IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS SOLUTIONS INC., BAYER INTELLECTUAL PROPERTY GMBH, and BAYER PHARMA AG,	)	
Plaintiffs,	)	
v.	)	Civ. No. 14-1422-SLR
CUSTOPHARM, INC.,	)	
Defendant.	)	

Jack B. Blumenfeld, Esquire and Derek J. Fahnestock, Esquire of Morris, Nichols, Arsht & Tunnell LLP, Wilmington, Delaware. Counsel for Plaintiffs. Of Counsel: Adam K. Mortara, Esquire, J. Scott McBride, Esquire, Nevin M. Gewertz, Esquire, Faye E. Paul, Esquire, and Taylor A.R. Meehan, Esquire of Bartlit Beck Herman Palenchar & Scott LLP.

Richard L. Horwitz, Esquire, David E. Moore, Esquire, and Bindu A. Palapura, Esquire of Potter Anderson & Corroon LLP, Wilmington, Delaware. Counsel for Defendant. Of Counsel: Douglass C. Hochstetler, Esquire, Constantine Koutsoubas, Esquire, Mark J. Scott, Esquire, Beth D. Jacob, Esquire, and Clifford Katz, Esquire of Kelley Drye & Warren LLP.

OPINION

Dated: February 10, 2017
Wilmington, Delaware

ROBINSON, Senior District Judge

I. INTRODUCTION

This action arises out of the filing of Abbreviated New Drug Application ("ANDA") No. 207583 by defendant Paddock Laboratories, LLC seeking to produce and market a generic testosterone undecanoate intramuscular injection. (D.I. 67 at ¶ 10) On November 20, 2014, plaintiffs Endo Pharmaceuticals Solutions Inc., Bayer Intellectual Property GmbH, and Bayer Pharma AG (collectively "plaintiffs") brought this action alleging infringement of U.S. Patent Nos. 7,718,640 (the "'640 patent") and 8,338,395 (the "'395 patent") (collectively, "the patents-in-suit").[1] (D.I. 1) Defendants Paddock Laboratories, LLC and Perrigo Company (collectively, "Paddock")[2] answered the complaint and counterclaimed alleging invalidity of the patents-in-suit on December 23, 2014. (D.I. 11) Plaintiffs answered the counterclaims on January 16, 2015. (D.I. 14) Thereafter, Paddock stipulated to infringement of certain claims. (D.I. 30) The court held a final pretrial conference on September 7, 2016, and a four-day bench trial from September 26 to 29, 2016 on invalidity. The parties have since completed post-trial briefing. The 30-month stay of FDA final approval on Paddock's ANDA expires on April 9, 2017. (D.I. 3, 17) The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a), and venue is proper pursuant to 28 U.S.C. §§ 1391 (b) and (c) and 1400(b). Having considered the documentary evidence and testimony, the court

---

[1] In the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" ("Orange Book"), the '640 and '395 patents are listed in the entry for Aveed® ("Aveed").

[2] Paddock was substituted with new defendant Custopharm, Inc. ("defendant"). (D.I. 79, so ordered January 13, 2017)

makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Technology at Issue

The '640 patent was filed on March 12, 2004 and issued on May 18, 2010. (JTX 1) The '395 patent was filed on February 24, 2009 and issued on December 25, 2012.[3] (JTX 2) The patents-in-suit are titled "Methods and Pharmaceutical Compositions for Reliable Achievement of Acceptable Serum Testosterone Levels." (JTX 1, 2) Male hypogonadism is a condition characterized by a deficiency of endogenous testosterone production resulting in abnormally low levels of serum testosterone. ('640 patent, 1:32-34) Men with this condition generally experience symptoms including sexual dysfunction, reduced muscle mass and strength, depression, and osteoporosis. (*Id.* at 1:48-50) In 2003, the standard therapy required frequent doctors' visits to receive intramuscular injections administered every two to three weeks. "[P]atients complain[ed] about variations in well-being due to short-term fluctuations of serum testosterone levels resulting from the pharmacokinetic profile after intramuscular injection of . . . testosterone enanthate." (*Id.* at 1:51-62) A need existed for "reliable standard regimens acceptable for a broad population of men, . . . without the need of occasional control of serum testosterone levels, and . . . where[] steady state conditions are achieved within a shorter time period." (*Id.* at 2:49-54)

The invention is directed to injectable compositions using long-term acting testosterone esters for testosterone replacement therapy. After injection,

[3] The patents-in-suit have a priority date of March 14, 2003.

