United States Court of Appeals for the Federal Circuit

ENDO PHARMACEUTICALS SOLUTIONS, INC., BAYER INTELLECTUAL PROPERTY GMBH, BAYER PHARMA AG,
Plaintiffs-Appellees

v.

CUSTOPHARM INC.,
Defendant-Appellant

2017-1719

Appeal from the United States District Court for the District of Delaware in No. 1:14-cv-01422-SLR-SRF, Judge Sue L. Robinson.

Decided: July 13, 2018

NEVIN M. GEWERTZ, Bartlit Beck Herman Palenchar & Scott LLP, Chicago, IL, argued for plaintiffs-appellees. Also represented by ADAM MORTARA, JOHN SCOTT MCBRIDE, TAYLOR A.R. MEEHAN, FAYE PAUL.

DOUGLASS C. HOCHSTETLER, Kelley Drye & Warren, LLP, Chicago, IL, argued for defendant-appellant. Also represented by CONSTANTINE KOUTSOUBAS, SARITA MUTHA, MARK J. SCOTT; CLIFFORD KATZ, New York, NY.

Before MOORE, LINN, and CHEN, *Circuit Judges.*

CHEN, *Circuit Judge*.

Endo Pharmaceuticals Solutions, Inc. (Endo) holds the approved New Drug Application for Aveed®, a testosterone undecanoate (TU) intramuscular injection. Bayer Intellectual Property GmbH and Bayer Pharma AG (Bayer) own the two patents listed in the Orange Book for Aveed®, U.S. Patent Nos. 7,718,640 (the '640 patent) and 8,338,395 (the '395 patent). Custopharm Inc.'s (Custopharm) predecessor-in-interest, Paddock Laboratories, LLC, submitted an Abbreviated New Drug Application (ANDA) to the U.S. Food and Drug Administration (FDA) for approval to produce and market a generic version of Aveed®. In connection with the ANDA filing, Custopharm made a Paragraph IV certification and gave notice of the certification to Endo and Bayer on October 8, 2014. On November 20, 2014, Endo and Bayer brought an action alleging infringement of the '640 and '395 patents. During the proceedings, Custopharm stipulated to infringement, and Endo and Bayer limited their asserted claims to claim 2 of the '640 patent and claim 18 of the '395 patent. After a four-day bench trial on invalidity, the district court concluded that Custopharm had not proven that the claims were invalid under 35 U.S.C. § 103. Custopharm appealed. For the reasons below, we find no reversible errors in the district court's conclusion and accordingly, we affirm.

BACKGROUND

Aveed® is a long-acting injectable testosterone replacement therapy for men suffering from physiologically low levels of testosterone, also known as hypogonadism. Before the 2003 priority date for the invention claimed in the '640 and '395 patents, then-existing testosterone replacement therapies had three significant shortcomings. First, the existing injectable therapies required patients

to visit their doctors every two or three weeks to receive intramuscular injections, and the available topical therapies required daily application. Second, the available therapies required the prescribing doctor to adjust the dosage or intervals of administration for each patient, which required doctors to frequently monitor their patients' testosterone levels. Third, the pre-2003 therapies did not provide stable testosterone levels, leading to periods of low testosterone between treatments. Patients would experience elevated testosterone levels immediately after an injection, but testosterone levels would fall to below the normal physiological range before the next injection.

Aveed®'s patented formulation addressed some of these shortcomings: (1) after the initial two injections, Aveed® is only administered five times a year; (2) it is a treatment that works for nearly all men suffering from hypogonadism, thus obviating the need for doctors to personalize testosterone replacement therapy; and (3) patients on Aveed® avoided the fluctuations in testosterone levels associated with other injectable products on the market before 2003. Claim 2 of the '640 patent and claim 18 of the '395 patent cover Aveed®'s formulation and injection regimen. Both patents, entitled "Methods and Pharmaceutical Compositions for Reliable Achievement of Acceptable Serum Testosterone Levels," issued from the same parent application and share a common specification.

