865 F.3d at 1351. The compound was taught by a reference known as Inagaki, but the patentee argued that Inagaki did not teach combining that compound with the specified lubricant. *Id.* The patentee further argued that, because of the unpredictability of finding suitable lubricants and the unexpected stability and miscibility of the claimed combination, the combination of the compound and the lubricant would not have been obvious. *Id.* at 1352. The Patent Trial and Appeal Board rejected that argument on the ground that the stability and miscibility of the combination were inherent properties that could not confer patentable weight. *Id.* The Federal Circuit reversed, holding that "[w]hat is important regarding properties that may be inherent, but unknown, is whether they are unexpected." *Id.* at 1355. The Board's obviousness analysis, the court explained, ignored the unpredictability in the art and erroneously relied on inherent but unknown properties in finding a motivation to combine.[11]

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[11] The Federal Circuit's non-precedential decision in *Endo Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.*, 731 F. App'x 962 (Fed. Cir. 2018), is not to the contrary. In that case, the patentee claimed specific controlled-release oxymorphone dosages that were configured to result in the observed pharmacokinetic properties upon administration. The court explained that because the prior art "did not give any indication to a person of ordinary skill that

Pernix does not dispute that the pharmacokinetic parameters recited in the asserted claims are necessarily present in Devane, because the formulations in Devane and in the patents-in-suit are identical. Trial Tr. 195:2–16. There was no evidence at trial that the pharmacokinetic parameter limitations in the asserted claims are either absent from or only sometimes present in the recited formulations. Accordingly, under the governing precedents, the pharmacokinetic limitations are inherent in any obviousness combination that contains the Devane formulation.

3. "Administering to the patient having mild or moderate hepatic impairment"

As discussed above in connection with anticipation, the Court finds that Devane does not teach administering a formulation comprising extended-release hydrocodone, with hydrocodone serving as the sole active ingredient, to patients suffering from mild or moderate hepatic impairment. However, the Court finds that in light of the state of the art, and based on the Jain patent application, the Lortab label, and the Vicodin label, it would have been obvious to a person of ordinary skill to administer Devane's formulation to such patients. The Court makes the following specific findings on this issue:

1. As the parties agree, a person of skill in the art has a substantial level of educational achievement and professional work experience, including specialized work experience in the field of administering or developing pharmaceuticals. The Court finds that such a person would have been familiar with articles such as those by Johnson and Smith, and would have been

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oxymorphone could have been developed into a controlled release formulation providing effective analgesia over a twelve-hour period, the pharmacokinetic limitations were neither 'necessarily . . . present' nor 'the natural result of the combination of elements explicitly disclosed by the prior art.'" *Id.* at 971 (quoting *Par Pharm.*, 773 F.3d at 1195–96). In this case, by contrast, the formulation recited in the claims was explicitly disclosed by Devane, and the pharmacokinetic limitations were necessarily present in, and a natural result of the administration of, that formulation.

familiar with the opioid drug labels discussed at trial. Based on the literature in the field, such a person would have appreciated that hydrocodone could be administered to patients with mild or moderate hepatic impairment. *See, e.g.*, JTX32, at 6–7 (Johnson article, describing hydrocodone use in patients with hepatic impairment); JTX34, at 8 (Smith article, describing administration of hydrocodone in patients with hepatic impairment). Even Dr. Gudin's article makes clear that a person of ordinary skill would have understood that opioids such as hydrocodone could be administered to hepatically impaired patients. *See* JTX11, at 8–9. Although, as Pernix argues, a person of ordinary skill might not have known with certainty the proper dose to administer to hepatically impaired patients, that person would have had a reasonable expectation of success in safely treating pain in such a patient using Devane's formulation.

2. The Jain, Lortab, and Vicodin references all reinforce this conclusion. All three are combination products that contain hydrocodone and acetaminophen. All three teach treating pain in patients with hepatic impairment using such a combination product. The Lortab and Vicodin labels both include a caution regarding dose levels for patients suffering from severe hepatic impairment, but are silent regarding dose levels for patients with only mild or moderate hepatic impairment. JTX15, at 1; JTX20, at 2. Although Pernix's expert and Alvogen's experts disagreed about what a person of ordinary skill would understand the silence of those references to teach about the proper starting dose for patients with mild or moderate hepatic impairment, Trial Tr. 202:9–21, 203:24–204:5 459:2–23, 694:14–696:2, no expert testified that those labels would teach that the product should not be administered to patients with mild or moderate hepatic impairment. Moreover, Jain's pharmacokinetic study describes the pharmacokinetic profiles of hydrocodone in normal subjects and in patients with mild or moderate hepatic impairment as "similar." That characterization indicates that a hydrocodone-containing

extended-release product could be safely administered to a patient with mild or moderate hepatic impairment. JTX38 ¶ 64. Accordingly, the Court finds that Jain and the Vicodin and Lortab labels teach that hydrocodone, in a formulation such as Devane's, could be administered to patients with that level of hepatic impairment.

3. Pernix argues that there is no motivation to combine Devane, an opioid-only formulation, with Lortab, Vicodin, and Jain's Vicodin CR because each of the latter three formulations is a combination product that contains acetaminophen. Dkt. No. 244, at 27–28; Dkt. No. 246, at 12–13. The Court finds that the evidence does not support Pernix's argument, for four reasons.

First, acetaminophen, unlike hydrocodone, is hepatotoxic. *See* Trial. Tr. 493:8–495:23. That would suggest that removing acetaminophen, as in the Devane formulation, would make the drug safer for patients with hepatic impairment, rather than less safe.

Second, the new drug application for Zohydro ER relied in part on Vicoprofen, an immediate-release combination hydrocodone/ibuprofen drug, as a reference product. Doing so allowed Zogenix to rely on some of the Vicoprofen safety and efficacy testing in its new drug application for Zohydro ER. Trial Tr. 383:17–384:3. Andrew Hartman, one of the named inventors of the asserted patents, testified that Vicoprofen was chosen as the reference product for Zohydro ER because the FDA does not allow an applicant to use as a reference an opioid product with a different active pharmaceutical ingredient. He explained that the FDA does not permit an applicant to "extrapolate safety data from one molecule to another molecule." Trial Tr. 384:12–20. The Court finds the evidence of the FDA's willingness to accept safety data from a similar product containing ibuprofen, *see* Trial Tr. 385:11–15, supports the view that a person

of skill in the art would not have regarded a combination product containing hydrocodone as irrelevant to the obviousness of the invention.

Third, a person of ordinary skill in July 2012 would have been motivated to formulate analgesics that minimized or avoided the use of acetaminophen. In January 2011, the FDA issued a safety announcement that asked drug manufacturers to "limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids."[12] The FDA stated that reducing the amount of acetaminophen to no more than 325 milligrams per tablet, capsule, or other dosage unit, as well as including a warning on the label, would reduce the risk of severe liver damage associated with acetaminophen. In the table listing the affected drugs, a number of combination products that contain acetaminophen and hydrocodone are listed, including various forms of Vicodin and Lortab.

Finally, and most significantly, a person of skill in the art would have appreciated that acetaminophen and hydrocodone are metabolized differently, and that acetaminophen would not

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[12] Food & Drug Admin., *FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure* (Jan. 13, 2011). The Court takes judicial notice of the FDA's safety notice pursuant to Federal Rule of Evidence 201, as it finds that the safety announcement cannot reasonably be questioned. *See* Jiten Parikh, RPh, BSPharm, and Kammi Wilson, MA, *The Effects of New FDA APAP Regulations on Pharmacy Practice*, Pharm. Times (Sept. 16, 2011) (describing the January 2011 FDA action); *see also Mitchell v. Qualitest Pharm.*, 187 F. Supp. 3d 831, 832 n.2 (W.D. Ky. 2016) (taking judicial notice of FDA approval of drug label); *Stanifer v. Corin USA Ltd., Inc.*, No. 6:14-CV-1192, 2014 WL 5823319, at *3 (M.D. Fla. Nov. 10, 2014) (proper to take judicial notice of public records on FDA's website); *Albrecht v. Fort Dodge Animal Health, Inc.*, No. 12-11429, 2013 WL 823325, at *3 n.2 (E.D. Mich. Mar. 6, 2013) (taking judicial notice of FDA website reflecting approval of product); *Peviani v. Hostess Brands, Inc.*, 750 F. Supp. 2d 1111, 1116 (C.D. Cal. 2010) (taking judicial notice of FDA regulatory guideline).

have had a significant impact on the metabolism or pharmacokinetic profile of hydrocodone. Trial Tr. 257:1–8. Devane's description of the results of the bunionectomy study confirms this understanding. In the study, certain patients were administered an extended-release formulation containing 10 milligrams of hydrocodone, and others were administered an immediate-release hydrocodone and acetaminophen combination product, such as Vicodin, also containing 10 milligrams of hydrocodone. Various pharmacokinetic data measurements were then made. JTX37 ¶ 104. Among the relevant pharmacokinetic parameters were C_{max}, which measures the maximum plasma concentration of the administered drug, and $AUC_{0\text{-}inf}$, which measures the total exposure to the drug over time. JTX37 ¶ 105; *see* Trial Tr. 197:15–17, 226:21–11, 229:19–20. Devane's Table 9 reports that the mean C_{max} was 8.9 ng/mL for the extended-release hydrocodone formulation, and 19.5 ng/mL for the immediate-release hydrocodone-acetaminophen formulation. JTX37 ¶ 104. That data is consistent with the difference between an immediate-release and an extended-release product: an immediate-release product would release all of the active ingredient at once, resulting in a much higher maximum plasma concentration, whereas an extended-release product would release the active ingredient slowly over time, resulting in a lower maximum concentration.