"physiologically normal levels of testosterone in serum are reached within a short time period . . . [and] maintained for an extended period of time, without showing fluctuations in the hypogonadal range." (*Id.* at 2:57-64) Claim 2 of the '640 patent provides for a 750 mg version of the composition of claim 1, which recites "[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 %." Claim 18 of the '395 patent provides for a 750 mg version of the composition and method described by claim 14, which recites:

> 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.

The embodiment of the invention is Aveed, which contains testosterone undecanoate (TU) as an active ingredient. It is approved by the FDA as a testosterone replacement therapy in adult males for conditions associated with testosterone deficiency or absence of endogenous testosterone. Aveed is sold in the United States as a series of 3 ml (750 mg) intramuscular injections given at initiation, at four weeks, and then every 10 weeks thereafter. Each vial of Aveed contains 750 mg testosterone undecanoate dissolved in a mixture of 885 mg castor oil and 1500 mg benzyl benzoate.

(D.I. 67, ex. 1 at ¶¶ 6-7) Hypogonadism is a chronic condition requiring lifelong therapy. (D.I. 73 at 524:12-18)

B. Obviousness Standard

"A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements

in the manner claimed." *Id.* at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

A combination of prior art elements may have been "obvious to try" where there existed "a design need or market pressure to solve a problem and there [were] a finite number of identified, predictable solutions" to it, and the pursuit of the "known options within [a person of ordinary skill in the art's] technical grasp" leads to the anticipated success. *Id.* at 421. In this circumstance, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*

A fact finder is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17-18.

"Patents are presumed to be valid, and overcoming that presumption requires clear and convincing evidence." 35 U.S.C. § 282; *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1333 (Fed. Cir. 2015) (citing *Microsoft Corp. v. i4i Ltd. P'ship.*, 564 U.S. 91, 95 (2011) (holding that an invalidity defense must be proved by clear and

convincing evidence)). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (citations omitted).

C. Prior Art

A trio of prior art scientific articles – Behre,[4] Nieschlag,[5] and von Eckardstein[6] (collectively "the Articles") – describe small clinical studies using an injectable composition of 250 mg/ml TU in castor oil dosed at 1000 mg injections.[7] The Articles report that the 250 mg/ml of TU was dissolved in castor oil, but do not disclose or describe the use of a co-solvent. (JTX 3, 4, 5; D.I. 67, ex. 1 at ¶ 15; D.I. 72 at 81:2-19, 92:19-23; D.I. 73 at 463:6-14) The compositions described by the Articles are TU

---

[4] Hermann M. Behre et al., *Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies*, 140 Eur. J. Endocrinol. 414 (1999). (JTX 3)

[5] Eberhard Nieschlag et al., *Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men*, 51 Clin. Endocrinol. 757 (1999). (JTX 4)

[6] Sigrid von Eckardstein and Eberhard 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). (JTX 5)

[7] The specifications of the patents-in-suit reference Behre and von Eckardstein. ('640 patent, 2:10-16, 37-44) Dr. Jan-Peter Ingwersen ("Dr. Ingwersen"), plaintiffs' 30(b)(6) designee on issues related to the development of the product and inventor on the patents, testified that the background section of the patent does not disclose the particular vehicle used in Behre and he did not know why. (D.I. 72 at 207:8-208:11)

dissolved in 40% castor oil and 60% benzyl benzoate (the "vehicle"). The parties agree that the vehicle was unknown to the person of ordinary skill in the art in 2003.[8] (D.I. 72 at 107:5-108:6; D.I. 73 at 338:5-22, 393:24-394:8, 463:9-20)

Behre compared the half-life of a single dose of 1,000 mg TU in castor oil with a single dose of 1000 mg TU in tea seed oil. (JTX 3) Nieschlag investigated the suitability of using four intramuscular injections of 1000 mg TU in castor oil at six week intervals. (JTX 4) 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. (JTX 5)

Pushpalatha[9] described a commercially marketed product Proluton Depot ("Proluton"), an injectable composition of hydroxyprogesterone dissolved in a mixture of 40% castor oil and 60% benzyl benzoate. Proluton is administered weekly to pregnant women to prevent miscarriage. (JTX 42, 38 at 73; D.I. 72 at 86:10-87:17) Riffkin[10] described using castor oil for the parenteral administration of steroids. (JTX 6) It refers