Claim 2 of the '640 patent covers a 750 mg dosage of TU in the composition described in claim 1:

> A composition formulated for intramuscular injection in a form for single injection according to claim 1, which contains ***750 mg testosterone undecanoate***.

'640 patent, col. 13, ll. 29–31 (emphasis added). Claim 1 reads:

> A composition formulated for intramuscular injection in a form for single injection which contains ***250 mg/ml testosterone undecanoate*** in a vehicle containing a mixture of ***castor oil and benzyl benzoate*** wherein the vehicle contains ***castor oil in a concentration of 40 to 42 vol %***.

Id. at col. 13, ll. 24–28 (emphases added).

Claim 18 of the '395 patent covers a 750 mg dosage of TU in the composition and method described by claim 14:

> The method of claim 14, in which each dose contains ***750 mg of TU***.

'395 patent, col. 16, ll. 1–2 (emphasis added). Claim 14 reads:

> A method of treating a disease or symptom associated with deficient endogenous levels of testosterone in a man, comprising administering by intramuscular injection a composition comprising testosterone undecanoate (TU) and a ***vehicle consisting essentially of castor oil and a co-solvent***, the castor oil being present in the vehicle at a concentration of ***42 percent or less by volume***, the method further comprising:
>
> > (i) an ***initial phase comprising 2 initial intramuscular injections of a dose of TU at an interval of 4 weeks between injections***, each dose including 500 mg to 1000 mg of TU, followed by,
> >
> > (ii) ***a maintenance phase comprising subsequent intramuscular injections of a dose of TU at an interval of 10 weeks between injections***, each dose including 500 mg to 1000 mg of TU.

Id. at col. 15, ll. 17–31 (emphases added). The key elements of both claims in dispute are: (1) 750 mg TU, (2)

vehicle consisting of castor oil and a co-solvent (benzyl-benzoate in the '640 patent) where the castor oil is 42% or less by volume, and (3) an injection schedule comprising two initial injections at an interval of four weeks followed by injections at ten week intervals ('395 patent only).

Bayer and Endo sued Custopharm for infringement of the '640 and '395 patents on November 20, 2014. The case proceeded to a bench trial on the sole issues of whether claim 2 of the '640 patent and claim 18 of the '395 patent would have been obvious to a skilled artisan in view of the prior art, which consisted primarily of three scientific articles: Behre,[1] Nieschlag,[2] and von Eckardstein[3] (Articles). These Articles describe small clinical

---

[1] H.M. Behre et al., *Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies*, 140 Eur. J. Endocrinol. 414 (1999). Behre compared the half-life of a single dose of 1000 mg TU in castor oil with a single dose of 1000 mg TU in tea seed oil.

[2] E. Nieschlag et al., *Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men*, 51 Clin. Endocrinol. 757 (1999). Nieschlag studied the suitability of using four intramuscular injections of 1000 mg TU in castor oil at six week intervals.

[3] S. von Eckardstein & E. Nieschlag, *Treatment of Male Hypogonadism with Testosterone Undecanoate Injected at Extended Intervals of 12 Weeks: A Phase II Study*, 23(3) J. Androl. 419 (2002). von Eckardstein studied the efficacy and safety of prolonged TU treatment at extended injection intervals—starting at injections every six weeks followed by a gradual increase in the interval to every twelve weeks after the tenth injection—over a 3.2 year period.

studies involving 1000 mg TU injections. The Articles report using a composition of 250 mg/ml TU in castor oil. The parties agree that the Articles do not disclose or describe the use of a co-solvent. While the actual formulation of the vehicle used in the studies was 40% castor oil and 60% benzyl benzoate, this was not reported and thus unknown to a skilled artisan until 2007, years after the 2003 priority date for the patents-in-suit. In 2007, Saad[4] disclosed that the vehicle formulation used in the Articles was 40% castor oil and 60% benzyl benzoate, also sold as Nebido®, a 1000 mg TU injection later marketed in Europe by Bayer.

