IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

PAR PHARMACEUTICALS, INC. and ALKERMES PHARMA IRELAND LTD.	:	
v.	:	Civil No. CCB-11-2466
TWI PHARMACEUTICALS, INC.	:	

MEMORANDUM

Plaintiffs Par Pharmaceuticals Inc. and Alkermes Pharma Ireland, Limited (collectively, "Par") filed this action against TWi Pharmaceuticals, Inc. ("TWi") alleging infringement of U.S. Patent 7,101,576 ("the '576 patent"). The patent relates to Par's Megace ES medication, a nanoparticulate formulation of megestrol acetate used to treat anorexia, cachexia, and unexplained weight loss in patients with HIV and AIDS. After this court's summary judgment order, and prior to trial, the parties stipulated that TWi's generic version of Megace ES would infringe the asserted claims of the '576 patent, leaving before this court only TWi's defense that the '576 patent is invalid and its claim that Par Pharmaceuticals, Inc. does not have standing to bring suit as co-plaintiff. A five-day bench trial to determine the remaining claims was held in October 2013. After hearing the evidence and considering the post-trial briefs, the court concludes that the '576 patent was obvious, and thus invalid.[1] Pursuant to Federal Rule of Civil Procedure 52(a), the following memorandum constitutes the court's findings of fact and conclusions of law.

BACKGROUND

In 1993, Bristol Meyers Squibb ("BMS") began marketing Megace OS, an oral

[1] Because the court finds the claims are obvious, it does not need to decide whether Par Pharmaceuticals, Inc. has standing, whether the claims of the '576 patent are enabled, or whether the patent claims patentable subject matter.

suspension of micronized megestrol acetate,[2] to treat anorexia and cachexia in AIDS patients. The drug was a medical and commercial success. In fact, the FDA subsequently approved five abbreviated new drug applications ("ANDAs") for generic versions of Megace OS, including one submitted by Par. According to TWi, by 2005, Par had the majority of the generic Megace OS market, with approximately $25 million in annual sales.

During experimentation with reformulating the drug to reduce the particle size of the megestrol acetate to the nanoparticulate range (using Alkermes's already patented "NanoCrystal" technology), the inventors of the '576 patent discovered, "surprisingly," according to Par, that BMS's Megace OS exhibited low bioavailability when administered to a patient without food and much higher absorption when administered with food. Par asserts that this "strong food effect" was previously unknown and that it is a significant weakness in Megace OS because the target patients of the drug are individuals suffering from conditions with low appetites, thus making it unlikely the drug can be administered in a sufficiently fed state. The '576 patent inventors discovered, however, that their new nanoparticulate formulation resulted in dramatically improved bioavailability in the fasted state and reduced the absorption difference between the fed and fasted states. The '576 inventors filed for patent protection for this new formulation in 2002. The Patent Office rejected the application several times because it deemed the claimed invention obvious in light of the prior art. (*See, e.g.*, Pl.'s Trial Ex., [hereinafter PTX], 359.) After Par amended its application to highlight the reduced fed-fasted effect, (Def.'s Trial Ex., [hereinafter DTX], 248), the Patent Office eventually granted the application and issued the patent in 2006.

The '576 patent claims a method of treating wasting in humans. Claim 1 is representative

[2] Megestrol acetate is a synthetic derivative of the naturally occurring steroid hormone progesterone.

of the asserted independent claims:

> "A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:
>
> (a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;
> (b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and
> (c) the administration is once daily;
> 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,
> wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing."

(DTX 1 at Claim 1; *see also* Claim 4.) The asserted dependent claims claim the use of the method in treating wasting associated with HIV/AIDS, (*Id.* at Claims 2, 10, 21, 24), various plasma concentration levels, (*Id.* at Claims 5, 7, 12-15, 19, 26-29), and the use of a surface stabilizer, (*Id.* at Claims 16, 17, 30, 31).

Around the same time the '576 patent was approved, the FDA approved Par's New Drug Application for Megace ES, a nanoparticulate megestrol acetate oral suspension that the parties have stipulated embodies the claims of the patent. (Stipulation, ECF No. 174, ¶ 4(a).) Unlike Megace OS, the FDA-approved label for Megace ES states that the drug can be taken "without regard to meals."[3] (PTX 70 at 2.) According to Par, Megace ES has been a resounding

[3] A 2012 version of the Megace OS label does not direct patients to take it with food, only stating, "[t]he effect of food on the bioavailability of MEGACE Oral Suspension has not been evaluated." (PTX 71 at 3, 12.)

commercial success, resulting in more than $600 million in net sales since its launch in 2005.[4]

TWi filed an ANDA seeking FDA authorization to market a generic version of Megace ES. TWi timely notified Par of this filing, and, under 21 U.S.C. § 355(b)(2)(A) (a "Paragraph IV" certification under the Hatch-Waxman Act), asserted that the '576 patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." Par filed suit in September 2011 to block the sale of TWi's generic product on the grounds that it infringed the '576 patent. Par asserts claims 1-2, 4-5, 7, 10, 12-17, 19, 21, 24, and 26-31 against TWi. In defense, TWi argues the asserted claims are invalid because they are obvious in light of the prior art, are not enabled, and do not cover patentable subject matter. TWi also claims Par Pharmaceuticals, Inc. does not have standing.

OBVIOUSNESS

I. Standard of Review

Patents are presumed valid and a party claiming invalidity must prove it by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S.Ct. 2238, 2242 (2011); *In re Cyclobenzaprine*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012). A patent is invalid for obviousness "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103.

Obviousness is a question of law based on underlying factual findings as to (1) the level

[4] Par pled guilty in March 2013 to misbranding Megace ES, between 2005 and 2009, by marketing it to geriatric patients, although the FDA had approved its use only for patients with AIDS-related anorexia, cachexia, and unexplained weight loss, and for claiming superior clinical efficacy without conducting relevant clinical studies. (*See* Guilty Plea Transcript, DTX 247 at 14:19-16:1.)

of ordinary skill in the art, (2) the scope and content of the prior art, (3) differences between the prior art and the claimed subject matter, and (4) secondary considerations of non-obviousness such as commercial success, long-felt but unsolved needs, and failure of others. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)). "An invention is not obvious just 'because all of the elements that comprise the invention were known in the prior art.'" *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1335 (Fed. Cir. 2013) (quoting *Power-One,* 599 F.3d 1343, 1351 (Fed. Cir. 2010)). "Generally, a party seeking to invalidate a patent as obvious must demonstrate . . . that a skilled artisan would have had reason to combine the teaching 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." *In re Cyclobenzaprine*, 676 F.3d at 1068-69. "Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co.*, 550 U.S. at 418. Further, the court does not have to rely only on teachings directly aimed at the claimed subject matter, but can take into account inferences and creative steps a person skilled in the art would have taken. *Id.* The inquiry is "expansive and flexible," *id.* at 415, and the court is not required to set aside its common sense, *see id.* at 421.

Once the party challenging validity has made out a prima facie case of obviousness, the patentee can offer evidence of objective secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved need, and failure of others. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359-60

(Fed. Cir. 2007). That the defending party can provide such evidence does not, however, shift the burden away from the challenging party. *Pfizer*, 480 F.3d at 1359-60. Further, secondary considerations cannot overcome a strong prima facie showing of obviousness. *Wyers*, 616 F.3d at 1246.

II. Experts

Before continuing with the merits of the case, it is helpful to describe the backgrounds and qualifications of the various experts on whom the parties relied and to whose testimony the court will refer. TWi relied on the testimony of Dr. David Beach, who has a Ph.D in Pharmacy. He was qualified at trial as an expert in pharmaceutics and has over thirty years of experience working in drug formulation and development, including conducting human clinical trials. (DTX 273; Trial Tr. Day 2, Volume 2, [hereinafter Tr. 2:2], at 15:12-14.) Dr. Beach also has specific experience working with nanoparticles. (Tr. 2:2 at 5:24-6:4; 12:20-13:1.) Par introduced testimony from Dr. Lawrence Fleckenstein, who was qualified as an expert in pharmacokinetics, biopharmaceutics, and clinical trial design.[5] (Trial Tr. Day 3, Volume 2, [hereinafter Tr. 3:2], at 31:1-7.) Dr. Fleckenstein has been a professor of pharmaceutical sciences and Director of the Clinical Pharmacokinetics Laboratory at the University of Iowa for over twenty years, where he conducts studies of the pharmacokinetics and bioavailability of drugs in humans. (PTX 180 at 1; Tr. 3:2 at 22:6-23:5.) He also has published numerous papers on pharmacokinetics, (PTX 180 at 2-16), and has taught pharmacokinetics to university students and FDA reviewers, (Tr. 3:2 at 22:3-5; 25:6-19).