The more relevant parameter is $AUC_{0\text{-}inf}$, because it reflects how quickly the active ingredient is metabolized. Devane's Table 10 reports that the mean $AUC_{0\text{-}inf}$ for the 10 milligram extended-release hydrocodone product was 136.9 ng * hr/mL, and that the mean $AUC_{0\text{-}inf}$ for the immediate-release hydrocodone/acetaminophen product was 137.6 ng * hr/mL. JTX37 ¶ 105. Those numbers, as Dr. Schmidt testified, are "virtually identical values." Trial Tr. 256:12–20. Because the presence of acetaminophen had no appreciable effect on the $AUC_{0\text{-}inf}$ for hydrocodone, a person of ordinary skill would have understood that "acetaminophen is not

something that would have a significant impact on the metabolism or the pharmacokinetic profile of hydrocodone." Trial Tr. 257:1–8. Accordingly, the Court finds that a person of ordinary skill would not have been deterred from relying on combination products that contain acetaminophen, such as Jain, Vicodin, or Lortab, in designing an extended-release drug to treat patients with hepatic impairment based on Devane's formulation.

4. Most of Pernix's trial testimony is directed to what the proper dose would be for patients with hepatic impairment and whether a dose adjustment would be necessary. *See, e.g.*, Trial Tr. 693:7–17 (Dr. Gudin testifying that none of the labels for the immediate-release products included pharmacokinetic data, so they do not teach *how* to dose an extended-release hydrocodone formulation in a patient with mild or moderate hepatic impairment); Trial Tr. 695:17–696:2 (Dr. Gudin testifying about the expectation of a person of skill in the art about the need to adjust the dose). For purposes of these limitations, that evidence is largely beside the point. Whether or not Jain or the Vicodin and Lortab labels teach precise dosing levels, they indisputably teach that a hydrocodone-containing product can safely be administered to a patient with mild or moderate hepatic impairment.

5. Accordingly, the Court finds that a person of ordinary skill in the art, upon reading Devane, would have had a reasonable expectation of success in administering Devane's formula to patients with hepatic impairment based on the state of the art in 2012. The Court further finds that a person of ordinary skill would have been motivated to combine Devane with the teachings of Jain and the Vicodin and Lortab labels, and would have reasonably expected that Devane's formulation could be administered to hepatically impaired patients.

4. "Wherein the starting dose is not adjusted relative to a patient without hepatic impairment"

As discussed with regard to anticipation, Devane does not teach administering to a hepatically impaired patient a starting dose of a hydrocodone formulation that is not adjusted relative to a patient without hepatic impairment. Alvogen argues that the non-adjustment limitation of the two-step claims would have been obvious in light of Devane in combination with Jain, the Vicodin label, and/or the Lortab label. The Court agrees that, based on the information in Jain and the Vicodin and Lortab labels, a person of ordinary skill in the art would have been motivated to administer an unadjusted dose of the Devane formulation to hepatically impaired patients and would have had a reasonable expectation of success in so doing.

a. Motivation to combine

The evidence at trial shows that a person of skill in the art would have looked to immediate-release products containing the same active ingredient to determine the proper dosing levels for extended-release products. As noted, the FDA allowed Zogenix to rely on Vicoprofen, an immediate-release combination product, as a reference product for safety and efficacy testing for Zohydro. Trial Tr. 383:17–385:21. The evidence shows that the FDA would not have permitted the use of a formulation containing a different opioid as a reference product. Trial Tr. 383:17–385:21.[13] And a person of ordinary skill would have appreciated, from Devane's

[13] Similarly, the FDA permitted the Opana immediate-release product label to reference the pharmacokinetic testing for hepatically impaired patients reported in the Opana ER extended-release product label, as both formulations contained the same opioid. *See, e.g.*, JTX65, at 17 (Opana ER label, reporting pharmacokinetic data in patients with mild or moderate hepatic impairment); PTX103, at 12–13 (Opana immediate-release label, referring to the Opana ER pharmacokinetic study and making dosing recommendations based on that study).

pharmacokinetic clinical study results, that the acetaminophen in Jain's Vicodin CR, Vicodin, and Lortab would not affect the relevant pharmacokinetic parameters for hydrocodone.

As a counterexample, Pernix points to the differences between the 2006 label for Percocet, which is an immediate-release combination product that contains oxycodone and acetaminophen, and the 2010 and 2012 labels for OxyContin, which is an extended-release formulation that contains only oxycodone. Dkt. No. 244, at 28. The Percocet label states that care should be exercised when oxycodone is used in patients with hepatic impairment, PTX92, at 2, while the OxyContin label contains stronger language, requiring a dose reduction for all hepatically impaired patients, JTX66, at 17–18; JTX18, at 17.

The Court does not find that the Percocet/OxyContin example detracts from the motivation to combine, or the expectation of success, that a person of skill would have held in adapting dosing instructions between immediate-release and extended-release products. Despite that one contrary example, the overwhelming evidence at trial indicates that a person of skill would have expected that an immediate-release product would inform the proper dosing for an extended-release product.[14] The Court therefore finds that a person of ordinary skill in the art would have looked to immediate-release hydrocodone products, such as Lortab and Vicodin, in establishing the proper dosing for an extended-release hydrocodone product.

Pernix argues that a person of ordinary skill would not have relied on combination products for dosing instructions, because the FDA required Zogenix to perform a hepatic impairment study as part of its new drug application for Zohydro ER and did not allow Zogenix

[14] In addition, given that the Percocet label was from 2006 and the OxyContin labels were from 2010 and 2012, it could be that "there was an opportunity for a lot of new science to have been developed during that time that would influence that dosing recommendation." Trial Tr. 294:6–9.

to rely on Vicoprofen's safety information with regard to hepatic impairment. Dkt. No. 244, at 27; Trial Tr. 385:7–387:4, 433:13–22. To the contrary, the fact that Zogenix sought to use Vicoprofen in seeking approval for Zohydro ER suggests that a person of ordinary skill would look to combination products to inform the dosing for an extended-release opioid-only product. The fact that the FDA found the comparison insufficient to satisfy its safety and efficacy standards does not speak to the issue of obviousness: The standard to find a motivation to combine is far below what is sufficient to prove safety and efficacy to the FDA, and the Court does not find that the FDA's exacting approval requirements undermine the force of the evidence as to obviousness.

Pernix also argues that a person of skill in the art would not look to Jain based on unpredictability in the art. For support, Pernix cites the patent examiner's notice of allowance of the '760 patent over the Jain reference. JTX2, at 177. The examiner explained that "various oxycodone only extended release products are disclosed by Applicants at instant specification ¶¶ 12–16 which do not demonstrate the desired consistent pharmacokinetics. Thus, the predictability of producing an extended release with only hydrocodone bitartrate as the active appears to be unpredictable in the art and would thus not lead the skilled artisan to start the dosage at a dose similar to a normal patient." JTX2, at 177 (citation omitted); *see* Trial Tr. 702:11–704:9.

The Court finds that the patent examiner's stated reason does not support his conclusion: the differences between oxycodone and hydrocodone may demonstrate some unpredictability in the art between different opioids, but that is not evidence that one hydrocodone-containing product could not be used to predict the pharmacokinetic parameters of another hydrocodone-containing product. Indeed, that is precisely what the FDA did in allowing the use of Vicoprofen

as a reference drug for some of the safety characteristics for Zohydro ER. Trial Tr. 383:17–385:15.