In addition to the Articles, Custopharm introduced Pushpalatha[5] and Riffkin[6] as prior art. Pushpalatha is an article that describes the effects of a commercially marketed product—Proluton Depot (Proluton). Proluton is an injectable composition of hydroxyprogesterone in a mixture of 40% castor oil and 60% benzyl benzoate. It is administered once a week to pregnant women to prevent miscarriage. Riffkin is an article that describes the use of castor oil for the parenteral administration of steroids. It discloses a castor oil and benzyl benzoate vehicle to improve the solvent abilities of castor oil.

After a four-day trial, the district court found that Custopharm had not met its burden of proving that the

---

[4] F. Saad, et al., *More than eight years' hands-on experience with the novel long-acting parenteral testosterone undecanoate*, 9(3) Asian J. Androl 291 (2007).

[5] T. Pushpalatha, et al., *Effect of prenatal exposure to hydroxyprogesterone on steroidgenic enzymes in male rats*, 90 Naturwissenschaften 40 (2003).

[6] C. Riffkin, et al., *Castor Oil as A Vehicle for Parenteral Administration of Steroid Hormones*, 53(8) J. Pharm. Sci. 891 (1964).

disputed claims would have been obvious. Specifically, the district court found that the prior art did not disclose the 750 mg TU injection dosage, and that Custopharm had not shown, by clear and convincing evidence, that a skilled artisan would have been motivated to lower the dosage of TU from 1000 mg to 750 mg due to concerns patients were being overdosed. Further, the district court found that the Articles do not inherently disclose benzyl benzoate as a co-solvent or the particular ratio of solvent to co-solvent claimed by the patents-in-suit simply because this formulation was what had been used in the studies forming the basis of the Articles. Citing *Par Pharmaceutical, Inc. v. TWI Pharmaceutical, Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014), and *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268–69 (Fed. Cir. 1991), the district court noted that inherency may only supply a missing claim limitation if the limitation at issue is the "natural result" of the combination of prior art elements or a "necessarily present" limitation. Custopharm, the district court reasoned, failed to establish that alternative vehicles could not have been used in the Articles. Finally, the district court found that the prior art did not disclose the specific injection schedule claimed in the '395 patent and was unpersuaded by Custopharm's argument that it would have been obvious to a skilled artisan to arrive at this specific schedule.

Custopharm appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

"Obviousness is a question of law based on underlying findings of fact." *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009). We review the district court's conclusions of law de novo. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1372 (Fed. Cir. 2017). And we review the district court's factual findings for clear error. *Par Pharm.,* 773 F.3d at 1194. The inherent teaching of a

prior art reference is a question of fact. *Id*. (citing *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995)).

The '640 and '395 patents disclose three primary elements in the composition and administration of Aveed®: (1) 750 mg TU in (2) a 40% castor oil and 60% benzyl benzoate vehicle (the benzyl benzoate element only applies to the '640 patent; the '395 patent only requires a co-solvent) (3) administered at an initial interval of two injections four weeks apart and maintenance injections at ten week intervals thereafter ('395 patent only). Custopharm contends that the Articles inherently describe the vehicle formulation (40% castor oil and 60% benzyl benzoate). And a skilled artisan would have recognized that patients were being overdosed with 1000 mg TU injections at a concentration of 250 mg/ml (for a total of 4 ml injected fluid). Relying on that premise, Custopharm argues that it would have been obvious to a skilled artisan to reduce the amount of injected fluid to 3 ml while maintaining the same TU concentration for a total of 750 mg TU per injection. This dose adjustment would in turn make the injection interval adjustment, including the use of a two-phase dosing regimen, obvious. We disagree, as we see no clear error in the district court's underlying factual findings. Below, we discuss each of the elements in further detail.