---

[8] Saad 2007 disclosed for the first time that the composition used in the Nieschlag article was what is now sold as Nebido® ("Nebido"). (D.I. 67, ex. 1 at ¶ 15; D.I. 72 at 92:9-18, 185:11-188:11); Farid 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). (DTX 20)

[9] Pushpalatha, T. et al., *Effect of prenatal exposure to hydroxyprogesterone on steroidogenic enzymes in male rats*, 90 Naturwissenschaften 40 (2003). (JTX 42)

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

to using a castor oil/benzyl benzoate vehicle to "increase the solvent power of the oil." (*Id.* at 892; 87:18-89:2)

The 2002 guidelines of the American Association of Clinical Endocrinologists (AACE) ("the AACE guidelines") describe a normal testosterone range as "generally between 280 and 800 ng/dl" (9.7 to 27.7 nmol/l). (JTX 41 at 448) The FDA refers to a normal testosterone range of 300-1000 ng/dl.[11] (JTX 49 at 18, 104) The Articles also describe a normal range of testosterone as 10-25 nmol/l (300-1000 ng/dl). (JTX 3 at 416, JTX 4 at 759, JTX 5 at 422) The Aveed label references a normal range of 300 to 1000 ng/dl. (JTX 58 at 10)

D. Evidence

Defendant's expert, Dr. Peter Schlegel ("Dr. Schlegal"),[12] opined that it would have been obvious from the prior art to decrease the dose of TU from 1000 to 750 mg and to modify the dosing intervals after the dose amount was reduced to 750 mg. (D.I. 73 at 268:20-269:1) He explained that the prior art disclosed injectable testosterone drugs and monitoring of the patient's testosterone levels. A clinician could choose to decrease the dose amount or change the interval between injections to maintain the level of testosterone. A clinician would determine such routine dosing adjustments, and might make dosing estimates outside the recommendations of the drug label.[13] (*Id.* at

---

[11] A book chapter edited by defendant's expert stated that "[t]he most common [testosterone range] in clinical practice is a Food & Drug Administration range of 300 to 1000 nanograms per deciliter." The book also refers to the AACE range. (D.I. 73 at 322:3-24)

[12] A urologist.

[13] Plaintiffs' expert, Dr. Anthony Sliwinski ("Dr. Sliwinski"), testified that he also made routine dose adjustments for injectable testosterone in about 30-40% of his patients, but did so "within the confines of the package insert." (D.I. 74 at 548:18-549:19, 528:16-24)

286:4-289:8, 350:3-25; PTX 166, 169) Dr. Schlegel agreed that individual dose adjustments are different than dose determinations for an entire population, but clarified that both are based on the same principles. (*Id.* at 326:7-12) He admitted that his obviousness opinion was based on the premise that the composition of the vehicle was known, as it was in the historical data. (*Id.* at 338:1-4) Defendant's expert, Dr. Ralph Tarantino ("Dr. Tarantino"),[14] similarly opined that the disputed claims were obvious as von Eckardstein disclosed single injections of 250 mg/ml TU; the 40/60 castor oil/benzyl benzoate vehicle was known in the art for use with steroids in a commercial product (Proluton); and using 750 mg of TU is a trivial change, by using 3 rather than 4 ml of product disclosed by von Eckardstein. (D.I. 72 at 78:5-80:2, 94:10-96:23)

1. Co-solvent

Dr. Tarantino explained that although the Articles only disclosed dissolving TU in castor oil, "the issues of viscosity and . . . solubility would make it obvious that another vehicle was being used." (D.I. 72 at 91:13-93:10; 107:13-20) He admitted that he did not cite to any prior art data or do any testing of the solubility of TU in castor oil for his opinions. Instead, he testified based on what he "saw here" and his knowledge of lipidation.[15] (*Id.* at 116:23-117:6) He testified that a formulator would know to use another solvent to make the castor oil less viscous to improve injectability and

[14] A formulation scientist.