[5] Although Dr. Beach was only qualified in "pharmaceutics," he defined the field as "the science behind the whole development of pharmaceutical products," which includes the physical chemistry and chemistry of compounds, the manufacture of compounds into dosages for humans, as well as administration, pharmacokinetics, and pharmacodynamics of drugs. (Tr. 2:2 at 14:15-24.) Accordingly, his area of expertise, as relevant to this case, is essentially similar to that of Dr. Fleckenstein.

Dr. Cory Berkland also testified for Par and was qualified as an expert in pharmaceutical formulations, with specific expertise in pharmaceutical particles and nanoparticles. (Trial Tr. Day 4, Volume 2, [hereinafter Tr. 4:2], at 79:1-8.) He started studying drug particles during his thesis work for his Ph.D in Chemical Engineering and has continued his work in the ten years since receiving his Ph.D. (Tr. 4:2 at 70:25-71:2; 72:25-74:2.) He is currently a professor of Chemical Engineering and Pharmaceutical Engineering at the University of Kansas. (PTX 176 at 1.)

Par also offered testimony from Dr. Christine Wanke, a Professor of Medicine, Director of the Division of Nutrition and Infection, and Associate Chair of the Department of Public Health and Community Medicine at Tufts Medical School. (PTX 184 at 1.) Dr. Wanke was qualified as an expert in the clinical treatment of nutritional and metabolic complications of HIV and AIDS. (Tr. 4:2 at 24:24-25:5.) Her work is focused on nutritional and metabolic complications of HIV and other infectious diseases, and she has experience in conducting clinical trials. (*Id.* at 19:1-8; 20:11-21:2; 21:12-23:14.)

Finally, both parties introduced expert testimony regarding Megace ES's commercial success. Par introduced the testimony of Dr. Walter Vandaele, an economist and managing director of Navigant Economics, who was qualified as an expert in economic, financial, statistical, and general business issues concerning pharmaceutical products. (PTX 226; Trial Tr. Day 5, Volume 1, [hereinafter Tr. 5:1], at 47:21-48:6.) He has over two decades of experience in the economics of the pharmaceutical industry, with specific experience in the area of commercial success of both brand and generic pharmaceutical companies. (*Id.* at 44:5-45:25.) Mr. Charles Boghigian, testifying for TWi, was qualified as an expert in portfolio management, commercialization, marketing, and promotion of pharmaceutical products. (Trial Tr. Day 5,

Volume 2 [hereinafter Tr. 5:2], at 54:19-55:2.) He has over forty years of experience in pharmaceutical sales and marketing, thirty of which were spent with Hoffman-LaRoche, where he started in sales, but moved to managing sales and marketing for entire regions and drug products—including HIV/AIDS treatments—and eventually heading marketing for the company's entire United States drug market. (DTX 311; Tr. 5:2 at 44:16-18; 45:16-50:2; 51:18-52:22.)

III. Level of Ordinary Skill in the Art

The parties' experts—Dr. Beach for TWi and Dr. Fleckenstein for Par—did not appear to disagree materially over the definition of a person of ordinary skill in the art. Both agreed that a degree of some kind—B.S., M.S., or Ph.D.—was necessary in pharmacy, chemistry or chemical engineering, pharmacokinetics, medicine, or pharmacology. (Tr. 2:2 at 37:6-7; Tr. 3:2 at 59:18-20.) Further, both testified that the person's experience would depend on his level of education: those with less education would require more experience. (Tr. 2:2 at 37:10-17; Tr. 3:2 at 59:17-22.) Finally, there was agreement between the experts' testimony that a person skilled in the art would have basic knowledge of how to formulate the relevant drug compounds as well as their physical and chemical properties. (*See* Tr. 2:2 at 37:8-10, 38:6-9; Tr. 3:2 at 59:13-15.) The court agrees with the experts' conclusions regarding the level of education, experience, and knowledge a person skilled in the art would have and sees no significant difference in their definitions. Dr. Fleckenstein testified that a person of ordinary skill also would have basic knowledge of the treatment of weight loss disorders, (Tr. 3:2 at 59:13-16, 61:2-7), and the court will accept this addition.[6]

[6] It does not appear that Par claims this additional element should make any material difference in the court's analysis. (*See* Pl.'s Brief, ECF No. 201, at 7 n.1 (noting TWi's expert's conclusion regarding the matter "was not materially different").)

IV. Scope and Content of the Prior Art

The effective filing date of the '576 patent for the purposes of § 103 is April 12, 2002, the date of the first provisional application filed by the inventors. *See* 35 U.S.C. §§ 103, 119(e)(1). Thus, relevant material known to the public at that time will constitute the prior art in this case.[7] *See OddzOn Products, Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1402 (Fed. Cir. 1997) (citing *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir. 1984)).

A. Megestrol Acetate

At the time of the application for the '576 patent, Megace OS, a micronized oral suspension of megestrol acetate used in the treatment of anorexia, cachexia, and unexplained weight loss in HIV/AIDS patients, had been available on the market for almost ten years.[8] (Tr. 3:2 at 43:20-25.) It contained 40 milligrams (mg) of micronized megestrol acetate per milliliter (mL). (Megace OS Product Monograph, DTX 10 at ALK_M035677.) The recommended dosage was 800 mg/day (20 mL/day), but, according to the product monograph, doses of 400 and 800 mg/day were found to be clinically effective. (*Id.* at ALK_M035685.) Several prior art references disclose a once-daily dosage regime. (Graham et al., DTX 205 at 581; Oster et al, PTX 92 at 401; Camaggi et al., PTX 86 at 357.) In addition, it was known to be highly viscous, which could decrease patient compliance in taking the medication, as patients had to take a very large amount (20 mL) of the thick liquid. (DTX 1 at col. 6, ll. 49-51; Trial Tr. Day 1, Volume 2, [hereinafter Tr. 1:2], at 52:4-8; Trial Tr. Day 4, Volume 1, [hereinafter Tr. 4:1], at 83:8-15.) This was particularly problematic because the drug was used by patients who had trouble

[7] Although there may be certain instances in which non-public prior art known to the inventor may be considered in an obviousness analysis, *see OddzOn Products*, 122 F.3d at 1403-04, neither party appears to claim those circumstances are present in this case.

[8] Although Megace OS is only a particular embodiment of the prior art oral suspension of micronized megestrol acetate, for ease of discussion, the court refers to it as a proxy reference for the prior art.

swallowing. (Tr. 4:1 at 83:11-15.) Prior to the development of Megace OS, megestrol acetate had also been administered for a number of years as a tablet of 20 and 40 mg, in a dose of 160 mg/day or 40 to 320 mg/day in divided doses, and used for the treatment of advanced carcinoma of the breast or endometrium. (Tr. 3:2 at 43:12-19.)

At the time of the invention at issue in this case, in addition to the patent covering the name-brand Megace OS—U.S. Patent No. 5,338,732 ("Atzinger")—which issued in 1994, a patent had issued in 2000 covering Par's generic version of Megace OS—U.S. Patent No. 6,028,065 ("Ragunathan"), and a patent application was pending for another generic—Patent Application Pub. No. US 2002/0028704A1 ("Brubaker"). The Ragunathan inventors had altered the composition of the existing formulation and found "different formulations of flocculated megestrol acetate suspensions which are also stable." (PTX 97 at col. 2, ll. 57-59.) The Brubaker application was aimed at providing more "pharmaceutically elegant and stable" formulations of an oral suspension of micronized megestrol acetate. (DTX 332 at [0020], [0021].)

By 2002, researchers had made several discoveries concerning the efficacy of megestrol acetate. Several reported its success in increasing body mass in AIDS patients. (*See e.g.*, Graham et al., DTX 205 at 583, 584; Von Roenn et al., DTX at 238 at 398; Oster et al., PTX 92 at 406; Camaggi et al., PTX 86 at 356.) The Graham reference, published in 1994, studied the pharmacokinetics and absorption of the oral suspension formulation of micronized megestrol acetate and reported a statistically significant relationship between weight gain and the percentage of the 24-hour dosing period during which plasma concentrations exceeded 300 ng/mL. (DTX 205 at 581, 585.) Further, it found no significant relationship between total absorption and weight gain, suggesting that weight gain in the early stages of therapy required

exposure in vivo above a threshold concentration. (*Id.* at 585.) With respect to dosage, the authors noted, citing other studies as well, that the 800 mg dose "provides on average the most consistent degree of weight gain in both cancer and AIDS patients," but also suggested that dose individualization may be necessary given observed interpatient variability. (*Id.* at 583, 585.) Similarly, the Von Roenn reference, published in 1994 and studying the relationship between dosage and weight gain, disclosed that patients gained weight in a dose-dependent manner, with a statistically significant difference in weight gain between those receiving an 800 mg/day dose and a placebo. (DTX 238 at 394-96.) In addition to their own study, Graham et al. cited other studies disclosing weight gain in patients receiving doses of megestrol acetate between 160 and 1,600 mg/day, as well as studies disclosing variability in the response to the therapy, even in those receiving 800 mg/day. (DTX 205 at 584-85.) One study cited by the Graham reference reported that two of three patients who failed to gain weight at a 320 mg/day dose gained weight at higher doses (460-640 mg/day). (*Id.*)