A. Testosterone Dose

Neither party contests that the prior art does not disclose a 750 mg dosage of TU. Custopharm argues that the district court clearly erred in finding no motivation for a skilled artisan to lower the dose of TU from 1000 mg to 750 mg because, in view of the American Association of Clinical Endocrinologists (AACE) Guidelines, patients in prior art clinical studies were being overdosed. The AACE Guidelines set the range of normal testosterone levels at 200 to 800 nanograms/deciliter (ng/dl) or 9.7 to 27.7 nanomoles/liter (nmol/l). Under these guidelines,

four of the fourteen patients in the Behre study would be regarded as having testosterone levels exceeding the normal range, based on a measurement three days after an injection of 1000 mg of TU. Accordingly, Custopharm contends that a skilled artisan would have recognized that these patients were being overdosed and would have been motivated to reduce the dose from 1000 mg to 750 mg by injecting patients with 3 ml instead of 4 ml of solution at a TU concentration of 250 mg/ml. The district court reasonably rejected this argument.

First, Custopharm's overdose argument is predicated on the assumption that a skilled artisan would have applied the AACE Guidelines to the exclusion of other guidelines that existed at the time, including the FDA Guidelines. Under the FDA Guidelines, the range of normal testosterone is 300 to 1000 ng/dl or 10 to 35 nmol/l. The record evidence sufficiently demonstrates that the most prevalently applied guidelines in clinical practice were the FDA Guidelines, not the AACE Guidelines. The studies underlying the Articles all employed the FDA Guidelines. The patents-in-suit also cited the FDA Guidelines. '640 patent, col. 8, ll. 59–61; '395 patent, col. 9, ll. 24–26. Aveed®'s label similarly references the 300 to 1000 ng/dl normal range. Moreover, a passage in a textbook that Custopharm's own expert Dr. Peter Schlegel edited confirms that "[t]he most common [guideline] in clinical practice is a Food & Drug Administration range of 300 to 1,000 nanograms per deciliter." Loren Jones & Craig Niederberger, *Medical Therapy for Male Infertility*, FERTILITY PRESERVATION IN MALE CANCER PATIENTS (John P. Mulhall, Linda D. Applegarth, Robert D. Oates, Peter N. Schlegel eds., 2013).

Under the FDA Guidelines, only one participant in the Behre study had testosterone levels that exceeded the normal range when measured three days after the injection of 1000 mg of TU. Four weeks after injection, however, this individual's testosterone level dropped below the

normal range. Further, Behre specifically reported that a single 1000 mg injection of TU "does not result in supranormal serum testosterone levels, but in much prolonged action." J.A. 1129.[7] Thus, the district court reasonably rejected Custopharm's argument that a skilled artisan would consider 1000 mg of TU to be an overdose and would have been motivated to lower the dosage to the patented 750 mg.

Second, Custopharm argues that the obviousness of an invention does not require using the "best" motivation[8]; only a "suitable" motivation is required. *Par Pharm.*, 773 F.3d at 1197–98. But this is a misunderstanding of Custopharm's burden. While the FDA Guidelines do not teach away from using the AACE Guidelines, the district court found that Custopharm had not shown, by clear and convincing evidence, that a skilled artisan would have recognized that patients injected with 1000 mg TU were being overdosed. To meet its burden, Custopharm needed to do more than merely show that the prior art does not preclude lowering the dose of TU. Custopharm needed to affirmatively demonstrate that a skilled artisan would have been motivated to lower the dose of TU despite no clear evidence of overdosing under the FDA Guidelines. *See Pfizer, Inc. v. Apotex, Inc.*, 480

---

[7] Moreover, Custopharm's argument that four of the fourteen patients in Behre's study were being overdosed under the AACE Guidelines is based on undisclosed data underlying the Behre study, which the district court correctly refused to consider because it is not prior art.

[8] Presumably, determining whether patients were being overdosed under the FDA Guidelines would constitute using the "best" motivation, though Custopharm does contest whether the FDA Guidelines were the "best" to apply.

F.3d 1348, 1361 (Fed. Cir. 2007) ("[T]he burden falls on the challenger of the patent to show 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 . . . .").