[15] On cross-examination, Dr. Tarantino was presented with documents that he had not seen before and asked whether such documents suggested that 250 mg TU is able to dissolve in 1 ml of castor oil in order to "impeach" his testimony. He did not give a definitive answer. (D.I. 72 at 123-138) The court does not find such testimony helpful to answer the ultimate question of solubility, as plaintiffs' expert did not opine on the disclosures of these documents.

manufacturability.[16] Moreover, it was known before 2003 that benzyl benzoate could be combined with castor oil to dissolve testosterone. (*Id.* at 81:5-7, 88:13-16) He agreed, however, that the prior art described other co-solvent choices for oily injectables, but opined that their practicality or actual usage make benzyl benzoate the "go-to" solvent for an oil solution.[17] (*Id.* at 153:12-22)

Dr. Tarantino opined that a person of ordinary skill would look to marketed products (which provide knowledge of safety, tolerance, and injectability) first. A formulator would be "remiss" in not trying the vehicle of Proluton since "both drugs are closely related chemically. Sometimes even when drugs aren't closely related chemically, co-solvent systems that were used in prior products are used." It is "common sense from every standpoint that you can imagine." (*Id.* at 76:13-77:9, 86:10-87:17, 89:19-91:1, 96:24-98:3, 169:7-170:13) Moreover, a formulator would expect that the "pharmaceutical dosage form . . . [of] 250 milligrams per ml testosterone . . . [could] be safely and effectively administered." (*Id.* at 98:4-12) He concluded that it would have been obvious to one of ordinary skill in the art "to replace [the testosterone ester of Proluton] with TU and test it, because you would anticipate little or no manufacturing or regulatory difficulties." (*Id.* at 93:12-94:4) Dr. Tarantino also pointed to Riffkin, which "mentions benzyl benzoate and benzyl alcohol resulting in a more favorable viscosity, making it easier to inject." (*Id.* at 87:18-89:2) He testified that benzyl benzoate was the

---

[16] He testified that it would be "next to impossible" to inject pure castor oil though a standard syringe needle, because of the viscosity. (D.I. 72 at 140:1-141:18)

[17] Defendant's citation to the testimony of Dr. Frank Diana, plaintiffs' 30(b)(6) witness, regarding the disclosures of plaintiffs' internal information about the dissolution of TU in castor oil is not prior art and not properly considered in the obviousness analysis. (D.I. 72 at 214:25-220:13; DTX 25, 39)

"go-to" excipient for reasons including safety and acceptability. (*Id.* at 89:24-90:2) He concluded that any ratio of castor oil to benzyl benzoate as a vehicle for testosterone injectables would be obvious, as the excipients "have been around a long time," therefore, combining and optimizing the solubility and viscosity is "what [he] did every day." (*Id.* at 150:23-151:19)

Plaintiff's expert, Dr. Robert Williams, III ("Dr. Williams"),[18] disagreed that the Articles "teach[] the need for a co-solvent." He testified that "one would actually have to confirm whether" a co-solvent was necessary for solubility and injectability reasons.[19] (D.I. 73 at 463:15-464:7) He testified that there are other co-solvents available to use. (*Id.* at 467:19-468:2, 469:8-19; JTX 6; PTX 108, 109, 118) He also explained that other ratios of castor oil to co-solvents are present in the prior art. (*Id.* at 479:19-481:9, 481:20-483:12, 484:3-10; JTX 6, 7; PTX 46) He explained that he did not know if 250 mg of TU could be soluble in 1 ml of castor oil or in "50 castor oil/benzyl benzoate at a rate of 250" mg/ml. (*Id.* at 496:24-497:14) He testified that a person of ordinary skill "would choose the excipient vehicle" from an approved product if the formulation was equal in all other ways. (*Id.* at 503:7-504:12) He agreed that, assuming a person of ordinary skill could create a 250 mg/ml solution of TU in the Proluton vehicle, it could be injected intramuscularly. (*Id.* at 499:18-500:10) Dr. Williams also agreed that a person of ordinary skill would know that TU was compatible with castor oil and benzyl benzoate. (*Id.* at 507:18-508:4) He admitted that he did not provide an "example of a commercialized intramuscular injectable product that used castor oil and any one of

---

[18] A formulation scientist.

[19] Dr. Ingwersen testified that the viscosity of castor oil would cause difficulties during injection. (D.I. 72 at 203:9-204:6)

these [other] co-solvents." (*Id.* at 508:22-509:5) Dr. Williams concluded, however, that a person of ordinary skill would not be motivated to consider the vehicle of Proluton "to create vehicles that have long-acting activity like the patents-in-suit" because Proluton requires weekly injections and are not directed to prolonged activity. (*Id.* at 488:4-20)