Several studies published in 1994 also reported interpatient variability in response to the oral suspension of micronized megestrol acetate. The Graham reference reported "a high degree of interpatient variability" in pharmacokinetics—maximum plasma concentration ("C_{max}"), total absorption ("AUC"), and time to maximum concentration ("T_{max}")—with an eight-fold range in values in the rate of absorption and a five-fold range in values in the extent of absorption. (*Id.* at 582.) The authors also discovered two distinct patterns in absorption, with four of nine patients experiencing rapid absorption, with an initial elimination phase during the first 10 hours, and the other five experiencing more prolonged absorption followed by a slow decline. (*Id.* at 583.) The Von Roenn reference also reported interpatient variability in the effectiveness of Megace OS, noting that even within the group of patients receiving 800 mg/day, only about 64 percent

gained more than five pounds. (DTX 238 at 398.) Finally, Oster et al., studying the effects of Megace OS on weight gain, found that it did not stimulate weight gain in all patients. (PTX 92 at 406.) In addition, a study focused on bioavailability of solid dosage forms of micronized megestrol acetate found high interpatient variability in blood plasma levels and pharmacokinetic parameters. (Farinha et al., DTX 219 at 570 (noting that "megestrol acetate, with respect to C_{max}, behaves as a highly variable drug").) Although finding interpatient variability,[9] the prior art did nothing more than speculate as to the underlying causes. Graham et al. opined that variability in absorption may be due to factors altering gastrointestinal physiology, (DTX 205 at 584), while Oster et al. attributed variability in weight gain to the extent of wasting in the patient, (PTX 92 at 406).

TWi also claims that, in 2002, the prior art disclosed that Megace OS suffered from a food effect and poor bioavailability. While TWi has shown by clear and convincing evidence that it was known the steroid megestrol acetate was a BCS Class II drug and had poor bioavailability, (Tr. 2:2 at 92:11-15 (Dr. Beach's testimony); Farinha et al., DTX 219), the court does not find that TWi has demonstrated a known bioavailability problem with Megace OS.

By 2002, Farinha et al. had discovered that micronizing particles in a megestrol acetate formulation resulted in improved bioavailability. (DTX 219 at 569.) This demonstrates that one skilled in the art would have known megestrol acetate itself was not fully bioavailable. It does not, however, demonstrate whether a person skilled in the art would have known that micronizing the particles did not fully resolve the bioavailability issues, and TWi offers no other

[9] Par's expert Dr. Fleckenstein testified at trial that in the 2002-2003 timeframe, "there were really no reports of any problems of [Megace OS] in terms of efficacy or safety." (Tr. 3:2 at 62:10-11.) The court does not agree with this statement given the evidence from the Graham, Von Roenn, and Oster studies demonstrating interpatient variability. There clearly were reported efficacy problems in at least some patients.

evidence to demonstrate that Megace OS's specific bioavailability was known. TWi's claim that the Von Roenn study, (DTX 238), demonstrated a bioavailability problem is without merit. Finding that patients have a dose-dependent response to a drug does not provide evidence of bioavailability, without more. A drug could be fully bioavailable—meaning it is fully absorbed—but still be more effective at higher doses where more of the drug would be available for absorption.

Although not disclosing anything regarding the specific bioavailability of Megace OS, however, the prior art did disclose several things about Class II drugs, generally. First, it disclosed that Class II drugs had low solubility and high membrane permeability, and that slow dissolution rates were the primary limiting aspect to absorption. (Dressman & Reppas, DTX 281 at S73-74 (defining Class II drugs as those having "solubilities too low to be consistent with complete absorption").) Thus, it was known that, generally, bioavailability was a problem for Class II drugs. The inventors of nanoparticles stated as much during the prosecution of the U.S. Patent No. 5,145,684 ("the '684 patent"), the patent originally disclosing nanoparticles.[10] (DTX 5 at col. 1, ll. 17-20 ("Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water."); *see also* DTX 6B at 5 (stating the same in a filing in the prosecution of the '684 patent).) The prior art also disclosed that "[a]ny interaction that increases solubility and dissolution rate in the gastrointestinal ("GI") tract will have a positive effect on GI absorption of class II drugs," and listed taking drugs with meals as one means of doing so. (DTX 316 at 245.) The prior art also disclosed, however, that many factors can affect dissolution rates in a drug—both physical and physiological—and that absorption will not be the

[10] Elan's touting of nanotechnology's benefits for poorly soluble drugs also provides evidence of this. (DTX 13 at PAR-MEG945718; DTX 177 at 1.)

same across all drugs in the same class or in all individuals. (*See* DTX 281 at S74; DTX 316 at 237, 238 tbl. III & IV; *see also* FDA Guidance for Industry, PTX 83 at 2.) The Dressman & Repas reference disclosed that particle size "is an important physical determinant of the surface area available for dissolution." (DTX 281 at S74.)

The remaining evidence to which TWi points regarding food effects and bioavailability does not convincingly demonstrate that, by April 2002, one skilled in the art would have known the extent of Megace OS's bioavailability, or that Megace OS, or megestrol acetate for that matter, was more effectively absorbed when taken with food. First, TWi points to what was known about danazol, another poorly soluble steroid classified as a BCS Class II, and expressly listed in the prior art as having poor bioavailability and a food effect. (DTX 5 at Example 2 (noting improved bioavailability in danazol when formulated with nanoparticulates); DTX 316 at 245-46, 246 tbls. IX & X (noting danazol's improved absorption when taken with a high-fat meal).) TWi claims a person skilled in the art would have known in 2002 that megestrol acetate was similar to danazol such that it would behave like danazol with respect to food effects. The only evidence TWi proffered, however, is Dr. Beach's testimony at trial that he believed danazol and megestrol acetate were similar because they share a four-ring structure, as all steroids do, (Tr. 2:2 at 72:20-23:5), and a statement by a Par representative in a 2001 email noting that those testing the nanoparticulate formulation of megestrol acetate expected a reduction in fed-fasted variability based on the data they had for danazol, "which is almost structurally identical." (DTX 120.) The statement made by Par cannot provide any guidance on what was known in the prior art; the statement was not publicly available and there is no indication of the basis for the statement. Further, Dr. Beach's testimony cannot be credited given Dr. Fleckenstein's testimony that a person skilled in the art would have known the two steroids had different

absorption mechanisms and, although sharing the four-ring structure of all steroids, had other structural differences that affected absorption. (Tr. 4:1 at 76:2-77:19, 78:16-79:25.) TWi offers no evidence addressing his testimony. The court thus finds that TWi has not offered clear and convincing evidence that danazol's similarities to megestrol acetate were enough for a person skilled in the art to conclude that megestrol acetate would suffer from the same food effect or have the same absorption rates as danazol.

Second, TWi points to statements made by Par, Alkermes—then known as Elan—their representatives, and the FDA that patients were instructed to take Megace OS with food. All the statements, however, were made well after April 2002, and TWi provides no evidence that the statements reflect what was known in April 2002. Dr. Liversidge's statement that "you had to take [Megace OS] with food," is from his testimony in a 2008 trial. (*See* Tr. 1:2 at 50:18-51:11, 52:3-16.) There is nothing in Dr. Liversidge's testimony to indicate when the food effect was discovered; there is nothing to suggest it was not discovered at the time a nanoparticulate formulation was first made, as Par claims.

The statements made by the FDA and Par while Par was seeking a New Drug Application ("NDA") for Megace ES were not separate statements at all. Instead, the initial statement that "patients are instructed to take Megace OS with food," was made by an FDA representative in a letter dated September 10, 2003, well over a year after the critical date for determining the prior art, and all subsequent statements TWi points to were actually references to that original letter. (*See* DTX 83 at PAR-MEG281946 (FDA's September 10, 2003 letter to Par stating, "patients are instructed to take Megace with food"); DTX 86 at PAR-MEG94451 (Par's response to the FDA's September letter repeating the FDA's prior statement); DTX 255 at PAR-MEG322900 (relaying the FDA's statement to clinical trial site directors in 2004); PTX

3A at PAR-MEG000370 (Par's NDA repeating the statement from the FDA's letter and attributing it to that letter); DTX 546 at ALK_M121566 (same).) As with Dr. Liversidge's 2008 testimony, TWi provides no evidence that the statement made by the FDA reflected knowledge in April 2002 or was not a result of what Par claimed to have discovered about Megace OS when developing the nanoparticulate formulation.

TWi also points to Elan's website and various drafts of it that appear to be from, at the earliest, 2006, stating that the oral suspension of micronized megestrol acetate had to be taken with food. (DTX 116 at ALK-M160963; DTX 183 at 1; DTX 184 at ALK_M019448.) Again, TWi provides no evidence that the statement reflects knowledge in 2002 and is not the result of hindsight.