For these reasons, and for those described in the immediately previous subsection, the Court finds that a person of ordinary skill, when considering whether a dose adjustment of Devane's formulation would be necessary for patients with mild or moderate hepatic impairment, would have been motivated to look to Jain and to the Vicodin and Lortab labels for a guidance as to the appropriate dosing levels of Devane's formulation for patients with mild or moderate hepatic impairment.

b. Reasonable expectation of success

The Court also finds that a person of ordinary skill in the art would have had a reasonable expectation of success in treating hepatically impaired patients with an unreduced starting dose of an extended-release hydrocodone formulation. Contrary to Pernix's contention, the evidence in Devane and Jain, as well as in the Lortab and Vicodin labels, would have provided ample support for such an expectation. Pernix's principal argument to the contrary is that the effects of the extended-release hydrocodone-only formulation in Devane could not have been predicted absent quantitative pharmacokinetic data, which was not presented in Devane or Jain, or in the Lortab or Vicodin labels. Dkt. No. 244, at 25–27, 29–30; Dkt. No. 246, at 11–14. The Court, however, finds that Jain provides sufficient pharmacokinetic data to give rise to a reasonable expectation that Devane's formulation would not require a dose adjustment for patients suffering from mild or moderate hepatic impairment.

The Jain reference describes in detail more than a dozen examples of studies that have been conducted on the safety and efficacy of Vicodin CR, the controlled-release form of Vicodin, which contains hydrocodone and acetaminophen. JTX38 ¶¶ 88–288; *see, e.g.*, JTX38

¶¶ 35, 79–83 (describing two double-blind, placebo-controlled clinical studies, one involving patients with chronic lower back pain and the other involving patients with osteoarthritis pain, and detailing adverse reactions); JTX38 ¶¶ 36, 84 (describing a double-blind, placebo-controlled study on patients following bunionectomy surgery); JTX38 ¶¶ 37, 85 (describing an open-label safety study, detailing adverse effects); JTX38 ¶ 63 (describing in vitro study of ethanol effects on Vicodin CR).

Among those studies, Jain describes a study directed to the "effects of hepatic insufficiency on the pharmacokinetics of Vicodin CR." JTX38 ¶ 64. Jain describes a study of 24 subjects—eight with normal hepatic function, eight with mild hepatic impairment, and eight with moderate hepatic impairment—all of whom were given Vicodin CR. *Id.* The Jain reference reports that the "mean C_{max} and AUC values of hydrocodone were similar" in all the subjects, while the "[m]ean C_{max} and AUC values of acetaminophen were similar in normal subjects and subjects with mild hepatic impairment, and 34 to 42% higher in subjects with moderate hepatic impairment." *Id.*

The Court finds that a person of ordinary skill would have understood that Jain's qualitative statement that the pharmacokinetic parameters for hydrocodone were "similar" means that a dose adjustment would not be not required for patients with mild or moderate hepatic impairment. As Dr. Schmidt credibly testified, a person of ordinary skill would have appreciated that "there was a real clinical study behind this" and that the values were not "brought up out of thin air." Trial Tr. 198:20–22. Jain is a published patent application submitted by a reputable pharmaceutical company, Abbott Laboratories, and it describes more than a dozen studies in great detail. *See* JTX38 ¶¶ 88–288. The Court finds that a person of ordinary skill would not

discount the teachings of Jain's hepatic impairment study, even though not all of the underlying quantitative data was set forth in the application.

The fact that Jain reported that the pharmacokinetic parameters for hydrocodone were "similar" for all three subject groups and that the pharmacokinetic parameters for acetaminophen were "similar" for normal subjects and those with mild hepatic impairment, while the acetaminophen parameters were 34 to 42% higher for the subjects with moderate hepatic impairment, is significant: it indicates that the term "similar" was used to refer to an increase less than that reported for the acetaminophen parameters in patients with moderate hepatic impairment. If the increases for hydrocodone had been greater than 34 to 42%, Jain presumably would have so indicated. It appears that Jain's summary of the hepatic impairment study notes only where the increases in serum concentrations were significant enough to give rise to possible grounds for concern. *See* Trial Tr. 484:7–485:1. A person of ordinary skill would have understood that a hepatic impairment study is conducted to determine whether a dose adjustment is required, and the Court finds that a report of "similar" pharmacokinetic parameters would be understood to mean that a dose adjustment is not required. Trial Tr. 197:1–198:22, 486:5–23.

The FDA's guidance on dose adjustments for patients with impaired hepatic function suggests that a label can state that no dose adjustment is required when the pharmacokinetic parameters are less than 1.25-fold greater in patients with hepatic impairment than in patients with normal liver function. A dose adjustment should be recommended, according to the FDA, when the effect of hepatic impairment is "obvious (e.g., two-fold or greater increase in AUC)." JTX31, at 10–11; *see* Trial Tr. 290:21–291:8. A person of ordinary skill would understand from Devane's bunionectomy study that the presence of acetaminophen would not have had a significant impact on the metabolism or pharmacokinetic parameters of hydrocodone. JTX37

¶¶ 104–05; Trial Tr. 256:21–257:8. Given that Jain suggests that the pharmacokinetic parameters for the hydrocodone in Vicodin CR are "similar"—*i.e.*, less than 34 to 42% greater—for patients with mild or moderate hepatic impairment, a person of ordinary skill would understand that Jain provides, at the very least, a reasonable expectation of success that a hydrocodone formulation would not require a dose adjustment for such patients.

Pernix argues that even if Jain's Vicodin CR did not require a dose adjustment, a person of ordinary skill would not "extrapolate" from that conclusion to Devane's formulation, which differs from the Vicodin CR formulation. Dkt. No. 246, at 12–13. That argument, raised for the first time in the post-trial briefs, is not supported by any trial testimony. In any event, the argument is undermined by Pernix's own expert, Dr. Gudin, who testified that a person of ordinary skill would have looked to various extended-release opioid products that do not contain hydrocodone in assessing whether there was a reasonable expectation of success. *See* Trial Tr. 693:7–21. Given that Pernix's expert would make such a cross-product comparison, the Court finds that comparing two different extended-release products that contain the same primary active ingredient would provide a reasonable expectation of success, even if the formulations were not identical.

Pernix seeks to discredit Jain because the Vicodin CR hepatic impairment study was neither published nor peer-reviewed. *See* Dkt. No. 244, at 29; Trial Tr. 701:19–25; *see also* PTX57; PTX58. The Court, however, credits Dr. Schmidt's explanation that the Jain study was a Phase I clinical study that is not required to be published, *see* Trial Tr. 198:8–200:1; *see also* JTX31, at 10 (FDA publication acknowledging that hepatic impairment studies usually involve a "small numbers of subjects"). The Court therefore finds no reason to believe that a person of

skill would discredit the study described in Jain on the ground that the study report was not published.

Pernix further argues that the silence of the Vicodin and Lortab labels as to the proper dosing for patients with mild or moderate hepatic impairment does not justify the inference that a dose adjustment is not required for those patients. Dr. Gudin testified that "it was common knowledge that clinicians were required to adjust the dose and adjust the starting dose of opioids when administering these agents to patients with liver issues." Trial Tr. 12:7–10. Therefore, he testified, a person of ordinary skill would not read the silence of those labels regarding mild or moderate hepatic impairment as suggesting that no dose adjustment would be required for such patients.

The Court does not credit Dr. Gudin's testimony on that point, as none of the authorities he cited at trial support his broad conclusion. Trial Tr. 12:14–14:9 (citing PTX14, at 5 (the Chandok article); PTX33, at 2 (the Verbeeck article); and JTX11, at 8 (the first Gudin article)); *see supra* sec. III.b.i. Although the Court does not depend solely on the Vicodin or Lortab labels as teaching that no dose adjustment of hydrocodone is required for patients with mild or moderate hepatic impairment, those labels, together with Alvogen's experts' testimony about the labels, are consistent with Jain's teaching. *See* Trial Tr. 202:9–206:17, 459:2–23.

Pernix contends that a person of ordinary skill would have looked to other extended-release opioid products, many of which contained pharmacokinetic data, rather than to Jain or the immediate-release hydrocodone combination products. Dkt. No. 246, 13–15. As described above, the Court finds that a person of skill, heeding the procedures of the FDA, would have preferred to look to products that contain the same active ingredient rather than to extrapolate from different drugs. *See* Trial Tr. 259:2–10 (Dr. Schmidt testifying that each opioid has

"different pharmacokinetic properties" so "you cannot extend from one to another with any degree of expectation that you are going to get it right"); Trial Tr. 478:17–24 (Dr. Weinberger testifying that a person of ordinary skill "would have understood that each one of these . . . opioids are different and they're handled by the body in different ways").