2. Using a lower dose of TU

Dr. Schlegel explained that "[t]he two most common changes that are made in terms of treating patients with injectable agents are to change the dose amount or the dose interval, frequency between injections." (D.I. 73 at 264:21-265:2, 287:1-23) Dr. Schlegel testified that he uses the AACE guidelines (which reflected the state of the art at that time) in his practice. (*Id.* at 271:24-274:23, 308:9-13, 349:10-350:2) He relied on the AACE guidelines for the normal range of testosterone (280 to 800 ng/dl) to formulate his opinions. According to Dr. Schlegel, although the FDA sometimes refers to a 300-1000 ng/dl range, a testosterone level of 1000 ng/dl or more is "relatively unusual" and "not a common physiologic observation." (*Id.* at 275:2-23)

Dr. Schlegal testified that a person of ordinary skill would not need to know the exact composition of the formulation before modifying the dose amount because "it [was] common practice to adjust doses based on the results that you get with serum testosterone levels, and that is independent of the exact formulation of the medication." (D.I. 73 at 280:9-17) He analyzed Nieschlag and explained that "a proportion of patients who are treated with a single dose of 1000 mg [of TU] are going to have testosterone levels above 800" ng/dl (27.7 nanomoles per liter). He observed that the first dose provides an overdose and the subsequent injections also overdose the patient. He concluded that it would be obvious to reduce the 1000 mg dose to get the

patient into normal range without "overshooting" the target. Dr. Schlegel opined that Behre and von Eckardstein describe similar overdosing. He concluded that the reduction from 1000 mg (given in 4 ml) to 750 mg is an obvious change as it would be easy to draw up 3 ml ("a whole millimeter change").[20] (*Id.* at 276:14-281:16, *see also* D.I. 72 at 152:6-22)

Dr. Schlegel agreed that the Articles do not suggest lowering the dose of TU from 1000 mg to 750 mg, but maintained that they "pointed out specifically overdosing" certain patients.[21] (D.I. 73 at 300:4-23) He observed that one of the fourteen patients in Behre exhibited a testosterone level "nowhere near an acceptable range" after treatment. He opined that there were likely other patients "possibly in this trial, who are out of what would be considered normal range." (*Id.* at 340:23-341:9) He agreed that the observed testosterone level, however, fell within the range of testosterone allowed by the FDA for approved testosterone replacement therapies. (*Id.* at 344:4-345:2)

Dr. Sliwinski[22] testified that the "normal" testosterone range used varies with individual laboratories and clinician patient populations. In 2003, his reference laboratory used a range of 349-1149 ng/dl for his patient population. He used the AACE guidelines in his practice, but did not adopt its definition of normal testosterone levels in treating his patients. (D.I. 74 at 530:9-12, 531:20-532:16) In 2013, he created

---

[20] He testified that he did not rely on the underlying data (not publicly disclosed) to form this opinion. (D.I. 73 at 351:13-352:12) As the underlying data is not prior art, the court declines to discuss the opinions and arguments based thereon. (PTX 208)

[21] He described plaintiffs' disclosure to the FDA in 2013, wherein the testosterone dose was decreased to 750 mg after a 1000 mg dose was evaluated in a study and found to yield levels exceeding criteria set by the FDA. (D.I. 73 at 352:13-354:13)

[22] A urologist.

his own guidelines for his own laboratory, based on internal testing and now uses an upper limit of 800 ng/dl. (*Id.* at 550:10-552:20) Dr. Sliwinski explained that an elevated level of testosterone of 40.8 nmol/l (1054 ng/dl) would require consideration of factors (including when the level was drawn during treatment or if the patient is exhibiting symptoms) before causing concern. (D.I. 74 at 533:12-25)

Plaintiffs' expert, Dr. Hartmut Derendorf ("Dr. Derendorf"),[23] opined that during a study it is common to have a patient who behaves differently for some reason. He testified that "the goal of this exercise is to find the population dose, . . . the best dose for the majority of the patients." (D.I. 73 at 402:25-403:25) He explained that Nieschlag does not disclose whether any of the patients had testosterone levels outside of the therapeutic range after a single 1000 mg injection. From the plasma concentration curve, he observed that after the first dose, the patients are "far away from the upper end of the curve." The peaks after the third and fourth injection indicate that the testosterone level is above the upper threshold. This issue "calls for a modification," such as "an extension of the dosing interval." (*Id.* at 404:21-405:21) Dr. Derendorf agreed that four of the fourteen patients in the Behre study had testosterone values exceeding the AACE guidelines. (*Id.* at 435:21-25)