Third, TWi relies on the Graham reference as proof that Megace OS was known to be more effective when taken with food. Its claim is based entirely on the fact that the Graham authors instructed patients to take their daily dose of the oral suspension before breakfast and then, when testing plasma concentrations, had the patients take their dose after an overnight fast with a low-fat breakfast following two hours later. (DTX 205 at 581.) The court finds no support for TWi's claim that the Graham reference demonstrates that those skilled in the art knew absorption of Megace OS was enhanced when taken with food. TWi's apparent claim that the authors were trying to minimize the known food effect by having patients take their doses in a fasted state is unpersuasive in light of Dr. Fleckenstein's testimony that investigators administering a drug study to human patients would want to ensure they were administering the drug in optimal conditions, to make it as effective as possible. (Tr. 3:2 at 79:14-25.) If the Graham investigators knew the drug was more effective when taken with food as TWi alleges, it does not make sense that they would purposefully make it less effective by having patients take it

in a fasted state. The Graham reference does not demonstrate a known food effect in the absorption of the oral suspension of micronized megestrol acetate.

Finally, TWi relies on the '576 patent inventors' statement in the patent's specification that "[t]here is a need in the art for megestrol formulations which exhibit increased bioavailability." (DTX 1 at col. 4, ll. 28-29.) It is true that statements of the prior art in a patent's specification are binding on the patentee when determining obviousness. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007). The '576 inventors' statement is not, however, best characterized as a statement of what was in the prior art in 2002. In the cases on which TWi relies to convince this court otherwise, the inventors expressly identified references as "prior art" or expressly stated what was previously known from the prior art. *See, e.g., id.* at 1361-62; *Constant v. Adv. Micro-Devices, Inc.*, 848 F.2d 1560, 1569-70 (Fed. Cir. 1988); *In re Nomiya*, 509 F.2d 566, 570-71 (C.C.P.A. 1975). By contrast, there is nothing to suggest the statement in the '576 patent specification is anything more than the inventors' own evaluation of the prior art upon inventing the nanoparticulate formulation of megestrol acetate, nor do there appear to be prior art references cited in the specification from which the statement about bioavailability is drawn. Eurand's "modified form of megestrol acetate having increased bioavailability," cited in the specification, is not clearly prior art as there is no indication of when it would have been known to a person skilled in the art.[11] (DTX 1 at col. 4, ll. 4-20; *see also* Tr. 4:1 at 100:6-13 (Dr. Fleckenstein's testimony that it was true that Eurand "advertised they also were trying to develop a megestrol product with improved increased bioavailability").) Further, there is no indication of whether Eurand's formulation is a

[11] In fact, the only evidence TWi provides of when the Eurand formulation was disclosed is an email calling the work to the attention of several individuals associated with Par and dated October 30, 2002. (DTX 130 at ALK_M002623.) The webpage included with the email has a copyright year of 2002, with no specific date listed. (*Id.* at ALK_M002624.)

modification of conventional or micronized megestrol acetate. As discussed earlier, it was known conventional forms of megestrol acetate suffered from bioavailability problems. For these reasons, although the Eurand invention may suggest others were aware of a bioavailability problem, the '576 inventors citation to it is not an admission of prior art that provides clear and convincing evidence of what was known about micronized megestrol acetate formulations.

That TWi has failed to prove a known food effect is further bolstered by the fact that Graham and other researchers, in several studies conducted in 1994, 1995, and 2000, instructed participants to take Megace OS without food. (*See* Graham et al., DTX 205 at 581; Oster et al., PTX 92 at 401; Camaggi et al., PTX 86 at 357; Farinha et al., DTX 219 at 568.) In addition, Dr. Wanke, a doctor and academic focusing on infectious diseases—predominantly HIV and AIDS—and nutrition and metabolism issues associated with such diseases, testified that during the 1990s, while an attending physician at a Harvard-affiliated hospital, she did not tell hundreds of HIV/AIDS patients for whom she prescribed Megace OS to take it with food, because neither she nor others at the clinic knew of the food effect. (Tr. 4:2 at 20:17-21:9.) Further, the product monograph for Megace OS expressly reported, in 2002, that "the effect of food on the bioavailability of Megace [OS] has not been evaluated."[12] (DTX 10 at ALK_M035679.) The product monograph, Dr. Wanke's testimony, the manner in which the prior art studies were conducted, and Dr. Fleckenstein's testimony that those conducting human trials would attempt to administer the drug in the most effective manner (Tr. 3:2 at 79:3-25), provide substantial

[12] TWi claims this statement cannot be credited because the label as of 2012 still said the food effect had not been studied even though Par's study results were well known in 2012. Although the statement may not be a proper reflection of the art as it exists today, however, TWi has failed to offer any reason to believe it did not reflect what was known in the prior art in 2002.

evidence that the food effect was unknown.[13]

B. Nanoparticulate Technology

The prior art includes several patents disclosing the attributes and advantages of nanoparticles. The '684 patent first disclosed nanoparticles in 1992. (DTX 5.) It disclosed particles with an effective average size of less than about 400 nanometers (nm), 250 nm, or 100 nm. (*Id.* at Claims 1-3, 6, 9-10, 16, 17.) It also disclosed the use of a surface modifier with the chosen drug substance, and stated that it was "believed that the surface modifier hinders the flocculation and/or agglomeration of the particles by functioning as a mechanical or steric barrier between the particles, minimizing the close, interparticle approach necessary for agglomeration and flocculation." (*Id.* at col. 4, ll. 28-30, col. 8, ll. 21-27.)

The patent specification disclosed that the invention could be practiced with a number of drug substances, preferably those intended for oral and intravenous administration, as long as they were poorly soluble. (*Id.* at col. 3, l. 32-col. 4, l. 20.) In fact, the inventors stated during the patent's prosecution that the "invention can be practiced with *virtually all* poorly soluble drug substances," provided numerous examples of successfully-made nanoparticles, and stated that the examples "illustrate[d] that eleven soluble drug substances of radically different chemical structure and from a wide variety of therapeutic classes have been prepared in the form of

[13] Par points to two other references—Schindler et al. (2003), (PTX 117), and the FDA's approval of Roxane Laboratories' ("Roxane") generic version of Megace OS (PTX 513)—which it claims undercut any finding that Megace OS was known to have poor bioavailability or suffer from a food effect, (Pl.'s Brief at 11), but the court does not find them persuasive. First, there is no evidence that either constitutes a prior art reference: Schindler was published in 2003 and, although the approval date of Roxane's generic was February 15, 2002, there is no evidence of when its contents were made public. Second, the Schindler reference offers no evidence or reasoning to support its claim that "the bioavailabilty of [megestrol acetate] is nearly 100%," (PTX 117 at S12), and in the face of Farinha et al., (DTX 219), it carries little weight with the court. The FDA file on Roxane's generic only states that megestrol acetate is "well absorbed," with no indication of how "well absorbed" is empirically defined (PTX 513 at PAR-MEG573872.).

nanoparticles." (DTX 6B at 8 (emphasis added).) The '684 patent specifically listed "sex hormones (including steroids)" as a preferred drug substance, with danazol and steroid A providing representative examples, sharing several nanoparticulate formulations of the two drugs. (DTX 5 at col. 4, l. 3, col. 4, ll. 15-20, col. 8, l. 36-col. 15, l. 26, Claim 5; *see also* DTX 6C at ¶ 7 (statement by the '684 patent inventors that "[l]aboratory work has demonstrated that the wet grinding process . . . is broadly applicable to a wide variety of classes of poorly-soluble drug substances including steroids").)

In addition, the '684 patent specification stated that "pharmaceutical compositions according to this invention include the particles described above and a pharmaceutically acceptable carrier therefor . . . includ[ing] . . . acceptable carriers . . . for oral administration," and that "[i]t is contemplated that the pharmaceutical compositions of this invention will be particularly useful in oral . . . administration." (*Id.* at col. 7, ll. 53-60, col. 8, ll.10-13.) Finally, the patent disclosed that the invention related to the use of nanoparticles in pharmaceutical compositions and methods of treating mammals. (*Id.* at col. 1, ll. 8-10, col. 2, ll. 57-62; *see also id.* at col. 7, ll. 60-64 ("A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described pharmaceutical composition."), Claim 15.)

United States Patent No. 5,399,363 ("the '363 patent"), entitled "Surface Modified Anticancer Nanoparticulates" and issued in March 1995, and European Patent No. 0577215B1 ("the '215 patent"), entitled "Process for Obtaining Surface Modified Anticancer Nanoparticles" and issued in March 2000, followed the '684 patent and claimed nanoparticulate formulations of anticancer agents that exhibit reduced toxicity and/or enhanced efficacy.[14] (DTX 3 at [45], [57];

[14] The '215 patent is essentially the European version of the '363 patent.