In any event, however, the evidence regarding extended-release drugs presented at trial would not have suggested that a reduced dose of a hydrocodone drug would be required for patients suffering from mild or moderate hepatic impairment. First, the label for TussiCaps, which is an extended-release hydrocodone product that includes chlorpheniramine, contains no dosing instruction for patients with mild or moderate hepatic impairment; it includes only a caution against using the product in patients suffering from severe hepatic impairment. DTX65, at 3. As Dr. Schmidt testified, the lack of any caution for patients with mild or moderate hepatic impairment would "give you some confidence that you could use this [at] the same dose level in patients with mild to moderate hepatic impairment as you would use in a healthy subject." Trial Tr. 206:10–17.

Second, the evidence as to non-hydrocodone extended-release opioid products is mixed, and it does not support Pernix's position that a person of skill in the art would expect that a dose adjustment would be required. As described above, four of the six non-hydrocodone extended-release opioids in evidence are either silent on the dosage for patients with mild hepatic impairment or explicitly state that no adjustment is required. DTX27, at 6–7; DTX67, at 18; DTX91, at 1, 5; DTX66, at 9; JTX65, at 5; JTX66, at 17–18. Four of the six are either contraindicated for or require reducing the starting dose in patients with moderate hepatic impairment. DTX27, at 6–7; DTX67, at 18; DTX91, at 1, 5; DTX66, at 9; JTX65, at 5; JTX66, at 17–18. Given this mixed picture, a person of ordinary skill reading Devane and Jain would

have understood that hydrocodone would be likely to perform more like those drugs that do not require a dose adjustment than like those that do.

In sum, the Court finds that a person of ordinary skill would have had a reasonable expectation of success that Devane's extended-release hydrocodone bitartrate could be administered to patients with mild or moderate hepatic impairment without adjusting the starting dose.

D. Secondary Considerations

It is well settled that what the Supreme Court has referred to as secondary considerations, *see KSR Int'l*, 550 U.S. at 406, 415—often referred to as "objective indicia"—must be taken into account in any obviousness analysis, and that such evidence can support a finding of nonobviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012). The Court finds that, as a whole, the secondary considerations are neutral or entitled to only minimal weight.

Pernix's expert Dr. Gudin offered testimony directed to three secondary considerations: unexpected results, long-felt unmet need, and the failure of others. Trial Tr. 745:8–9. As to unexpected results, Dr. Gudin testified that a person of ordinary skill "would have understood that in the face of organ dysfunction like hepatic impairment, patients required a dose adjustment for safety purposes." Trial Tr. 745:16–20.

As noted above, Dr. Gudin's testimony as to unexpected results is not supported by other evidence adduced at trial. Most significantly, the Jain reference disclosed that an extended-release hydrocodone could have similar pharmacokinetic properties in both normal and hepatically impaired patients. Moreover, there were a number of opioid products—both

hydrocodone products and products based on other opioids—that either did not require a dose adjustment in some hepatically impaired patients, or were silent on the dosage and did not expressly require a dose adjustment. DTX66, at 9 (Nucynta ER); DTX60, at 5 (Vicoprofen); DTX65, at 3 (TussiCaps); JTX15, at 1 (Lortab); JTX20, at 2 (Vicodin); DTX27, at 6–7 (Kadian); DTX67, at 18, 21 (Avinza); DTX91, at 5 (Exalgo).

Pernix also relies on testimony from the named inventors of the asserted patents that they expected that Zohydro ER would require a dose adjustment. *See* Trial Tr. 396:22–397:7 (Dr. Cynthia Robinson testifying that the results were "unexpected from our perspective"); Trial Tr. 373:10–15 (Andrew Hartman testifying that "we were looking at something novel and unexpected"); Trial Tr. 412:23–413:12 (Dr. Christopher Rubino testifying that he was "surprised" by the results of the hepatic impairment study).

The inventors' assessments, however, were based on a misunderstanding of the teachings of the articles and drug labels cited in the specification. For example, the common specification states that the Johnson article teaches that for hydrocodone, "the recommendation was to start with 50% of the usual dose." '760 patent, col. 2, ll. 48–54; '499 patent, col. 2, ll. 50–56. Later, in describing the inventors' discovery that their formulation of extended-release hydrocodone does not require a dose adjustment, the specification states, citing Johnson's article, that "[t]his is quite surprising and non-obvious, especially given recommendations in the literature to dose patient [sic] with hepatic impairment at 50% of the normal dose." '760 patent, col. 16, ll. 10–14; '499 patent, col. 16, ll. 10–14. As discussed above, however, Johnson states that 50 percent dosing is required only for patients with *severe* hepatic impairment; the article is silent as to the proper dosing of hydrocodone for patients with mild or moderate hepatic impairment. JTX32, at 7; *see* Trial Tr. 209:21–212:13. Dr. Schmidt testified that the summary of Johnson in the

patents' specifications is "a misinterpretation of Johnson's recommendation." Trial Tr. 212:8–13. The specification also describes the dosing recommendation for Nucynta ER, noting that the label requires a lower dose for patients with moderate hepatic impairment. '760 patent, col. 3, ll. 28–51; '499 patent, col. 3, ll. 30–53. The specification, however, omits reference to the portion of the Nucynta label that specifically states that "[n]o dosage adjustment is recommended in patients with mild hepatic impairment." DTX66, at 9.

Moreover, the inventors' testimony at trial did not address the hepatic impairment study reported in Jain, and Mr. Hartman, the project manager and team leader for the Zohydro ER project, testified that at the time of the Zohydro ER hepatic impairment study, he believed the Zohydro ER study "was the first time that the pharmacokinetics of hydrocodone had ever been studied in subjects with hepatic impairment." Trial Tr. 363:7–10. To be probative of non-obviousness, unexpected results "must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d at 967. In the absence of evidence that the inventors had adverted to the hepatic impairment study published by Jain in January 2010, prior to the 2011 Zohydro ER hepatic impairment study, their testimony about the putatively unexpected results from the Zohydro ER study is entitled to less weight. For these reasons, the Court finds the inventors' testimony that they were surprised by the results of the hepatic impairment study does not provide significant support for Pernix's position on non-obviousness.[15] In view of all the

[15] Evidence of unexpected results typically comes in the form of testimony or other evidence from experts in the field. *See, e.g.*, *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017); *Burlington Indus., Inc. v. Quigg*, 822 F.2d 1581, 1582–83 (Fed. Cir.

evidence at trial, the Court finds that a person of ordinary skill in the art would not have found the results of the Zohydro ER hepatic impairment study to be unexpected, and therefore concludes that this secondary consideration is, at best, neutral as to the issue of obviousness.

Pernix's argument that there was a long-felt unmet need for the invention is also not persuasive. Dkt. No. 244, at 31–32; Trial Tr. 747:14–748:14. The evidence at trial made clear that several products that did not require a dose adjustment, including some opioid-only formulations, were available on the market as of July 2012. *See, e.g.*, Trial Tr. 260:20–261:19, 490:23–492:18. Pernix's evidence on that issue was brief and conclusory in nature. Thus, the evidence of a long-felt unmet need, such as it was, does not weigh in favor of a finding of nonobviousness.

Finally, Pernix argues that there was a failure of others to achieve the invention. Pernix's evidence on that issue consisted entirely of Dr. Gudin's testimony that Vantrela, Cephalon's hydrocodone extended-release product, requires a dose adjustment for patients with mild or moderate hepatic impairment. Trial Tr. 748:15–749:1. That single data point, however, does not stand up against the other evidence at trial. Jain's Vicodin CR product demonstrates that others had succeeded in developing hydrocodone-containing products that do not require a dose adjustment. JTX38 ¶ 64. In addition, Purdue's Hysingla ER formulation of a hydrocodone-only extended-release opioid, which was being developed and tested at about the same time as Zohydro ER, does not require a dose adjustment for patients with mild or moderate hepatic

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1987). The inventors' testimony regarding unexpected results is less compelling, coming as it does from persons with an interest in the validity of the patent, one of whom (Mr. Hartman) was not a person of ordinary skill in the art. *See* Trial Tr. 382:10–383:11. As the Federal Circuit has noted, unsupported statements by the inventors, including in the specification, "cannot support a finding of unexpected results." *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370,1377 (Fed. Cir. 2011).

impairment. Trial Tr. 785:3–25; JTX13, at 19; *see generally* DTX7. The development of Hysingla ER thus undercuts Pernix's argument about the failure of others. Moreover, the development of Hysingla ER suggests that there was near-simultaneous invention of a product having similar properties and similar recognized advantages to the claimed formulations, a factor that also weighs in favor of a finding of obviousness. *See George M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010). In short, the evidence at trial relating to objective considerations is of minimal significance and does not offset Alvogen's strong showing of a motivation to combine references in the prior art with a reasonable expectation of success.

IV. Written Description

Section 112(a) of the Patent Act provides, in pertinent part, that the specification "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112(a). That portion of the statute embodies both the written description requirement and the enablement requirement of the Act.