Third, Custopharm's overdose theory improperly assumes that the only solution to overdosed patients is to reduce dosage rather than extending the injection intervals. Endo and Bayer argue that this data would likely teach a skilled artisan formulating a long-acting testosterone injection not to decrease the dose—because four weeks after the initial injection of 1000 mg TU, five out of the fourteen patients had testosterone levels below the normal range—but to alter the injection schedule. Accordingly, the district court did not err in rejecting Custopharm's overdose theory.

B. Vehicle Formulation

Regarding the vehicle formulation, Custopharm makes two arguments on appeal. First, Custopharm argues that the district court erred in finding that the vehicle formulation—40% castor oil and 60% benzyl benzoate—was not inherently described by the Articles. Second, Custopharm argues that the district court erred in finding no motivation to combine the vehicle formulation of Proluton with the lowered dose and modified injection schedule. We discuss each in turn.

Inherency

To establish that a prior art reference inherently—rather than expressly—discloses a claim limitation, "the limitation at issue necessarily must be present, or [is] the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm.*, 773 F.3d at 1196. Here, Custopharm argues that the vehicle formulation was "necessarily present" in the Articles because it was later revealed to be the actual formulation the authors of

the Articles used in their reported clinical studies. We disagree.

An inherent characteristic of a formulation can be part of the prior art in an obviousness analysis even if the inherent characteristic was unrecognized or unappreciated by a skilled artisan. *See In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011). But, inherency "may not be established by probabilities or possibilities." *Par Pharm.*, 773 F.3d at 1195 (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Id.* (citing *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993); *Oelrich*, 666 F.2d at 581 ("[M]ere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art."); *In re Shetty*, 566 F.2d 81, 86 (CCPA 1977) ("[T]he inherency of an advantage and its obviousness are entirely different questions. . . . Obviousness cannot be predicated on what is unknown." (quoting *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966))).

Custopharm argues that the vehicle formulation was inherently disclosed because the Articles provide a detailed recitation of the TU injection composition's pharmacokinetic performance, from which a skilled artisan could derive that the vehicle consisted of 40% castor oil and 60% benzyl benzoate. The district court reasonably found that this was not enough "to establish that the Articles barred the possibility of an alternative vehicle being used in the prior art compositions" to meet the rigorous standard of inherency. J.A. 38.

First, Custopharm has not demonstrated that a skilled artisan could extrapolate the vehicle formulation used in the Articles from pharmacokinetic performance data. Custopharm's own opening brief does not argue that the pharmacokinetic performance reported in the

Articles can *only* be attributed to the claimed vehicle formulation. *See* Appellant's Opening Br. at 28 ("Differences in the formulation *could* produce pharmacokinetic differences.") (emphasis added). Moreover, Custopharm's brief incorrectly shifts the burden of proof to Endo and Bayer. Custopharm argues that Dr. Derendorf, Endo and Bayer's pharmacokinetic expert, failed to provide any evidence to support his view that "it was possible to have the same pharmacokinetic profile with two different formulations." *See id.* at 29. But, it is Custopharm's burden to present clear and convincing evidence that the Articles necessarily disclosed the vehicle formulation to one of skill in the art. *See Motorola Mobility, LLC v. Int'l Trade Comm'n*, 737 F.3d 1345, 1350 (Fed. Cir. 2013). And Custopharm's expert's testimony and briefing fall short of meeting this burden.