DTX 11 at (45), [0005].) Both patents disclose that the claimed invention can be practiced with a wide variety of anticancer agents as long as they are poorly soluble, and both expressly list megestrol acetate as one of many preferred anticancer agents.[15] (DTX 3 at col. 2, ll.35-38, ll.50-53, col. 3, ll.22-26; DTX 11 at [0015], Claim 1.) Further, both patents disclose that the claimed compositions could include an acceptable carrier for oral administration. (DTX 3 at col. 7, ll. 53-61, col. 8, ll. 53-58; DTX 11 at [0038].) In addition, both claim an effective particle size of less than 1000 nm and 400 nm, respectively, and disclose the use of a surface modifier absorbed on the surface of the anticancer agent sufficient to maintain the particle size and ensure the dispersion "exhibits no particle flocculation or particle agglomeration visible to the naked eye and particularly when viewed under the optical microscope at 1000x at least two days after preparation." (DTX 3 at Claim 1; DTX 11 at [0006], Claim 1.) Like the '684 patent, the '363 and '215 patents also claim a method of treating mammals by administering an effective amount of the resulting composition, and further claim increased efficacy and reduced toxicity. (DTX 3 at Claims 9-11; DTX 11 at [0010], [0039].)

Several prior art references disclosed the potential benefits of nanoparticulate technology. In the prosecution of the '684 patent, the inventors disclosed that nanoparticulate formulations of two steroids, Steroid A and danazol, demonstrated seven and sixteen fold increases, respectively, in bioavailability over conventional formulations when tested in dogs. (DTX 6C at ¶ 8; DTX 5

[15] Citing cases examining whether a prior art reference anticipated the challenged claims, Par attempts to argue the '363 and '215 patents did not disclose that megestrol acetate was a suitable agent to be used with nanotechnology because it was just one of many on a list of suitable agents and there is nothing directing a person skilled in the art to choose megestrol over others. That a compound may be one of many on a list, however, does not undermine the disclosure. *See In re Gleave*, 560 F.3d 1331, 1337-38 (Fed. Cir. 2009); *Perricone v. Medicis Pharm. Co.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005). Because this is a case under § 103, it does not matter whether the '215 and '363 patents enabled the claimed formulation of the '576 patent, only that they disclosed that megestrol would be a suitable agent to be used in such formulations.

at col. 9, l. 60-col. 10, l. 11). Observing the increased bioavailability of a nanoparticulate suspension of danazol in dogs over the conventional formulation, the '684 patent inventors therefore reported that the results "suggest[ed] that the nanoparticulate dispersion had overcome the dissolution rate limited bioavailability" of conventional suspensions of danazol. (DTX 15 at 97.) The '684 patent inventors also stated in filings with the U.S. Patent Office that particles prepared with the nanotechnology could be formulated into "pharmaceutical compositions exhibiting remarkably high bioavailability and other advantageous properties, including, for example, improved dose proportionality, decreased fed-fasted variability and more rapid onset of action." (DTX 6B at 7; *see also* DTX 6C at ¶ 9 ("Pharmaceutical compositions containing particles prepared according to the method . . . have exhibited improved dose proportionality and decreased fed-fasted variability.").) By 2001 and early 2002, Elan's website and brochure on its NanoCrystal technology (nanoparticulate technology) publicly touted the potential to increase bioavailability, reduce fed-fasted effects, allow higher dose loading with smaller dose volume, decrease time to therapeutic levels, and reduce viscosity in poorly soluble drugs.[16] (DTX 177 at 2; DTX 13 at PAR-MEG945718-19; *see also* Müller et al. (2000), DTX 16 at 401, 403 (noting nanoparticles resulted in increased bioavailability, increased dose proportionality, reduced fed-fasted effects, reduced intersubject variability, and enhanced absorption rates).) The Müller reference, from 2000, disclosed that nanoparticles reduced erratic absorption—interpatient variability—because the adhesion process associated with nanoparticles was highly reproducible

[16] TWi also introduced slides from a presentation allegedly given in Kyoto in 1996 on the benefits of nanoparticles. (DTX 314.) The court will not rely on the exhibit as prior art, however, because TWi has failed to show by clear and convincing evidence that it was in fact the presentation given in 1996, (*see, e.g.*, Tr. 1:2 at 29:8-15), and thus has failed to show that the slides would have been those publicly available, *see Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1305 (Fed. Cir. 2006) ("Art that is not accessible to the public is generally not recognized as prior art.").

and little affected by the nutritional status of the patient. (DTX 16 at 403.)

In addition, and more generally, it was known in the prior art that reducing particle size, either to nanoparticlulate or microparticulate size, could increase the bioavailability of poorly soluble drugs. (*See* Müller et al., DTX 16 at 384-85 (discussing the need to further reduce particles to nanoparticulate size in the most poorly soluble drugs to increase bioavailability by increasing the dissolution rate); U.S. Patent 6,045,829, DTX 188 at col. 1, ll.36-52 (discussing the problem of poor bioavailability due to poor absorption in poorly soluble drugs and stating "it is known that by increasing the surface area of a particulate drug, such as by decreasing the particle size of the drug, the rate of dissolution of the particulate drug is increased"); U.S. Patent 6,221,400, DTX 182 at (57) (same).) One study specifically found that a 160 mg dose of micronized megestrol acetate exhibited higher bioavailability than a 160 mg dose of non-micronized megestrol acetate. (Farinha et al. (2000), DTX 219 at 569.) Further, the Müller reference disclosed the superiority of reducing particle size to address issues of solubility over other possible solutions, and found that, when higher blood levels are required, micronizing particles was not enough of a reduction in size. (DTX 16 at 384.)

V. Differences between the Prior Art and the Claimed Invention and Prima Facie Obviousness

TWi has proved by clear and convincing evidence a prima facie case of obviousness. Not only does the prior art disclose every element of the challenged claims, but it discloses a motivation for a person of ordinary skill in the art to combine the elements in the way disclosed by the '576 patent and to do so with a reasonable likelihood of success. *See In re Cyclobenzaprine*, 676 F.3d at 1068-69 ("Generally, a party seeking to invalidate a patent as obvious must demonstrate . . . that a skilled artisan would have had reason to combine the teaching 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."); *Broadcom*, 732 F.3d at 1335 (noting that "[a]n invention is not obvious just 'because all of the elements that comprise the invention were known in the prior art.").

A. The prior art discloses all elements of the claimed invention.

As discussed in Part IV, the prior art disclosed the use of an oral suspension of megestrol acetate for increasing body mass in HIV/AIDS patients suffering from anorexia, cachexia, or unexplained weight loss—this is Megace OS and its generic replications. Further, the prior art disclosed the claimed single daily administration and dose range (claims 1, 4), as Megace OS had been administered daily and in doses within the range of 40 mg to 800 mg. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (finding a claimed range obvious where it overlapped with that disclosed in a prior art reference); *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (same). Further, the doses claimed do not represent optimization and there is no evidence they achieve unexpected results on their own. *In re Geisler*, 116 F.3d at 1469. The prior art disclosed each of the claimed therapeutic blood levels as well: a mean T_{max} of five hours, (Graham et al, DTX 205 at 582, tbl. 2), a therapeutically effective threshold blood level of 300 ng/mL, (*id.* at 585), steady-state C_{max} levels ranging from 295 ng/mL to 1,670 ng/mL, (*id.* at 582, tbl. 2), and increased C_{max} levels in formulations with reduced particle sizes (Farinha et al., DTX 219 at 570). The prior art also disclosed nanoparticulates, their use in pharmaceutical compositions for oral administration,[17] and how to create stable formulations using surface modifiers. In addition, the '215 and '363 patents expressly disclosed nanoparticle formulations

[17] Par claims that the '363 and '215 patents do not disclose oral administrations of nanoparticulate megestrol acetate because the patents are focused on intravenous ("IV") administrations. This argument is without merit. Whatever the primary purpose of the prior art, a person skilled in the art may find a teaching in addition to that purpose. *KSR Int'l Co.*, 550 U.S. at 421.

using megestrol acetate as the drug substance.

Par claims that the prior art does not disclose the claimed differences, or lack of substantial difference, between the C_{max} of megestrol in a fed versus fasted state (Claims 1, 4, 5). The claimed pharmacokinetic parameters with respect to a food effect, however, are inherent properties of the obvious nanoparticulate formulation claimed by the '576 patent, and, although functional limitations, they do not render the obvious formulation and method nonobvious.

Inherency may be considered in an obviousness analysis. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2013); *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011), *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009). A property that inherently results from an obvious combination of the prior art, although previously unknown, does not render the combination nonobvious. *See Allergan Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1294 n.1 (Fed. Cir. 2013) (suggesting that where the evidence establishes a claimed limitation is the necessary result or inherent property of a claimed administration it does not render an otherwise obvious claim nonobvious); *In re Kao*, 639 F.3d at 1070 (finding an inherent property of a compound used in a claimed method did not render the obvious claimed method nonobvious even though the property was unknown in the prior art); *cf. In re Best*, 562 F.2d 1252, 1254-55 (C.C.P.A. 1977) ("[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on." (citation omitted)).