The purpose of the written description requirement is to ensure that the "inventor actually invented the invention claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The written description requirement often becomes an issue in cases in which a broad genus is claimed and the specification discloses only one or a few species of that genus. In such cases, the issue is whether the species that were disclosed in the specification are sufficient to justify a conclusion that the inventor of the species actually invented—and is entitled to claim—the genus that is recited in the claims.

The written description problem presented by generic claims "is especially acute with genus claims that use functional language to define the boundaries of a claimed genus." *Id.* In such a case, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus." *Id.* Thus, an adequate written description of a claimed genus requires more than a generic statement of an invention's boundaries. Instead, it requires "the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568–69 (Fed. Cir. 1997)). In the chemical or biochemical arts, the written description must "distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004). If the disclosed species "only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus." *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) (*AbbVie Deutschland).*

A. Alvogen's Written Description Defense and Counterclaims

Simply put, Alvogen's written description defense comes down to this: All that the inventors contributed to the art was "to recognize that, based on the [pharmacokinetic] results of a routine [hepatic impairment] study, the HC-ER prior art formulation did not require a dose adjustment for patients with mild or moderate [hepatic impairment]." Dkt. No. 243, at 4. Rather than claim only that narrow invention, however, the inventors sought, and obtained, much

broader claims. Alvogen contends that because the full breadth of the claims is not supported by the common specification of the two patents-in-suit, the asserted claims are invalid for failure to satisfy the written description requirement.

As Alvogen observes, the asserted claims are broadly cast in generic form. Pernix argues that its claims are not generic, but that is clearly wrong. The asserted claims of the two Pernix patents do not recite methods of treatment involving the use of a particular identified formulation, or even a group of identified formulations. Instead, the formulation limitations recited in the claims read on all oral dosage units comprising extended-release hydrocodone in which hydrocodone is the only active ingredient. That genus of formulations incorporates an essentially limitless number of formulation species.

The other limitations in the asserted claims are all functional in nature. The functional limitations include the limitation that the starting dose of the formulation is not adjusted for persons with mild or moderate hepatic impairment relative to patients without hepatic impairment (claims 1–4 and 11 of the ’760 patent), as well as the limitations consisting of particular C_{max} or $AUC_{0\text{-}inf}$ levels in the release profile of the claimed hydrocodone formulation, either in absolute terms (claim 11 of the ’760 patent), or relative to persons not suffering from renal or hepatic impairment (claims 2–4 and 12 of the ’760 patent, and claim 1 of the ’499 patent), or both (claims 17 and 19 of the ’760 patent).

The functional limitations do not inform a person of skill in the art as to what the formulations must contain in order to exhibit those functional characteristics. Instead, the functional limitations define the claimed formulations according to whether they end up having those characteristics when tested. Thus, the claims are largely functional, and the only non-functional limitations are generic.

The common specification discloses only one formulation that was found to satisfy all the limitations of any of the claims, including the functional limitations. That formulation, set forth in Example 8 of the specification, was the formulation used in both Devane's bunionectomy study and the Zohydro ER hepatic impairment study, and it is the only formulation that is shown by the common specification to satisfy the functional limitations of the claims.

As disclosed in the specification, the Devane/Zohydro ER formulation contained hydrocodone bitartrate as its sole active ingredient in a mixture of 80 percent extended-release hydrocodone and 20 percent immediate-release hydrocodone. It also contained various excipients in prescribed amounts. The claims, however, are not limited to that single disclosed formulation. Instead, they cover any formulation that satisfies the functional limitations as long as it contains hydrocodone as the only active ingredient and comprises hydrocodone in extended-release form (thus permitting, but not requiring, the presence of some amount of hydrocodone in immediate-release form).

Pernix misses the point when it characterizes this case as involving "a new use of known compositions." Dkt. No. 246, at 1. To be sure, Zohydro ER was a known composition, and if the patentees had limited their claims to a method utilizing that composition, the patents likely would not have been vulnerable on written description grounds. Instead, they claimed expansively so as to capture a potentially huge number of compounds, none of which (except for Zohydro ER) had been shown to satisfy the functional limitations in the claims.

In its briefs, Pernix suggests that the disclosure of the 80:20 ratio of extended-release to immediate-release components in Zohydro ER distinguishes the claimed embodiments from other extended-release hydrocodone-only formulations. Dkt. No. 244, at 2; Dkt. No. 246, at 1. The problem with that argument is that the claims are not limited to compositions having any

particular ratio of extended-release to immediate-release components; the claims extend far beyond that, which is what gives rise to the written description problem.[16]

This case thus presents the problem highlighted by the Federal Circuit in *Ariad*, *AbbVie*, and *Regents of the University of California v. Eli Lilly & Co.*: whether the specification provides a sufficient written description of the claimed subject matter, given that the claims cover subject matter far beyond the scope of the embodiment described in the specification and do so in largely functional terms. Alvogen argues that the single embodiment set forth in the specification does not supply adequate written description support for the asserted claims. Pernix responds that the common specification describes more than just the single embodiment set forth in Example 8. Pernix contends that the specification contains several different sets of ingredients for the immediate-release component hydrocodone solutions and the modified-release coating solutions in Tables 1 and 2, and that the specification describes nine different dosage levels of the hydrocodone formulation, between 10 and 80 milligrams. Alvogen replies that there is nothing in the specification to indicate which, if any, of the formulations using those alternative solutions and dosages would produce the functional results set forth in the claims, other than the single

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[16] During closing argument, counsel for Pernix was asked whether the use of the term "comprising" in the claims indicated that the formulation could contain any amount of the immediate-release form of hydrocodone, as long as it contained some amount of the extended-release form of hydrocodone. Counsel for Pernix disagreed that a formulation consisting almost entirely of immediate-release hydrocodone, with only a small amount of extended-release hydrocodone, would fall within the scope of the claims, but he did not propose any particular limits on the percentage of the extended-release form of hydrocodone that would be covered by the claims. In particular, counsel did not suggest that the claims were limited to formulations containing 80 percent extended-release hydrocodone and 20 percent immediate-release hydrocodone, as in Devane. *See* Dkt. No. 254, at 104:11–109:10. To the extent that counsel's argument constitutes a late-blooming claim construction argument, the Court construes the claims to include hydrocodone-only formulations that contain at least some extended-release hydrocodone bitartrate, regardless of whether they also contain any immediate-release hydrocodone bitartrate.

tested embodiment set forth in Example 8 (the Devane/Zohydro ER formulation). According to Alvogen, the record reflects that clinical testing would be required in order to determine which if any of those formulations—or any other of the virtually infinite number of potential formulations covered by the claims—would produce the functional results recited in the asserted claims.

B. The Evidence

Whether the patentee has complied with the written description requirement is a question of fact, which the finder of fact must resolve in light of the governing legal standards and the disclosures and claims of the patents. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 962–63 (Fed. Cir. 2002); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). In order to find a claim invalid for failure to satisfy the written description requirement, the finder of fact must find the written description deficient by clear and convincing evidence. *See Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1351 (Fed. Cir. 2011); *Intirtool Ltd. v. Texar Corp.*, 369 F.3d 1289, 1294 (Fed. Cir. 2004).

The evidence at trial regarding written description came mainly from the invalidity experts, Dr. Mayersohn for Alvogen and Dr. Koleng for Pernix. Dr. Mayersohn testified that the breadth of the claims was not supported by the common specification, which contained only one operative embodiment that was known to satisfy the limitations of the claims. Trial Tr. 553:24–554:5, 562:1–17. The specification, Dr. Mayersohn testified, did not disclose what combination of components would give rise to the target pharmacokinetic properties in patients with hepatic impairment other than the single example set forth in Example 8. Trial Tr. 564:8–14. The task of creating a formulation that would produce similar results for hepatically impaired and normal patients, he said, would be "a much more difficult challenge." Trial Tr. 585:16. To determine what formulations would work, he testified, would require that each candidate formulation be

tested to see if it met the limitations of the asserted claims. Trial Tr. 561:19–23. He also testified that the common specification was "totally devoid of presentation of structural or formulation characteristics that would allow a person of skill to determine a member of a class such as that described here." Trial Tr. 563:13–16. That testimony was not contradicted either on cross-examination or by Pernix's expert, Dr. Koleng, and the court credits Dr. Mayersohn's testimony on those points.