Second, the prior art was replete with potential co-solvents such that a skilled artisan, reviewing the Articles, would not have necessarily recognized that the Articles' authors used benzyl benzoate as a co-solvent for their reported clinical studies. Endo and Bayer's expert testified that, based on the Articles' disclosures, a skilled artisan would not have recognized that a co-solvent was necessary. And even if a skilled artisan concluded that a co-solvent was necessary, there were any number of available co-solvents, including, for example, benzyl alcohol, ethanol, cottonseed oil, sesame oil, peanut oil, corn oil, fractionated coconut oil, ethyl lactate, ethyl oleate, and isopropyl myristate. Moreover, Custopharm's expert conceded that even knowing the identity of the co-solvent would not necessarily lead a skilled artisan to the particular ratio claimed in the '650 and '395 patents. J.A. 404 at 92:19–23 ("Q: Now, looking at von Eckardstein, two separate questions. A person of ordinary skill reading von Eckardstein, would he know that it's necessarily using a 40 percent castor oil, 60 percent benzyl benzoate solution? A: No."). Riffkin, for example, disclos-

es multiple vehicle formulations that range from 50% castor oil to 98% castor oil.

Third, the cases Custopharm cited to support its inherency argument are inapposite. In *In re Omeprazole Patent Litigation*, the claims at issue were directed to a process for making a pharmaceutical composition, which included an in situ separating layer or subcoating. 483 F.3d 1364 (Fed. Cir. 2007). We found claim 1 to be inherently anticipated in light of a Chong Kun Dan Corporation (CKD) patent application that disclosed an omeprazole tablet. *Id*. at 1373–74. While the CKD application expressly disavowed the presence of a separating layer, the record showed that the in situ separating layer was, in fact, a natural result of using the ingredients outlined in the CKD application. *Id.* at 1373. Thus, though the inventors "may not have recognized that a characteristic of CKD's Method A ingredients, disclosed in the CKD Patent Application, resulted in an in situ formation of a separating layer," we held that the in situ formation was inherent because "the record shows formation of the in situ separating layer in the prior art even though that process was not recognized at the time." *Id*. Unlike *Omeprazole*, where we found the in situ separating layer inherent because it would result each and every time a skilled artisan followed the prior art process, Custopharm has not demonstrated, discussed *supra*, that the pharmacokinetic performance profile (C_{max}—concentration maximum; t_{max}—time of reaching C_{max}; $T_{1/2}\beta$—terminal elimination half-life; and AUC—area under the concentration versus time curve) reported in the Articles could only be achieved using the claimed vehicle formulation of 40% castor oil and 60% benzyl benzoate.

Custopharm also analogizes the current situation to *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004). In *Crish*, the invention covered a purified oligonucleotide with a human involucrin gene (HiNV) promoter. *Id.* at 1254–55. The

specific nucleotide sequence was recited in the claim and called "SEQ ID No. 1." *Id.* A prior publication disclosed the structure of the HiNV gene, including the approximate size of the promoter region, but did not disclose the sequence of the promoter region. *Id.* at 1255. We held that the claimed invention—the specific nucleotide sequence—was inherently anticipated. *Id.* at 1258.

Custopharm argues that, as in *Crish*, where we found that "one cannot establish novelty by claiming a known material by its properties," Endo and Bayer are trying to claim a vehicle formulation that was disclosed earlier in a publication on the basis that the patented claims in dispute more fully characterize the vehicle formulation described in the prior publication. *Crish*, 393 F.3d at 1258. But as with Custopharm's analogy to *Omeprazole*, Custopharm's argument falls short because it has not shown through any evidence why the pharmacokinetic performance profile reported in the Articles could be obtained only by using the claimed 40% castor oil/60% benzyl benzoate formulation. In *Crish*, the record was clear that the known HiNV promoter region necessarily contained the sequence that the inventor tried to patent, whereas in this case, the record is devoid of any proof that only one vehicle formulation—the claimed vehicle formulation—can be used to achieve the pharmacokinetic performance reported in the Articles.

Importantly, *Crish* and *Omeprazole* were about inherently present properties or characteristics for a "known" prior art product. But here, the TU injection composition recounted in the Articles cannot be said to be "known" in the same way; the Articles failed to disclose that the composition's vehicle formulation included another, key ingredient, benzyl benzoate, let alone the ratio of benzyl benzoate to castor oil. And there was no evidence in the record that a skilled artisan could determine the non-disclosed vehicle formulation based on the reported pharmacokinetic performance profile, or that the non-

disclosed vehicle formulation was necessarily a feature of the TU injection studied in the Articles. Under the circumstances of this case, the incomplete description of the TU injection composition elements denied skilled artisans from having access to that composition, thereby precluding use of the inherency doctrine to fill in disclosure about the product missing from the Articles.