As discussed below, TWi has proven by clear and convincing evidence that combining nanotechnology with megestrol acetate would have been obvious to someone skilled in the art

because of the viscosity and interpatient variability associated with the micronized formulation. As Dr. Beach testified, an improvement in bioavailability necessarily results in a reduction in any food effect, whether previously known or not. (Tr. 3:1 at 11:11-12:5.) TWi has demonstrated that reducing particle size will improve bioavailability across all administrations claimed in the invention, thus any food effect will inherently be reduced. It is, therefore, an inherent result or property of the administration even if it was previously not known in the prior art that a food effect existed. "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Santarus*, 694 F.3d at 1354.

Par's attempt to liken this case to *In re Newell* is unconvincing. In that case, the Federal Circuit found the inventor had no motivation to combine the prior art other than his discovery of a previously unknown problem. 891 F.2d 899, 901-02 (Fed. Cir. 1989). Accordingly, the court found it was improper for the Board of Patent Appeals to rely on the inherency of the problem, and the inherency of the improvement, to find the invention obvious. *Id.*; *see also Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013). Here, the court is not using inherency as a hindsight substitute for motivation. Instead, the court has found motivations other than the food effect for combining the prior art, and the inherent property of a reduced food effect does not negate that.[18] *See In re Kao*, 639 F.3d at 1070 ("This is not a case where the

[18] It does not appear that any possible food effect associated with Megace OS was what motivated Par to create the nanoparticulate formulation in the first place. (*See* DTX 129 (noting the dog study disclosing the food effect was performed after Elan's Dr. Pruitt created the formulation); DTX 199 at 1, 4 (discussing the parameters of the dog study after the first successful formulations had been created); DTX 353 at 97:12-98:09 (Dr. William Bosch's deposition testimony that the dog trials were performed "to determine whether or not the reformulation had an impact on pharmacokinetics of the product").) Indeed, the evidence does not provide much insight into why Par pursued the nanoparticulate formulation of megestrol acetate. Dr. John Pruitt, one of the '576 inventors, testified at his deposition that, ordinarily, he

Board relied on an unknown property of prior art for a *teaching*. Rather, [the prior art's] express teachings render the claimed [formulation] obvious, and the claimed 'food effect' adds nothing of patentable consequence.").

B. The prior art provided a motivation for a person skilled in the art to combine the prior art elements.

Given that all the elements are disclosed in the prior art, the essential inquiry for determining obviousness in this case is whether a person of ordinary skill in the art would have seen a benefit to applying the nanoparticulate technology disclosed in the prior art to Megace OS and been motivated to do so. "[M]otivation to combine may be found explicitly or implicitly in market forces; design incentives; the interrelated teachings of multiple patents; any need or problem known in the field of endeavor at the time of invention and addressed by the patent; and the background knowledge, creativity, and common sense of the person of ordinary skill." *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354 (Fed. Cir. 2013) (internal citations and quotation marks omitted). The prior art does not have to expressly teach the invention at issue. It is enough if the prior art would have suggested the invention to a person skilled in the art. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

Although the court finds TWi has failed to prove by clear and convincing evidence that one skilled in the art would have known of the food effect associated with Megace OS and the extent of its bioavailability problem, there were other motivations to improve the existing formulation. *See KSR Int'l Co.*, 550 U.S. at 420 ("[T]he problem motivating the patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person

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was just told to see if he could create a stable formulation, while Dr. Bosch stated in an email at the beginning of the project that Par was seeking to make a more bioavailable formulation. (DTX 119; DTX 352 at 15:7-12.)

with ordinary skill in the art."); *Alcon*, 687 F.3d at 1368 ("We have repeatedly held that the motivation to modify a prior art reference to arrive at the claimed invention need not be the same problem the patentee was trying to solve."). TWi proved it was known that Megace OS was viscous and required more dosing and that absorption levels varied greatly among patients. The court finds that both of these problems provided sufficient motivation for a person skilled in the art to create a method of treatment using nanoparticles.

Dr. Fleckenstein testified that Megace OS was known to be highly viscous and that this created difficulties in the patient population because AIDS patients have difficulty swallowing viscous materials. (Tr. 4:1 at 83:8-15; *see also* Tr. 1:2 at 52:4-6 (Dr. Liversidge's testimony that the formulation was very viscous).) When asked by the court, he also testified that switching to the nanoparticulate formulation would be expected to help with the viscosity problem. (*Id.* at 16-23.) In addition, Dr. Liversidge testified that Megace OS was administered in a half-cup dose. (Tr. 1:2 at 52:6-8.) Par attempts to minimize the motivation that viscosity and large dose volume would provide by claiming they were merely a cosmetic factor of secondary concern to physicians. (Pl.'s Reply, ECF No. 205, at 14-15 (citing Tr. 4:1 at 84:10-12; DTX 24 at 4).) This flies in the face, however, of Dr. Fleckenstein's testimony and the acknowledgment in the '576 patent specification that "[t]ypical commercial formulations of megestrol, such as Megace, are relatively large volume, highly viscous substances that are not well accepted by patient populations, particularly subjects suffering from wasting." (DTX 1 at col. 6, ll. 49-51.) In addition, Par's marketing consistently emphasized reduced volume and reduced viscosity as benefits of Megace ES, seemingly reflecting a known, existing desire among those prescribing Megace OS for a less viscous, lower volume formulation. (*See, e.g.*, PTX 241 at PAR-MEG150891 (training materials for new hires stating that less volume and reduced viscosity "is

an important point with physicians who are treating patients with decreased or no appetite, and may have difficulty swallowing"); PTX 249 at PAR-MEG382865 (listing reduced volume and viscosity as "patient benefits"); PTX 449 at PAR-MEG100199 (including reduced volume and viscosity on marketing materials as features demonstrating "there's more to gain with Megace ES"; *see also* Tr. 5:1 at 83:9-18 (Dr. Vandaele's testimony that reduced volume and viscosity were part of "the three main messages" in marketing Megace ES).) In fact, in its post-trial brief, Par stated that "reduced volume" and "reduced viscosity" were "core messages" of its marketing materials. (Pl.'s Brief at 40-41.)

Par points out that others reformulating oral suspensions of megestrol acetate did not use nanotechnology to change viscosity. Yet, Par relies on the patent covering Megace OS—Atzinger—and a patent application for a generic form of Megace OS—Brubaker—to make this claim. The question at issue in this case is whether there was a motivation to change the existing oral suspension of *micronized* megestrol acetate, not conventional formulations. Further, it is unlikely that an inventor focused on creating a generic formulation of an already marketed drug would change an underlying structural aspect of the compound—such as particle size—where he must show bioequivalency to the FDA.

In addition to high viscosity and dose volume, the prior art taught that the oral suspension of micronized megestrol acetate suffered from high interpatient variability in drug absorption and weight gain, (DTX 205 at 582-83; DTX 238 at 398; PTX 92 at 406), providing another motivation to use nanoparticles to reformulate the drug. Although one skilled in the art would not have known the specific extent of the bioavailability problems of Megace OS, the person would have been aware that the underlying compound of megestrol acetate was poorly soluble and not fully bioavailable as demonstrated by the increase in bioavailability when it was

reformulated from the conventional particle size to micronized particles. (Farinha, DTX 219.) Further, the person would have known that it was a Class II drug and that absorption of such drugs are dissolution-rate limited such that "[a]ny interaction that increases solubility and dissolution rate in the GI tract will have a positive effect on GI absorption of class II drugs." (DTX 316 at 245.) A person skilled in the art also would have been aware that reducing particle size affects dissolution rates and that the smaller the particle size, the more surface area available for absorption, thus increasing dissolution velocity. (DTX 16 at 384.) This, along with the fact that reducing particle size had improved the bioavailability of megestrol acetate before, would have suggested to a person skilled in the art that the remaining variability in absorption levels in some patients may be due to bioavailability problems and that nanotechnology could address those issues in some patients. (*See* Tr. 3:1 at 9:17-11:13.) Although it does not constitute a prior art reference, Dr. William Bosch, at Elan, seems to have recognized the desire to improve bioavailability when he noted at the beginning of the project to reformulate Megace OS that "Par would like to see about developing a more bioavailable form of the liquid product." (DTX 119.) Nanotechnology would have been especially appealing given the Oster and Graham references that attributed interpatient variability to a patient's wasting or changes in their gastrointestinal physiology, (DTX 205 at 584; PTX 92 at 406), because the prior art disclosed that nanoparticulates' adhesion process was little affected by the nutritional status of the patient, (DTX 16 at 403). Given that using nanoparticles had the added benefit of reducing viscosity and dose volume, a person skilled in the art thus would have been motivated to use the technology to improve upon all known problems with one solution.