3. Two-phase dosing

Dr. Schlegel pointed out that drug accumulation was noted in Nieschlag. "In Nieschlag, without changing the interval of injections, the [authors] noticed increasing . . . testosterone . . . with subsequent injections, suggesting the need to have a second interval of injection after . . . reach[ing] a steady state." The "data on serum

---

[23] A pharmacokinetics expert.

testosterone levels with increasing intervals of injection" supports the concept of a maintenance phase. He opined that von Eckardstein "really is a two-phase treatment regimen, [with t]he second phase of treatment . . . really designed to figure out" the appropriate interval. Further, an initial or loading dose is common. "[D]ecreasing the amount of the initial dose would prevent the overshooting in terms of testosterone levels." He explained that once a steady state of testosterone is reached, a clinician "can allow a longer period of time for that testosterone to be absorbed into the body and still maintain normal testosterone levels, [which is] observed in the increasing intervals that are provided in von Eckardstein." (D.I. 73 at 281:18-286:3)

Dr. Derendorf explained that drug accumulation is a "normal phenomenon." (*Id.* at 365:13-22) He testified that the Articles did not disclose a different interval between the first and second injections compared to subsequent injections. Moreover, he opined that having a different dosing interval between the first two injections and subsequent injections is unusual. (*Id.* at 406:1-17)

4. Pharmacokinetics

Dr. Derendorf explained that as a pharmacokineticist, his "role is to help . . . identify the dose and dose regimen that has the highest probability of success. [His] role is usually to identify a population dose, something that would be used for the approval of a product where it ends up in a label . . . ."[24] (D.I. 73 at 358:25-359:21) Dr. Derendorf disagreed that the disputed claims are obvious and opined that

[24] On cross-examination, Dr. Derendorf agreed that claim 18 could be directed to a population dose or individual dose. (D.I. 73 at 439:25-441:12)

"intramuscular depot injections are complex and very difficult to predict."[25] There is no "motivation to shorten a dosage interval for a treatment where we really want to have long-lasting effects and long dosing intervals. [T]hat would be counter to the intention." (*Id.* at 366-368)

Dr. Derendorf explained that when trying "to identify the optimum dosing regimen," the starting point "is the assessment of dose linearity." The use of predictive models is easier with linear pharmacokinetics. (*Id.* at 368-369) He analyzed the Articles and opined that the published data and graphs are inconsistent with linear pharmacokinetics. He explained that "[a]n oily depot injection of a prodrug is a very complex route of drug administration." Some sources of variability are partition coefficient, viscosity, and patient effects. The formulation depends on what oil is used and what co-solvent if any (and how much) is used. He opined that "the likelihood of simple linear pharmacokinetics is not very high." (*Id.* at 372-389) He concluded that a person of ordinary skill could not "extrapolate with any reasonable likelihood of success from the prior art that a different dose and a different dosing regimen . . . would result in serum testosterone levels inside the therapeutic range." Moreover, the person of ordinary skill would need "[a]dditional studies with different doses and different dosing regimens in order to characterize the system[.]" (*Id.* at 391-392; JTX 19) Dr. Derendorf testified that to reach the change in dose and regimen disclosed in the disputed claims from the pharmacokinetic data in the prior art would require "complicated," "lengthy," and "expensive studies." (*Id.* at 409:17-410:2) In his opinion, Dr. Schlegel's

---

[25] Dr. Schlegel admitted that different ratios of castor oil and co-solvent might yield different pharmacokinetic data and different C_{max} levels (highest concentration). (D.I. 73 at 334:24-335:6; *see also* D.I. 72 at 147:15-22)

suggestions assumed dose linearity. Dr. Derendorf testified that dose linearity would need to be established with additional data before a person of ordinary skill "could start to come up with [a] prediction." (*Id.* at 408:11-24)

On cross-examination, Dr. Derendorf was asked a series of questions about certain statements made in the literature, such as, "drug absorption from an oil solution follows first-order kinetics after intramuscular administration." He responded that such statements were too general and explained that there were other variables to consider. (*Id.* at 411-426; JTX 11, 32, 38) He was also asked about an article published in 2006. He explained that the C_{max} are "not proportional . . . after later doses" and the "data [does not] confirm[] linearity," but conceded that the C_{avg} value[26] does approximately show linear dose proportionality. (*Id.* at 414:1-421:23; DTX 109) He admitted that a person of ordinary skill in March 2003 would generally know how to design studies to develop a formulation from the target profile to the final approved dosage form. (*Id.* at 504:14-505:16) He conceded that he did not know if Nebido has first order kinetics. (D.I. 74 at 512:25-513:2)

Dr. Willliams explained that the iterative process of formulation development requires that a formulator develop prototypes and then test them. If the prototype is deemed unacceptable, the process starts anew. (D.I. 73 at 454:17-458:15) He agreed that pharmacokinetic testing and research occurs prior to clinical testing. (*Id.* at 504:14-505:20)

C. Motivation to Combine

[26] Average steady state concentration.