For his part, Dr. Koleng testified that the patents-in-suit provide sufficient information to allow a person of skill in the art to "envision and make formulations that could yield [the] target PK properties to practice the invention." Trial Tr. 609:12–18. He was asked whether, "given the characteristics that we have discussed in Example 6, in the PK profile for healthy patients and patients with mild and moderate hepatic impairment in Example 8, one skilled in the art could envision and readily produce formulations to achieve that profile?" Trial Tr. 614:21–615:1. He answered in the affirmative, stating that he believed "a [person of ordinary skill in the art] with the patents in hand could readily envision and make formulations to hit target PK profiles provided in the patent." Trial Tr. 615:2–4. He explained that "the drug product formulation can be envisioned and made to deliver certain PK values when those PK values are known as is the case here." Trial Tr. 615:8–12.

Dr. Koleng testified that he did not think a person of ordinary skill in the art would need to "go through a series of exercises and trial and error to determine if these formulations can be used [to] practice the claimed method." Trial Tr. 620:20–25. He explained that a person of skill in the art would be able to use the examples in the common specification in "formulating a composition that could be used to practice the claimed invention, mostly targeting PK profiles and the no dose adjustment." Trial Tr. 621:3–7.

Dr. Koleng testified that Example 8 in the common specification "shows that the inventors actually invented the claimed invention." Trial Tr. 608:16–19. When a hepatic impairment test was conducted using that formulation, the pharmacokinetic data showed that subjects with mild or moderate hepatic impairment did not have unacceptably high levels of hydrocodone in their systems. For that reason, the inventors concluded that patients with mild or moderate hepatic impairment could safely be given the same dosage levels of the drug as were prescribed for patients without hepatic impairment.

According to Dr. Koleng, the disclosures in the specification were not limited to Example 8, the one example for which hepatic testing was conducted, but included 377 other examples of suitable formulations. He derived that number by multiplying the six different immediate-release component hydrocodone formulations set forth in Table 1 of the common specification, by the seven different modified-release coating solutions set forth in Table 2 of the specification, both of which were lifted verbatim from Devane, and then multiplying that product by the nine different dosage levels, between 10 and 80 milligrams of hydrocodone, that were listed in the specification. Trial Tr. 618:15–619:20.

Dr. Koleng further testified that a person of ordinary skill in the art could readily formulate a composition that could be used to practice the claimed invention. He noted that Example 3 of the specification contains a short list of potential excipients that could be used in such a formulation and that Table 1 of the specification contains various components in the immediate-release formulation that could be used in a mixed immediate-release and extended-release formulation. Trial Tr. 620:20–622:3, 627:4–15, 628:23–629:4. He added that Example 7 of the specification, which contains the dissolution profile for the Devane formulation, would provide formulators "with an in vitro target." Trial Tr. 628:23–629:4. He explained that after

determining which formulations "would match or conform to the in vitro targets," an investigator would regard those formulations as "leading candidates to potential dosing in a PK study" and could then conduct testing to determine whether "they exhibit PK parameters as well." Trial Tr. 629:13–16. What was provided in the specification, according to Dr. Koleng, was not merely an "invitation to conduct research," but a "target PK profile" to use in studying candidate formulations. Trial Tr. 629:19–630:1.

Dr. Koleng's testimony focused on the pharmacokinetic data from the hepatic impairment test on the Devane formulation and the dissolution rate for that formulation. He did not, however, point to anything in the specification that disclosed whether any other formulation would produce pharmacokinetic results equivalent to those discovered in the Devane formulation testing, or how those results could be obtained. In particular, Dr. Koleng did not point to any other formulation that would produce similar pharmacokinetic results for normal subjects and those with hepatic impairment. On cross-examination, he admitted that he would not know whether a particular formulation would practice the functional limitations recited in the claims without conducting a hepatic impairment study. Trial Tr. 643:6–11, 646:13–17.

Although Dr. Koleng acknowledged that Example 8 was the only actual embodiment of the invention set forth in the specification, Trial Tr. 645:19–647:20, he testified that he believed "that the specification would disclose to a [person of ordinary skill in the art] additional formulations that could be envisioned and made to test to see if it could be used to practice the invention." Trial Tr. 646:9–12. He admitted, however, that with respect to formulations other than the Example 8 formulation, including the other 377 formulations that he said were disclosed in the specification, it would be necessary to do a hepatic impairment study for each to determine if it would satisfy the limitations of the claims. Trial Tr. 653:19–655:15, 660:22–661:22.

C. The Court's Findings

Based on the patents and the testimony of Drs. Mayersohn and Koleng at trial, the Court makes the following findings regarding the written description issue:

1. The non-adjustment and pharmacokinetic limitations of the asserted claims are functional limitations, in that they describe the results that flow from a particular formulation rather than setting forth the components that can be used to obtain those results.

2. The claims are all generic in nature, in that they are directed to methods of treating pain by administering to patients any of an open-ended set of formulations that satisfy either the non-adjustment or the pharmacokinetic limitations of the various asserted claims.

3. Example 8 in the common specification is a species falling within the genus defined by the limitations of each of the asserted claims. The common specification does not disclose any other operative species that was shown to satisfy the functional claim limitations.

4. Example 8 is the formulation disclosed in the prior art Devane reference and is the formulation used in Pernix's opioid product, Zohydro ER. The inventors of the '760 and '499 patents did not invent the Devane composition, but instead merely determined that Devane's formulation has certain pharmacokinetic properties that permit it to be administered to persons with mild and moderate hepatic impairment at the same dosage level as for persons without hepatic impairment. They made that discovery after conducting a clinical hepatic impairment study to obtain FDA approval for Zohydro ER.

5. Example 8 describes the clinical study of the pharmacokinetic effects of Zohydro ER on subjects with hepatic impairment, as compared to normal subjects. '760 patent, col. 18, line 25, to col. 19, line 44; '499 patent, col. 18, line 25, to col. 19, line 44. The example relates the study results, which showed that the increases in serum concentration of hydrocodone in patients

with liver dysfunction, as compared to normal patients, were modest. The study reported an $AUC_{0\text{-}inf}$ 10% higher and a C_{max} 8% higher in subjects with mild hepatic impairment as compared to normal subjects, and an $AUC_{0\text{-}inf}$ 26% higher and a C_{max} 10% higher in subjects with moderate hepatic impairment as compared to normal subjects. Those differences, according to the specification, "would not be considered large enough to require dosage adjustment for patients with hepatic impairment." '760 patent, col. 23, ll. 42–44; '499 patent, col. 23, ll. 42–44.

6. Neither the specification nor any evidence offered at trial points to any structural features that would assist a person of ordinary skill in the art in identifying species falling within the asserted generic claims. The 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, and the sample components for the immediate release hydrocodone and modified release coating solutions in Table 1 and Table 2 would contain candidate components for the formulation, *see* Trial Tr. 615:13–616:16, but no assurance that any particular formulation using those components would work.

7. The inventors admitted at trial that they did not know why the Devane formulation functioned in the way it did, to produce pharmacokinetic results for patients with mild or moderate hepatic impairment similar to those for patients with normal hepatic function. Trial Tr. 380:6–11, 401:11–13, 436:20–438:8; *see also* Trial Tr. 441:1–6 (same testimony by Brooks Boyd, Zogenix vice-president of development).

8. Dr. Koleng admitted at trial that he did not "consider how specific attributes of Example 8 or the HC-ER formulation related to the PK results that that formulation generated." In particular, he admitted that he was not "asked to opine on what specific special sauce, if you will, in the formulation resulted in the PK profile." Trial Tr. 637:18–24. There was no other

evidence at trial indicating what component or combination of components was responsible for the pharmacokinetic results obtained from the hepatic impairment study on Zohydro ER.

9. The Court finds that much of Dr. Koleng's testimony as to background facts is credible. In particular, the Court accepts his factual description of what was disclosed in the examples, tables, and figures of the common specification. However, the Court does not credit Dr. Koleng's 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. His testimony about what was disclosed in the common specification merely shows that the specification revealed components that could usefully be combined in immediate-release and extended-release formulations, such as the excipients and the coating components that could be used in such formulations. Those disclosed components might make the formulation of testing samples easier, by providing a starting point that had produced one successful formulation. But what was left undisclosed in the specification was any way of predicting which formulations would work and which would not. Ultimately, as Dr. Koleng admitted, the only way to determine which formulations would satisfy the limitations of the claims would be to conduct hepatic impairment studies. Thus, Dr. Koleng's statements to the effect that a person of skill in the art, "with the patents in hand could readily envision and make formulations to hit target PK profiles provided in the patent," Trial Tr. 615:2–4, were subject to the considerable qualification that the task of determining which formulations would work for that purpose would require clinical hepatic impairment testing of each formulation.