Dr. Fleckenstein disputed that interpatient variability would have provided a motivation to create a nanoparticulate formulation of megestrol acetate, testifying that the 64% success rate

reported in the Von Roenn study was "remarkable" given that weight loss in AIDS patients is very complicated and results from a number of causes. He thus concluded that Megace OS was "remarkably effective" and would leave those skilled in the art with no motivation to improve upon it with nanotechnology. (Tr. 3:2 at 67:3-18.) The court finds it unlikely that those skilled in the art would not be interested in determining why Megace OS was only effective in a little over half of patients or in finding a way to make it more effective. The court further finds Dr. Fleckenstein's testimony to be less persuasive because it is also based on the Schindler reference, (Tr. 3:2 at 67:19-68:9), which as discussed above conclusively states that megestrol acetate is nearly 100 percent bioavailable with no underlying evidence or reasoning, *see supra* note 13.

The application of nanotechnology to megestrol acetate would not have been just "obvious to try," such that it constituted throwing "metaphorical darts at a board filled with combinatorial prior art possibilities." *In re Kubin*, 561 F.3d at 1359. The Federal Circuit has identified two classes of cases in which "obvious to try" is erroneously equated with obviousness under § 103. In the first, a patent is not invalid for obviousness where the prior art only made it obvious to try varying all parameters or to try each of numerous possible choices with no indication of which were critical parameters or which choices would lead to a successful result. *Id.* In the second, a claimed invention is not obvious under § 103 where it was only obvious to explore a new technology or general approach that seemed to be a "promising field of experimentation," but offered nothing more than "general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* (internal citation and quotation marks omitted). Neither of those scenarios is present in this case. TWi has proven that the problems known to exist with Megace OS were its viscosity, dose volume, and its varied efficacy in patients, and that each were known to be affected by a drug's particle size. It was not a matter of trying to

change various parameters or trying different solutions hoping one would solve the problem. The benefits of reducing particle size were known with respect to all known problems. Further, even if Par's expert, Dr. Berkland, is correct that there were other ways to address these issues that were less complex and tested, the list he provides is finite, (Tr. 5:1 at 14:1-15:23), and "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co.*, 550 U.S. at 421. Although nanotechnology may have been relatively new and untested, the nanotechnology patents provided a clear method for creating stable nanoparticles. The prior art did not merely direct those skilled in the art to reduce particle size, by whatever means a person could find. It provided a clear path forward with a clear prediction of the result.

C. The prior art did not "teach away" from the claimed invention.

Par claims that the Graham reference and known agglomeration of nanoparticles taught away from the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Kubin*, 561 F.3d at 1357 (internal citations and quotation marks omitted). According to Par, Graham's study of the pharmacokinetic and pharmacodynamic properties of Megace OS taught that more rapid absorption would lead to poorer patient outcomes and no weight gain and thus discouraged the use of nanotechnology which was known to lead to more rapid absorption. (Pl.'s Reply at 11.) Par bases its claim on Graham's finding that study participants experiencing more prolonged absorption and slower elimination also experienced superior weight gain. (DTX 205 at 584-85.) Par distorts the teaching of Graham, however.

From the difference in outcomes, Graham found a statistically significant relationship between weight gain and the percentage of the 24-hour dosing period during which plasma concentrations exceeded 300 ng/mL when patients were administered Megace OS. (*Id.* at 585.) From this Graham et al. concluded that "weight gain in the early stages of megestrol therapy requires drug exposure in vivo above a threshold concentration" and that weight gain would likely occur "when plasma megestrol concentrations exceed 300 ng/mL for at least 40% (10 h) of a 24-h dosing interval." (*Id.*) A person skilled in the art thus would have concluded that the longer a patient's blood plasma concentration could be maintained above the 300 ng/mL threshold, the better. To properly teach away from a claimed combination, the prior art reference must "criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Although cautioning a person skilled in the art that rapid absorption with rapid elimination and low blood plasma concentrations may cause Megace OS to be ineffective, Graham did not discredit a nanoparticulate formulation or teach that it would not have worked for its intended treatment purposes. *See id.*; *In re Icon Health*, 496 F.3d 1374, 1381 (Fed. Cir. 2007) ("[A] reference may teach away from a use when that use would render the result inoperable."). Nanoparticles were known to increase absorption levels and were associated with longer dose retention, (*See* DTX 177 at 2), features that ostensibly would contribute to higher concentration levels for longer time periods. The Graham reference nowhere suggests that rapid absorption when combined with these features would prevent sustained blood plasma levels above the effective threshold or that the resulting formulation would be wholly ineffective in sustaining blood concentrations for an effective time period, and thus cannot be said to discourage investigation into the claimed invention.

Par also claims that agglomeration was a known problem with nanoparticles and would

have taught away from combining the prior art in the way claimed by the '576 patent. (Tr. 5:1 at 16:10-17:8.) This argument is without merit as well. Although smaller particles may have resulted in a greater risk of agglomeration, the nanotechnology patents demonstrated that use of a surface modifier with nanoparticles could prevent agglomeration. (*See, e.g.*, DTX 5 at col. 8, ll. 21-27; DTX 11 at Claim 1.)

D. A person skilled in the art would have had a reasonable likelihood of success in creating the claimed invention.

Despite the touted benefits of nanotechnology for poorly soluble compounds, Par claims TWi has failed to demonstrate a person skilled in the art would have had a reasonable likelihood of success because nanotechnology was new, untested, and unpredictable. TWi has demonstrated by clear and convincing evidence, however, that a person skilled in the art in 2002 would have believed making nanoparticles was not extremely difficult, could successfully be implemented with a wide variety of drugs, particularly steroids, and would result in reduced interpatient variability, improved bioavailability, reduced viscosity and reduced dosing volumes. As discussed above, the expected benefits of nanoparticles were widely touted by 2002. Further, the relevant prior art references described the wide applicability of nanotechnology for creating pharmaceutical compositions and its "simplicity," with several examples of success. (*See* DTX 3 at col. 7, l. 51-col. 8, l. 5; DTX 5 at col. 3, l. 32-col. 4, l. 20; DTX 6B at 8; Müller et al., DTX 16 at 406 ("[T]he major advantage of this technology is its simplicity.")

Par claims Dr. Liversidge's, one of the '684 inventors, testimony at trial, that it is hard to predict which compounds can be successfully formulated with nanoparticles and that success is varied even among poorly soluble drugs, undermines this conclusion. (*See* Tr. 1:2 at 70:6-74:13.) Par further points to the fact that, as of trial, only six commercialized formulations with nanoparticles had made it to market. (*Id.* at 69:9-16.) Yet, Dr. Liversidge's testimony only

indicates what is now known about nanotechnology, not what was known in 2002 by a person of skill in the art.[19] *See In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371-72 (Fed. Cir. 2012) (noting that reasonable expectation of success is measured from the perspective of the person of ordinary skill in the art at the time of the invention (citing *Life Tech., Inc. v. Clontech Lab., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000))). There is no evidence to suggest a person of skill in the art, in 2002, would have believed anything other than that nanotechnology was sufficiently simple to apply and would result in the claimed benefits as TWi has shown with extensive evidence.

VI. Secondary Considerations

Before making its final conclusions with respect to obviousness, a court must consider any proffered objective indicia of nonobviousness. *In re Cyclobenzaprine*, 676 F.3d at 1079. Such evidence protects against inappropriate hindsight analysis and ensures the court considers obviousness only from the perspective of one skilled in the art at the time of invention. *Id.* Although the burden of persuasion never shifts away from the party challenging a patent's validity, *id.* at 1075 (finding the district court erred by shifting the burden of persuasion to the patentee on the issue of secondary considerations), the proponent of evidence of secondary considerations must establish a nexus between the evidence and the merits of the claimed invention, *In re Kao*, 639 F.3d at 1068. Further, the evidence must be commensurate with the scope of the claims, meaning, although the patentee does not have to demonstrate the existence

[19] For this reason, the court does not consider Par's evidence of specific failures with respect to nanoparticulate formulations of Clopidogrel, Orlistat, or Sorafenib persuasive evidence of what a person skilled in the art would have expected. There is either no evidence of when the attempts were made, (*see* DTX 47; DTX 49), or the attempts were made after 2002, (*see* DTX 48 (demonstrating attempts to create a nanoparticulate formulation of Orlistat in 2006)). Further, three examples of failure among many compounds does not show there is no reasonable expectation of success with other compounds. Obviousness only requires a reasonable expectation of success, not "absolute predictability." *In re Droge*, 694 F.3d 1334, 1338 (Fed. Cir. 2012) (quoting *In re Kubin*, 561 F.3d at 1360) (internal quotation marks omitted).

of the secondary indicia with respect to every embodiment of the claims, he does have to provide adequate evidence that other, untested embodiments falling within the claims would behave in the same manner. *Id.*

Par offers evidence of several secondary considerations of non-obviousness: unexpected results, long-felt but unmet need, copying, and commercial success. None of them sufficiently undermine a finding of obviousness.