Thus, the district court did not err in finding that Custopharm did not present clear and convincing evidence showing the 40% castor oil to 60% benzyl benzoate as claimed was necessarily present in the Articles.[9]

Motivation to Combine

Regarding the vehicle formulation missing from the Articles, Custopharm alternatively argues that the district court clearly erred in finding no motivation to combine the vehicle formulation of Proluton with the claimed lowered dose and modified injection schedule. Proluton was a commercially available, injectable steroid drug (hydroxy-progesterone) that used a vehicle consisting of approximately 40% castor oil and 60% benzyl benzoate. It

---

[9] Custopharm also made a public policy argument in its opening brief applying the policy rationale underlying the public use bar under pre-AIA § 102(b) to the inherency analysis. Appellant's Opening Br. at 21–23. Custopharm, however, did not respond to Endo's contention that Custopharm waived this argument by failing to raise it before the district court. We agree with Endo. In its reply brief, Custopharm argued that *Helsinn Healthcare S.A. v. Teva Pharmaceuticals USA, Inc.*, is a pertinent intervening case, but did not explain how it is an intervening change in law to the inherency doctrine, especially given that it is an on-sale bar case. 855 F.3d 1356 (Fed. Cir. 2017).

was administered on a weekly basis at a concentration of 250 mg/ml to prevent miscarriages. Custopharm argues that, even though Proluton was administered weekly, a skilled artisan would have been motivated to use the vehicle formulation from Proluton to formulate a long-acting testosterone injection because hydroxyl-progesterone and TU are both hormones injected at a high concentration of 250 mg/ml. Moreover, even before the vehicle in Proluton was disclosed, the combination of castor oil and benzyl benzoate was taught in Riffkin.[10] Custopharm's Proluton-based argument lacks merit.

The district court correctly noted that it is Custopharm's "burden to prove by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to combine the Articles (and other cited prior art) with the vehicle used in Proluton." J.A. 36. The district court found that Custopharm failed to meet its burden because, while Proluton and Riffkin do suggest the use of a co-solvent, they do not suggest that the co-solvent necessarily be benzyl benzoate as opposed to the other co-solvents known in the art (see discussion *supra* regarding the large number of possible co-solvents). Further, while Proluton was commercially available before 2003, it is not a testosterone product for men; rather, it is administered to pregnant women to prevent miscarriage. And importantly, it is not an injectable steroid with prolonged activity. The district court was not persuaded that a skilled artisan would have turned to the vehicle in Proluton when formulating a long-acting, injectable testosterone therapy.

---

[10] Riffkin teaches that the solubility of steroid hormones in oils can be improved through the addition of benzyl benzoate and specifically referred to Proluton as using a castor oil and benzyl benzoate mixture.

Given that Proluton is a weekly injection and is not directed to prolonged activity, we agree. We conclude that the district court did not err in rejecting Custopharm's argument that the patented formulation for Aveed® was obvious over Proluton in view of the prior art.

C. Injection Schedule

Custopharm also argues on appeal that once a skilled artisan recognized that patients injected with 1000 mg TU were being overdosed, the specific injection schedule claimed in claim 18 of the '395 patent would be the result of routine treatment of individual patients and thus obvious. Custopharm first argues that there is no basis for limiting the injection schedule to administration of "a population dose" because claim 18 would be infringed by the administration to a single patient. And viewing the injection schedule from the perspective of individual patients, it would have been obvious for a skilled artisan, such as a clinician, to adjust the injection interval for at least one patient to that disclosed in claim 18—two initial injections four weeks apart followed by maintenance injections every ten weeks.