The parties generally agree that the person of ordinary skill in the art would consist of a team made up of a pharmacokineticist, a clinician, and a formulation scientist. (D.I. 73 at 263:21-23, 267:8-12, 360:8-12, 452:23-453:10, 453:20-458:3) There is no dispute that the prior art does not disclose the use of a 750 mg TU injection dose or the specific interval regimen.

Defendant argues that plaintiffs focus on the motivation to create a long-acting testosterone replacement therapy (a problem identified in the patent) to the exclusion of other motivations such as problems of solubility and viscosity of a high TU concentration formulation or providing a safe and effective therapy to patients. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007) ("[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed."). Regardless, the patents and the prior art describe solving the same problem – treating men with hypogonadism. It is defendant'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.

Defendant first argues that a person of ordinary skill would have recognized that the formulation disclosed in the Articles must have used a co-solvent, and that such co-solvent was benzyl benzoate. The expert testimony on this point consists of opinion on whether or not the stated concentration of TU "could" have dissolved in the volume of castor oil. Beyond that question, the cited prior art (Riffkin and Proluton) does suggest the use of a co-solvent. However, it is certainly not a given (as defendant argues) that a person of ordinary skill would have understood that the particular co-solvent was benzyl

benzoate, as opposed to one of the other co-solvents known in the art. (JTX 6) Dr. Williams pointed out that there are other co-solvents to choose from. Moreover, even knowing the co-solvent would not provide a person of ordinary skill the particular ratio disclosed by the patents-in-suit. The court concludes that the Articles do not disclose benzyl benzoate as a co-solvent (or the particular ratio used by the patents-in-suit).[27]

Dr. Schlegal used the AACE guidelines to the exclusion of other published ranges for the normal levels of testosterone, and reached his opinion based on the notion that the Articles suggested "overdosing" of patients. He opined that the overdosing would provide a reason for a person of ordinary skill to reduce the TU dose from 1000 mg to 750 mg. This reasoning is contradicted by the fact that after Nieschlag, the same authors undertook another study (von Eckardstein) using 1000 mg of TU. Dr. Schlegal also opined that after reducing the dose, a person of ordinary skill would use routine experimentation to come up with the particular dosing regimen disclosed by the patents-in-suit. He bolstered this opinion by explaining that clinicians routinely make dose and regimen adjustments for testosterone therapies. In contrast, Dr. Derendorf opined that such dose and regimen changes would require more than routine experimentation.[28]

---

[27] Defendant's inherency argument is analyzed below.

[28] Defendant criticizes Dr. Derendorf's testimony as not reflective of the opinions of a person of ordinary skill. (D.I. 76 at 32-34) The court finds that Dr. Derendorf's disagreement with certain general statements (paired with his explanations thereof) do not discredit his opinions. Defendant also argues that an excerpt from a book (edited by E. Nieschlag and H.M. Behre) makes it clear that pharmacokinetic computer simulation was performed. (D.I. 76 at 31-32) The excerpt provides that "[a]s in the first study the duration of action of intramuscular testosterone undecanoate was six to eight weeks. Follow-up studies with multiple injections of 1000 milligram testosterone undecanoate every six to eight weeks are currently being performed which are based on

The record demonstrates that there were a number of co-solvents that could have been used for the formulation. Although defendant has successfully identified the elements of the asserted claims (but not the specific quantities of TU and solvents) in the prior art, defendant has not met its burden, by clear and convincing evidence, to show that a person of ordinary skill would combine the elements in the manner claimed.

D. Inherency

Defendant's contention that the Nebido composition is inherently disclosed in the prior art misapplies the doctrine of inherency. In the context of an obviousness inquiry, inherency may supply a missing claim limitation only if the limitation at issue is the "natural result" of the combination of prior art elements. *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014) (cautioning that "the use of inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of obviousness."); *see also Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991) (an inherent limitation is one that is "necessarily present" and not one that may be established by "probabilities or possibilities."). At bar, the presence of benzyl benzoate or its ratio with castor oil is not inherent in the prior art simply because the Nebido composition was used in the studies that formed the basis of the Articles. (JTX 3-5) Defendant has failed to establish that the Articles barred the possibility of an alternative vehicle being used in the prior art compositions.[29] *See In re*

---

pharmacokinetic computer simulation." (JTX 10 at 343) The court will not, absent expert testimony, conclude that such statement undermines Dr. Derendorf's opinions.