A. Unexpected results

Unexpected results must be established by factual evidence, and the evidence must demonstrate the claimed invention exhibits some superior property or advantage that would have been surprising to one skilled in the art. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Par claims that the reduced food effect associated with Megace ES and the increased weight gain exhibited by patients to whom it was administered were unexpected. Even if the court were to find the reduced food effect and increased weight gain unexpected,[20] however, TWi has provided clear and convincing evidence that there were motivations in the art other than fed-fasted variability and the need for increased weight gain to use nanotechnology with the existing method and that the technology's ability to reduce interpatient variability and viscosity were known. The fact that the use of nanotechnology may have surprisingly solved other problems as well does not undermine that finding. *See Allergan*, 726 F.3d at 1293 (finding unexpected results with respect to one property did not overcome the prima facie showing of obviousness where there were other issues providing motivation to combine prior art elements).

[20] Although not necessary to its findings, the court notes that the improvements do not appear to be more than what might be predicted given the known improvements in efficacy associated with nanotechnology. *See In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (holding that unexpected results require a difference in kind, not merely degree (citing *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996))).

B. Long-Felt Need

Evidence of a long-felt, but unmet, need is probative of non-obviousness where it demonstrates that a demand existed for the invention and that others had previously tried but failed to meet the demand. *In re Cyclobenzaprine*, 676 F.3d at 1082. Dr. Wanke provided testimony that, in her experience working with HIV/AIDS patients, a long-standing need existed for a more effective means of returning patients to their normal weight. (Tr. 4:2 at 47:5-49:9.) According to Par, the pilot study comparing Megace ES and Megace OS in HIV/AIDS patients demonstrates that the claimed invention met that longstanding need because participants in the study taking Megace ES experienced "significantly greater weight gain." (PTX 94 at 209, fig. 1, 215.) All but four of the asserted claims (Claims 2, 10, 21, 24) disclose a method of increasing body mass in human patients without regard to whether the weight loss is associated with HIV/AIDS. Evidence of a long-felt need for superior weight gain in HIV/AIDS patients, and the claimed invention's ability to meet that need, is thus not commensurate with these claims. Par has offered no evidence to support a conclusion that other embodiments falling within the non-HIV/AIDS specific claims would meet a long-felt, but unmet, need in populations other than those with HIV/AIDS.[21] *See MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264-65 (Fed. Cir. 2013); *In re Kao*, 639 F.3d at 1068.

With respect to the claims that are HIV/AIDS-specific, the proffered evidence is simply not sufficient to demonstrate that the claimed invention was in demand, i.e. that it met a long-felt need. Par claims the need was for a more effective means of returning patients to premorbid

[21] The parties' stipulation that Megace ES is an embodiment of the claims does not render Par's evidence of an unmet need with respect to the treatment of HIV/AIDS patients commensurate with the claims. The parties stipulated that Megace ES would "constitute *a* method claimed," not that it would constitute the only embodiment. (Stipulation Regarding Megace ES, ECF No. 174, ¶ 4(a) (emphasis added).)

weight. (*See* Pl.'s Brief at 36 (citing Tr. 4:2 at 47:14-49:9; PTX 143 at 565).) Yet, in the report of the study on which Par relies, researchers only conclude that "the use of the [Megace ES] formulation may be preferable to [Megace OS]." (PTX 94 at 215.) Although perhaps more effective, neither the study report nor Par provides evidence as to whether the superior efficacy of Megace ES was enough to meet the unmet need,[22] and the researchers' equivocal statement that it "may be" preferable is simply not enough to demonstrate that it was.

C. Copying

Par claims TWi's copying of Megace ES provides strong evidence of nonobviousness. Although copying often can provide evidence of nonobviousness, it cannot do so in this case. TWi was attempting to bring a generic version of Megace ES to market and copying in that context is not probative because FDA approval requires a showing of bioequivalence. *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *Purdue Pharma Products*, 377 F. App'x 978, 983 (Fed. Cir. 2010).[23]

D. Commercial Success

Commercial success can provide objective evidence of nonobviousness because "the law

[22] It should be noted that the court understands "significantly superior weight gain," as used in the study, to mean *statistically* significant superior weight gain. Par similarly claimed to understand it this way earlier in the litigation. (*See* Pl.'s Opp'n to Def.'s Mot., ECF No. 154, at 5.) The actual difference in mean weight gain between the two formulations was only ever, at most, two kilograms.

[23] Par claims the "ANDA exception" only applies when the FDA requires the filer to copy the invention. This is a misinterpretation of the Federal Circuit's holding. All ANDAs must demonstrate bioequivalence, either through a study or one of a limited number of alternatives. *See* 21 C.F.R. 320.20. The Federal Circuit held that, for that reason, copying is not compelling where it is in the context of an ANDA. *See Purdue Pharma Products L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 983 (Fed. Cir. 2010) ("[C]opying in the ANDA context is not probative of nonobviousness *because* a showing of bioequivalence is required for FDA approval." (emphasis added)); *see also Cephalon Inc. v. Mylan Pharm. Inc.*, -- F. Supp. 2d --, 2013 WL 3810858 at *26 (D. Del. 2013) (rejecting copying as valid evidence in the ANDA context without making a factual finding as to what the FDA required).

presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Commercial success is only significant, however, where there is a nexus between the novel aspects of the invention and the commercial success. *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013). The feature responsible for the commercial success must not have been known in the prior art. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006); *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Where the patentee shows commercial success with a product that is an embodiment of the invention, a court presumes the commercial success is due to the novelty of the invention. *J.T. Eaton*, 106 F.3d at 1571. The burden is then on the challenger to demonstrate otherwise. *Id.*

Although the parties have stipulated that Megace ES is an embodiment of the invention, the presumption that all of its commercial success was due to novel features cannot stand. Par's marketing documents demonstrate that in addition to selling Megace ES on the basis of its reduced food effect, Par touted the reduced volume and viscosity of the formulation. (*See, e.g.*, PTX 241 at PAR-MEG150891; PTX 249 at PAR-MEG382865; PTX 449 at PAR-MEG100199). In fact, reduced dose volume and reduced viscosity were two of the three "core messages" used to sell the drug. (Pl.'s Brief at 40-41.) Some portion of the claimed success, therefore, may be due to features that were not novel: it was known in the prior art that using nanoparticles would reduce dose volumes and viscosity. Commercial success founded on non-novel features does not provide persuasive evidence of nonobviousness. *See Ormco*, 463 F.3d at 1312 ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.").

Not only does the evidence suggest any success may stem from features of the drug other

than those that were novel, but Megace ES's market share and total sales figures do not provide evidence of commercial success sufficient to undermine a finding of obviousness. First, even assuming Par's expert, Dr. Vandaele, was correct that Megace ES held 19-23 percent of the market, (Tr. 5:1 at 53:21-22.) that leaves over 75 percent of the market still held by prior art products. In addition, 23 percent was the peak market share in 2007, two years after launch and after over $70 million was spent on marketing, (PTX 167 at 1), and it appears to have since declined to only 19 percent, (Tr. 5:1 at 62:6-12). In addition, the sales figures—$600 million in gross sales, $450 million in net sales, and over $100 million in aggregate operating profits, all over six years—and market share touted by Par must be discounted because, for the first four years the product was on the market, Par boosted its sales, at least to some degree,[24] by engaging in criminal conduct. (*See* Guilty Plea Transcript, DTX 247 at 15:13-16:1 (admitting that Par made false and/or misleading claims when it marketed Megace ES as having "superior clinical efficacy" over Megace OS despite lacking "adequate or sufficient data from well-controlled clinical trials" to support such claims).) After discounting sales and market share figures for Par's criminal conduct, and considering that some portion of sales may be due to the touting of non-novel features, the court does not find evidence of commercial success that persuasively undermines the claimed invention's obviousness.[25]

[24] It is somewhat difficult to assess what portion of sales or profits were due to Par's criminal conduct. In the plea agreement, Par and the Department of Justice agreed that Par received $11 million in pecuniary gain from its misbranded sales, (Plea Agreement, DTX 245, at 2), but Par ended up paying $45 or $46 million to settle the case, (Tr. 5:2 at 9:18-21).

[25] Par also claims that TWi's copying of Megace ES provides evidence of commercial success, but this argument is without merit. *See Galderma Labs, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) ("The mere fact that generic pharmaceutical companies seek approval to market a generic version of a drug, without more, is not evidence of commercial success that speaks to the non-obviousness of patent claims.")

CONCLUSION

For the foregoing reasons, the court finds that TWi has shown by clear and convincing evidence that the asserted claims of the ‘576 patent are invalid because they would have been obvious to a person of skill in the art at the time of invention. A separate Order follows.

February 21, 2014
Date

/s/
Catherine C. Blake
United States District Judge