Custopharm points out that both Nieschlag and von Eckardstein disclosed TU injections resulting in drug accumulation, i.e. increasingly high testosterone levels over time. Such drug accumulation makes it possible to extend the dosing interval. This, Custopharm reasons, suggests to a skilled artisan a two-phase dosing regimen. Nieschlag teaches four doses at six week intervals and that the intervals may be extended to up to ten weeks or more due to drug accumulation. von Eckardstein discloses that the interval between doses could be increased up to twelve weeks. Custopharm argues that together, these Articles suggest a first phase of dosing with a shorter interval between injections (Nieschlag) and a steady state phase consisting of a longer interval for maintenance (von Eckardstein). Further, because a skilled artisan would

have recognized that each dose would need to be reduced from 1000 mg to 750 mg to reduce the risk of overdosing, it follows that he would shorten the six-week interval in Nieschlag and the twelve-week interval in von Eckardstein to prevent TU levels from going below the normal range. The district court did not err in finding this argument unpersuasive.

First, this argument is predicated on Custopharm's overdose theory, which we have already rejected *supra*.

Second, read together, the Articles do not clearly contemplate a two-phase dosing regimen with initial loading doses followed by maintenance doses. The Articles themselves do not explicitly teach the use of loading doses. While it is possible to interpret von Eckardstein as using loading doses, the district court reasonably characterized von Eckardstein as a follow-up study to Nieschlag, seeking to investigate prolonged injection intervals. J.A. 25 ("von Eckardstein described a clinical trial investigating the efficacy and safety of prolonged TU treatment at extended injection intervals over a 3.2 year period. Seven patients (who had participated in the study described in Nieschlag) received four injections at six week intervals, followed by a gradual increase in the interval between the fifth and tenth injections. After the tenth injection, the interval was increased to twelve weeks."). Thus, the Articles reasonably teach a skilled artisan to increase the intervals between doses, not to initially shorten them to four weeks and then to lengthen them to ten weeks.

Third, Custopharm's explanation for why a skilled artisan would have a reasonable expectation of success that changing the injection regimen would result in a long-acting testosterone therapy is lacking. Endo presented evidence that oil based, depot (slow release) injections, such as TU injections can behave in unpredictable ways and that such dose and regimen changes would require more than routine experimentation. Namely, this is

because it was unclear from the Articles if there is a linear relationship between the dose amount and the amount of TU in the patient's body. Custopharm does not directly dispute this pharmacokinetic argument; rather, it contends on appeal that the district court did not give the proper weight to its argument that the invention should be viewed from the perspective of the individual patient. The invention, however, is meant to achieve a commercially viable testosterone therapy. '640 patent, col. 2, ll. 49–54 ("There is a need of providing reliable standard regimens acceptable for a broad population of men in need thereof, preferably regimens without the need of occasional control of serum testosterone levels, and regimens wherein steady state conditions are achieved within a shorter time period."); '395 patent, col. 2, ll. 57–60. And Custopharm made no claim construction arguments below in support of its individual patient rather than population dose argument. *Endo Pharm. Sols. Inc. v. Paddock Labs., LLC*, 1:14-cv-01422-SLR-SRF, Dkt. 32 (D. Del. July 20, 2015) (stipulating that neither party identified terms that require construction). Part of the obviousness inquiry involves examining what a skilled artisan would be motivated to do given "the effects of demands known to the design community or present in the marketplace." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The district court thus did not err in considering the obviousness inquiry from the perspective of a skilled artisan "confronted with the same problems as the inventor," which in this case is developing a commercially viable long-acting testosterone therapy. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Doing so, the district court properly found that Custopharm failed to meet its burden of showing that a skilled artisan would combine the lowered dose with the injection schedule in the manner claimed.

CONCLUSION

The district court did not commit reversible error in finding that claim 2 of the '640 patent and claim 18 of the '395 patent were not proven to be obvious over the prior art. We have considered Custopharm's other arguments and find them unpersuasive. Therefore, we affirm the district court's decision.

AFFIRMED