[29] In conjunction with the issue of inherency, defendant alleges that the claimed invention is invalid because the examiner's allowance was based on his purported misunderstanding that the concentration of castor oil in the co-solvent was not present in the prior art. (D.I. 76 at 27-28; D.I. 68 at ¶ 4) Defendant's contention misses the mark. The Articles did not teach a vehicle consisting of the claimed ratio of castor oil

Armodafinil Patent Litig. Inc., 939 F. Supp. 2d 456, 465 (D. Del. 2013) ("[I]f the teachings of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate."). In view of defendant's failure to establish inherency, the timing of the person of ordinary skill's recognition that the Nebido composition was used in the studies described in the Articles is irrelevant. *See In re Newell*, 891 F.2d 899, 901 (Fed. Cir. 1989) ("[A] retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination.").

D. Secondary Considerations[30]

Plaintiffs allege a long-felt but unmet need for a long-acting testosterone replacement. Dr. Sliwinski testified that the available therapies required frequent visits and resulted in unstable testosterone levels. The therapies also required clinicians to adjust dosages for individual patients. (D.I. 74 at 528:16-529:17, 526:11-21,) Dr. Sliwinski testified that he uses Aveed for certain of his patients, who find it convenient to come for an injection just five times a year. The testosterone levels are "smooth." He conceded that Aveed does not work for all patients. He opined that the occurrence of pulmonary oil micro-embolisms ("POME"), which prompted additional measures by the FDA for Aveed's administration, were likely due to improper injection technique. (*Id.* at

---

and benzyl benzoate. (JTX 3-5) The fact that the studies forming a basis for the Articles contained a vehicle consisting of 40.7% by volume castor oil and 59.3% by volume benzyl benzoate does not mean that the teachings in the Articles themselves were so limited.

[30] The court reads *In re Cyclobenzaprine*, *supra*, as requiring a review of such evidence even where it is apparent that defendant cannot meet its burden to prove obviousness by clear and convincing evidence.

534-538) In his opinion, in 2003, there existed a need for long term therapy, notwithstanding the available therapies (including an implantable pellet, Testopel). (*Id.* at 540-541)

Dr. Schlegel explained that Testopel was longer-acting than Aveed. Assuming there was a need, Dr. Schlegel explained that Aveed does not fulfil it due to the occurrence of POME and the additional measures required by the FDA. The additional measures make it difficult for busy offices to administer the injections. He concluded that Aveed "did and did not" meet the long felt need. The lower frequency of injections is convenient, but the administration is cumbersome and, therefore, seldom used. (D.I. 73 at 289-293) Defendant's expert, Ivan T. Hofmann, analyzed certain financial data on hormone and testosterone products and concluded that Aveed is not commercially successful.[31] (D.I. 75 at 565-566, 586-590, 592, 597-599; JTX 46, 59; DTX 152, 153, 156, 167)

The court concludes that, on the record at bar, there existed a need for a long-acting testosterone therapy. Defendant offers testimony (based on Aveed's commercial success) that Aveed did not fill such need. This testimony is more indicative of a lack of commercial success, a secondary consideration not advanced by plaintiffs.

III. CONCLUSION

For the foregoing reasons, the court finds that defendant has not met its burden to prove, by clear and convincing evidence, that claim 2 of the '640 patent and claim 18 of the '395 patent are invalid for obviousness. An appropriate order shall issue.

[31] The court declines to summarize the testimony herein.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS SOLUTIONS INC., BAYER INTELLECTUAL PROPERTY GMBH, and BAYER PHARMA AG,	)	
Plaintiffs,	)	
v.	)	Civ. No. 14-1422-SLR
CUSTOPHARM, INC.,	)	
Defendant.	)	

ORDER

At Wilmington this 10th day of February 2017, consistent with the opinion issued this same date;

IT IS ORDERED that:

1. The asserted claims of the '640 and '395 patents are valid.

2. The clerk of court is directed to enter judgment in favor of plaintiffs and against defendant.

Senior United States District Judge