10. The common specification discloses only one formulation that satisfies the limitations of the claims: the formulation set forth in Example 8 of the specification, which is the

formulation featured in the prior art Devane reference and which became Zohydro ER. Although the specification contains references to numerous other components, which can be combined into many other formulations, none of those other possible formulations were shown to satisfy either the "non-adjustment" or "PK" limitations of either set of asserted claims. As Dr. Koleng acknowledged at trial, the only way to determine whether any of those formulations would satisfy either the non-adjustment or the pharmacokinetic limitations of the asserted claims would be to conduct hepatic impairment tests on each one.

11. With the exception of Example 8, the "examples" set forth in the common specification are not really "examples" of the formulations covered by the claims. They consist, instead, of general descriptions of the kinds of components that can be found in a formulation such as the one described in Example 8. They describe, for example, dosage ranges for the hydrocodone component (Examples 1 and 2), a listing of possible inactive ingredients (Examples 2 and 3), and various possible combinations of ingredients for use in the immediate-release component hydrocodone solution and in the modified-release coating solution (Example 6), and the dissolution profile of the Example 8 formulation (Example 7 and Figures 7 and 8).

12. With the exception of Example 8, the examples do not indicate that any of the various formulations would satisfy the pharmacokinetic limitations of the one-step claims or satisfy the requirement of the two-step claims that reduced dosages of the claimed hydrocodone formulation would not be required for patients with mild or moderate hepatic impairment.

13. In the end, Dr. Koleng's testimony about the disclosures in the specification simply shows that there is a single embodiment, the Devane formulation that became Zohydro ER, that satisfies the limitations of the claims. The effect of Dr. Koleng's testimony is that by relying on the characteristics of the Devane formulation, a formulator could likely produce other similar

formulations that would fall within the scope of the claims. But all that evidence shows is that that the inventors had possession of a single species. It does not show that they had possession of the broad genus covered by the claims.

D. Analysis

Based on the findings set forth above, the Court concludes that the asserted claims of the '760 and '499 patents are not supported by an adequate written description, as required by section 112(a). The specification contains a detailed description of one embodiment, the Devane/Zohydro ER formulation, together with the test results from the hepatic impairment study on that formulation and characteristics of that formulation, such as its components and its dissolution profile. All of that information, however, relates to only a single embodiment within the broad scope of the claims. While that information could be of use in formulating other hydrocodone-only formulations, it would provide no guidance as to which of those formulations would satisfy the functional limitations of the claims and which would not. The Court therefore finds that the specification fails "to distinguish . . . infringing methods from non-infringing methods," *Univ. of Rochester*, 358 F.3d at 926; it discloses a species that "only abide[s] in a corner of the genus," and therefore does not "describe[] the genus sufficiently to show that the inventor invented, or had possession of, the genus." *AbbVie Deutschland*, 759 F.3d at 1301.

Pernix argues that the fact that experimentation would be necessary to determine whether particular formulations within the claimed genus satisfy the limitations of the claims is not fatal to the claims on written description grounds. Pernix relies, *inter alia*, on the opinion of the Court of Customs and Patent Appeals in *In re Fuetterer*, 319 F.2d 259 (C.C.P.A. 1963), to support that contention. *Fuetterer*, however, is distinguishable on an important ground, which is a theme that runs through a number of decisions of the Federal Circuit and its predecessor. In *Fuetterer*, the

invention related to a tread stock, usable in vehicle tire treads, that would improve the traction of the treads. The specification described the invention as follows:

> In accordance with the present invention, a carbohydrate, a protein, or mixture thereof, which is insoluble or which is only slightly soluble in cold water but which forms a colloidal suspension therein, together with one or more inorganic salts which are effective in maintaining the carbohydrate, protein, or mixture thereof, in colloidal suspension in the film of water which forms around the tire tread when the tire engages a wet or icy road or pavement, are incorporated in a finely divided state in rubber, together with the other compounding ingredients which have previously been utilized in combination with rubber, to form the rubber stock for forming the tire tread.

319 F.2d at 260 (footnote omitted).

The Board found that without evidence from testing, the claims were invalid for "undue breadth" on the ground that the specification did not disclose which inorganic salts would have that property and that one skilled in the art "would not know offhand which inorganic salts are capable of so functioning." *Id.* at 265. The court reversed, concluding that the applicant did not need to provide the experimental evidence "necessary to determine the suitability of *undisclosed* salts to operate in appellant's claimed combination," because the invention was "the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties." *Id.* at 265 (emphasis added).

This case differs from *Fuetterer* in a critical respect. In *Fuetterer*, the invention was not the discovery of inorganic salts that can maintain carbohydrates, proteins, or a mixture thereof in colloidal suspension. Instead, the invention was a combination that resulted in a tire tread that is effective in wet or icy conditions. The specification explained that the manufacturing process could employ any inorganic salt that maintains a colloidal suspension. In that setting, the court ruled, it was not essential for the inventor to identify the particular salts that could be effective in the claimed combination.

In this case, by contrast, the invention is a method of treating pain that consists of administering a particular formulation to patients with mild or moderate hepatic impairment. Identifying the formulation is essential to the invention. Simply saying that the method of treatment works with a formulation that performs the recited functions does little more than to say that the method of treatment is effective with a formulation that works. Absent a description of the class of formulations that will work, as the Federal Circuit stated in *Ariad*, a patent merely describes the problem to be solved and claims all solutions to it. Here, the efficacy of the claimed treatment method depends entirely on whether the particular formulation functions in the manner recited in the claims. It is therefore critical that the formulation be described with sufficient specificity to ensure that the inventors have invented the full scope of the formulations recited in the claims and not simply a single operative embodiment within that class.

In re Herschler, 591 F.2d 693 (C.C.P.A. 1979), also cited by Pernix, presented a similar issue. In that case, the court found adequate written description support for broad claims for topically administering a steroidal agent by administering the steroidal agent together with dimethyl sulfoxide. Even though the specification disclosed only a single example of a steroidal agent, the court found that the disclosure was sufficient because the claim was drawn to the method of administering the steroidal agent, and numerous active steroidal agents were known to persons of skill in the art. *Id.* at 701. As the court summarized its ruling: "[C]laims drawn to the [u]se of [k]nown chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description. In *Fuetterer* and here, such is the case." *Id.* at 702. The court noted that "[w]ere this application drawn to novel 'steroidal agents,' a

different question would be posed." *Id.* at 701; *see also Univ. of Rochester*, 358 F.3d at 928 (discussing *Herschler*).

In *Herschler*, the invention was the administration of certain physiologically active substances—in particular, steroids—with dimethyl sulfoxide. Because the steroids were well known compounds whose precise identity was only "auxiliary to the invention," there was no need for the specification to set forth in detail the entire range of species making up the genus of steroids. In this case, by contrast, the identity of the hydrocodone formulations that would have a similar effect on subjects with and without hepatic impairment was not known, other than the one tested formulation described in Example 8 of the specification.

Another case that Pernix relies on, *Erfindergemeinschaft UroPep GBR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629 (E.D. Tex. 2017) (*UroPep)*, is similar to *Fuetterer* and *Herschler*, and is similarly distinguishable from this case. In *UroPep*, the asserted claims were to the method of using a selective inhibitor of the enzyme PDE V to treat benign prostatic hyperplasia ("BPH"). Critically, the invention in *UroPep* was not a method for inhibiting PDE V, but a method for treating BPH by using selective PDE V inhibitors, which were well known in the pharmaceutical arts. While the invention in the present case entails the use of certain hydrocodone formulations that affect patients with and without hepatic impairment similarly, what is missing from the patent in this case is a description of what distinguishes the hydrocodone formulations that function in that manner from those that do not. The invention in *UroPep* was not the identification of particular PDE V inhibitors, but the use of a class of compounds, known to have that inhibiting feature, for a particular therapeutic purpose. The *UroPep* case therefore did not present the problem presented in the *University of Rochester* case and in this case, of an inventor

seeking claim coverage for a broad genus of compounds that perform a particular function, while only disclosing a small subset of such compounds.

Pernix also relies on *Monsanto Co. v. Scruggs*, 459 F.3d 1328 (Fed. Cir. 2006); *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 1073-74 (Fed. Cir. 2005); and *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). The facts of those cases, however, contrast sharply with the facts of this one in a way that underscores the written description problem with Pernix's patents. In each of those cases, the court found that given the state of knowledge in the art, the disclosure provided sufficient support for the claims. In *Monsanto*, the court held that it was unnecessary for the patentee to include specific DNA sequences when referring to the CaMV 35S promoter, since "those of ordinary skill in the art knew the DNA sequences of several strains of the CaMV virus, the location of the CaMV promoters, and the DNA sequences for several CaMV 35S promoters." 459 F.3d at 1337. Similarly, in *Invitrogen*, the court upheld the district court's determination that the disclosure in the specification was sufficient because "the sequences of RT genes were known and members of the RT gene family shared significant homologies from one species of RT to another." 429 F.3d at 1073. And in *Amgen*, the court observed that the written description requirement can be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure," which the court found to be true in that case. 314 F.3d at 1332. Moreover, the *Amgen* court found that the undisclosed matter pertained to a different method of making the claimed compositions, not to the invention claimed. *Id.* at 1333. In this case, by contrast, 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.

The Federal Circuit's decision in *AbbVie Deutschland* illustrates the difference between the cases on which Pernix relies and this case. The claims in *AbbVie Deutschland* were drawn to isolated antibodies that would neutralize the activity of human interleukin 12, and the patent purported to teach how to make such antibodies. The examples given in the patent, however, were limited to certain species of the claimed antibodies, and the specification did not disclose structural features common to the members of the claimed genus of antibodies. 759 F.3d at 1299. Under these circumstances, which closely resemble the circumstances of this case, the Federal Circuit held that the written description requirement was not satisfied.

A particularly important Federal Circuit precedent for this case is *In re Alonso*, 545 F.3d 1015 (Fed. Cir. 2008). In that case, the Federal Circuit upheld a decision of the Patent and Trademark Office Board of Patent Appeals and Interferences holding an invention unpatentable for failure to satisfy the written description requirement. The Federal Circuit's decision in that case answers several of Pernix's arguments regarding the written description requirement.

First, *Alonso* answers Pernix's argument that the claims in the asserted patents do not run afoul of the written description requirement, because they are directed to methods of treatment and not to the formulations that are used in those methods of treatment. The claim at issue in *Alonso*, like the claims in this case, involved a method of treating a particular disease by administering an effective amount of a particular type of antibody.

Second, *Alonso* answers Pernix's argument that certain written description decisions of the Federal Circuit do not apply because in those cases the specification contained no disclosed embodiments of the generic claims. In the *Alonso* case, as in this case, the specification contained an embodiment of the claims, thus showing that a failure to satisfy the written description requirement is not limited to cases in which there are no disclosed embodiments. *See*

also LizardTech, Inc. v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1345 (Fed. Cir. 2005); *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004); *Enzo*, 323 F.3d at 969; *Regents of the Univ. of Cal.*, 119 F.3d at 1568. Indeed, the court in *Alonso* rejected Alonso's effort to distinguish his case from the Federal Circuit's decision in *University of Rochester* on the ground that he had reduced his method to practice and identified the resulting compound, while the inventors in *University of Rochester* did not disclose any operative embodiments of the invention.

Third, *Alonso* answers Pernix's related argument that the single embodiment disclosed in the specification was sufficient to support the broad generic claims. As in this case, the specification in *Alonso* disclosed only a single species of the genus of claimed antibodies, which the court found "cannot be said to be representative of a densely populated genus." 545 F.3d at 1021. Even though the specification disclosed a species of the genus, the court in *Alonso* found the written description insufficient to satisfy the written description requirement for claims directed to the genus.

To be sure, the fact that some testing may be necessary to determine, for example, the effective dose of a claimed drug, is not fatal to the validity of a claim challenged on written description grounds. *See Takeda Pharm. Co. v. Impax Labs., Inc.*, No. C-11-1610, 2013 WL 2384240, at *17 (N.D. Cal. May 30, 2013). In this case, however, the evidence showed that testing would be necessary to decide which, if any, formulation within the genus would produce pharmacokinetic values in hepatically impaired patients roughly similar to the pharmacokinetic values obtained in normal patients. Given that the testing results would be fundamental to determining which formulations would satisfy the asserted claims, it is apparent that, in the absence of such testing data, the inventors cannot be said to have possessed the full scope of the claimed invention. All that the specification discloses is that one such formulation will work for

that purpose. Whether any others will work, and which they are, would depend entirely on testing, and thus cannot be said to have been within the scope of what the patentees invented.

Pernix repeatedly emphasizes that the specification of its patents shows a specific method that works. What Pernix fails to acknowledge, however, is that it has claimed not just the formulation disclosed in the common specification, but any formulation that will work to produce the results recited in the claims, i.e., pharmacokinetic profiles for subjects with mild or moderate hepatic impairment that are close to those for normal patients.

Therein lies the written description problem: the claims are far broader than the disclosure. As the Federal Circuit put the matter in *Ariad*, the claims are defective because they "cover any [formulation] later actually invented and determined to fall within the claim's functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention." 598 F.3d at 1353. In short, what was claimed did not correspond to what was described. *Alcon*, 745 F.3d at 1191.

In that respect, this case is akin to *Novozymes A/S v. DuPont Nutrition Bioscience APS*, 723 F.3d 1336 (Fed. Cir. 2013). In that case, as in this one, the specification was very broad, providing "only generalized guidance listing several variables that might, in some combination, lead to a useful result." *Id.* at 1346. The court held that the written description requirement was not satisfied. In response to Novozymes' argument that a person of skill in the art would have known how to test all of the possible variants within the scope of the invention as described, the court ruled that to possess the embodiments within the general scope of the specification "would have required Novozymes to confirm its predictions by actually making and testing individual variants or at least identifying subclasses of variants that could be expected to possess the claimed properties." *Id.* at 1350. The same is true here.

In its post-trial response brief, Pernix makes a final argument that Alvogen failed to elicit evidence at trial "about any ER hydrocodone formulation that could be used in the claimed method besides HC-ER [the tested Devane formulation]." That failure is fatal to Alvogen's written description argument, according to Pernix, "because Alvogen has no evidence—let alone clear and convincing evidence—that: (1) species falling within the 'genus' differ from those in the patents, and (2) a [person of ordinary skill in the art] could not envision those undisclosed species." Dkt. No. 246, at 4–5.

The Court rejects that argument. The problem with the claims is that the specification provides no basis for believing that all species falling within the genus display the functional features of the single embodiment that was tested for those features. Nothing in the specification would indicate to a person of skill in the art which, if any, of those species, i.e., all oral dosages of hydrocodone-only formulations containing at least some of the hydrocodone in extended-release form, would satisfy the functional limitations of the claims. As the Federal Circuit stated in *University of Rochester*, the written description must allow a person of ordinary skill in the art to "distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods." 358 F.3d at 926. A patentee may not disclose only a particular species and "leav[e] it to others to explore the unknown contours of the claimed genus." *AbbVie*, 759 F.3d at 1300.

To the extent that Pernix means to argue that the claims, even though broadly worded, may actually cover only one embodiment—Zohydro ER—and that Alvogen's written description challenge fails because Alvogen has not adduced evidence that there are any other operative species within the genus of formulations covered by the claims, the Court rejects that argument. A patentee may not draft claims that are sweepingly broad and then defend against a challenge to

their breadth by pointing out that the challenger has failed to show that there are any operative embodiments within the broad scope of the claims other than those that were specifically disclosed in the specification. To sustain patent claims on that ground would permit a patentee to "attempt to preempt the future before it has arrived," *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993), and then be rewarded in that effort if the challenger cannot point out exactly how the future will unfold.

What Pernix is asking the Court to do is, in effect, to narrow the scope of the claims to cover only the embodiment disclosed in the specification. As the Federal Circuit pointed out in *Alcon Research, Ltd. v. Apotex Inc.*, in response to a similar argument: "This is not how patent law works. . . . [Y]ou can't simply disavow the invalid portion and keep the valid portion of the claim. . . . Courts do not rewrite the claims to narrow them for the patentee to cover only the valid portion." 687 F.3d at 1368. In any event, the evidence indicates that Purdue's Hysingla ER formulation, which does not require a dose adjustment for patients with mild or moderate hepatic impairment, satisfies the asserted claims while containing a formulation different from that in Pernix's Zohydro ER. Trial Tr. 785:5–19, 794:6–797:9. Moreover, the record contains evidence of another extended-release hydrocodone-only formulation that, according to Pernix's expert, was shown by testing not to satisfy the pharmacokinetic limitations of the claims. *See* '760 patent, col. 2, ll. 56–67; '499 patent, col. 2, line 58, to col. 3, line 2; JTX8; Trial Tr. 667:6–16. That evidence demonstrates that products satisfying the formulation limitations of the claims might satisfy the pharmacokinetic limitations, but would not necessarily do so.

For the reasons stated, the Court finds, by clear and convincing evidence, that the disclosures of the '760 and '499 patents fail to provide an adequate written description of the

inventions set forth in the asserted claims, as required by 35 U.S.C. § 112(a), and that the asserted claims are therefore invalid.

Judgment will be entered in accordance with the foregoing Findings of Fact and Conclusions of Law.

IT IS SO ORDERED.

SIGNED this 24th day of August, 2018.

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WILLIAM C. BRYSON
UNITED STATES CIRCUIT JUDGE