UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A., Plaintiff, v. DR. REDDY'S LABORATORIES, LTD. et al., Defendants.	:	Civil Action No. 14-4274 (SRC) Civil Action No. 14-6341 (SRC) (Consolidated) **OPINION & ORDER**

CHESLER, U.S.D.J.

This matter comes before the Court on the motion for a preliminary injunction by Plaintiff Helsinn Healthcare S.A. ("Helsinn") against consolidated case Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd. (collectively, "Teva"). This Court held oral argument on this motion on January 22, 2018. For the reasons stated below, the motion will be denied.

BACKGROUND

This case arises from a patent infringement dispute involving a pharmaceutical treatment method patent. Helsinn owns U.S. Patent No. 8,729,094 (the "'094 patent") directed to, among other things, a method for reducing chemotherapy-induced nausea and vomiting using palonosetron, a compound which Helsinn markets under the brand name Aloxi®. Teva has submitted ANDA No. 090713, which seeks FDA approval to engage in the commercial manufacture and sale of generic palonosetron hydrochloride intravenous solutions prior to the expiration of the '094 patent.

The present dispute over the '094 patent is one piece of a larger group of cases involving

various palonosetron patents and various pharmaceutical companies. In brief, Judge Cooper of this Court, after conducting a trial in a subset of related cases, had issued a judgment that found a number of other palonosetron patents (but not the '094 patent) valid and infringed. Teva appealed this judgment and, on May 1, 2017, the Court of Appeals for the Federal Circuit reversed the judgment of infringement, finding the patent claims at issue to be invalid under the on-sale bar of 35 U.S.C. § 102. Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc., 855 F.3d 1356, 1375 (Fed. Cir. 2017). Helsinn then petitioned for rehearing *en banc*. In September of 2017, with the petition pending, Helsinn raised with this Court its concern that, should the Federal Circuit deny rehearing, Teva would immediately launch its generic palonosetron product. The parties agreed to complete briefing on the instant motion while the petition was pending, which they did. On January 16, 2018, the Federal Circuit denied the petition for rehearing and stated that the mandate would issue on January 23, subsequently amended to January 29. This Court then heard oral argument on the motion on January 22, 2018.

APPLICABLE LEGAL STANDARDS

I. Preliminary Injunction

"The grant of a preliminary injunction under 35 U.S.C. § 283 is within the discretion of the district court." Curtiss-Wright Flow Control Corp. v. Velan, Inc., 438 F.3d 1374, 1378 (Fed. Cir. 2006). "A plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." Winter v. NRDC, Inc., 129 S. Ct. 365, 374 (2008). The Supreme Court has held that injunctive relief is "an extraordinary remedy that may only be awarded upon a clear showing that

the plaintiff is entitled to such relief." Id. at 376.

As to the requirement that the movant establish that he is likely to succeed on the merits, the Federal Circuit has held:

> [T]he patentee seeking a preliminary injunction in a patent infringement suit must show that it will likely prove infringement, and that it will likely withstand challenges, if any, to the validity of the patent. In assessing whether the patentee is entitled to the injunction, the court views the matter in light of the burdens and presumptions that will inhere at trial. . . .

Titan Tire Corp. v. Case New Holland, Inc., 566 F.3d 1372, 1376 (Fed. Cir. 2009) (citation omitted). "An accused infringer can defeat a showing of likelihood of success on the merits by demonstrating a substantial question of validity or infringement." Trebro Mfg. v. FireFly Equip., LLC, 748 F.3d 1159, 1165 (Fed. Cir. 2014). "A preliminary injunction should not issue if an alleged infringer raises a substantial question regarding either infringement or validity, i.e., the alleged infringer asserts an infringement or invalidity defense that the patentee has not shown lacks substantial merit." AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1050 (Fed. Cir. 2010).

ANALYSIS

I. Plaintiff has not demonstrated that it is likely to succeed on the merits.

Helsinn moves for injunctive relief on the ground that Teva's generic product will infringe claim 4 of the '094 patent. Claim 4 depends on independent claim 1, and they state:

> 1. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof a pharmaceutical single-use, unit-dose formulation comprising a 5 mL sterile aqueous isotonic solution buffered at a pH of about 5.0.+-.0.5, said solution comprising: about 0.05 mg/mL palonosetron hydrochloride based on the weight of its free base; about 41.5 mg/mL mannitol; about 0.5 mg/mL EDTA; and a citrate buffer, wherein said formulation is stable at 24 months when stored at room temperature, and wherein said intravenous administration to said human occurs before the start of the cancer chemotherapy.

> 4. The method of claim 1, wherein said intravenous administration reduces the likelihood of delayed nausea and vomiting in said human.

Teva opposes the motion on the ground that, *inter alia*, Helsinn cannot show that it is likely to succeed on the merits because claim 4 is invalid under the pre-AIA on-sale bar. In support, Teva makes two arguments: 1) the Federal Circuit has already decided this issue, and Helsinn is precluded from relitigating it; and 2) there is overwhelming evidence that claim 4 is invalid under the on-sale bar.

In its decision in Helsinn, the Federal Circuit held, in short, that the claims at issue in the four other patents at issue in that litigation are invalid under the on-sale bar. Helsinn, 855 F.3d at 1360. On this motion, Helsinn distinguishes the issues litigated in the companion cases and resolved by the Federal Circuit on one ground only: "claim 4 of the '094 patent requires administering 0.25 mg palonosetron to reduce the likelihood of delayed CINV, as opposed to acute CINV or CINV generally."[1] (Pl.'s Br. 4.) Helsinn contends that, unlike the claims invalidated by the Federal Circuit, claim 4 of the '094 patent had not been reduced to practice before critical date of January 30, 2002, and it is therefore not invalid under the on-sale bar. On this motion, the issue of the validity of claim 4 turns on the question of whether claim 4 had been reduced to practice before the critical date.

In Helsinn, the Federal Circuit held:

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[1] Teva agrees that, for issue preclusion to apply, the Third Circuit requires, *inter alia*, that "the identical issue was previously adjudicated." Raytech Corp. v. White, 54 F.3d 187, 190 (3d Cir. 1995). Given that the Helsinn decision involved CINV generally and *not* delayed CINV, Teva has not persuaded this Court that the identical issue was previously adjudicated. Indeed, at oral argument, counsel for Teva stated that the subject matter of the patents before the Federal Circuit was the broader area of treatment of CINV generally, whereas the subject matter of the '094 patent is the narrower area of treatment of delayed CINV. On this basis alone, the identical issue was not previously adjudicated.

> An invention is reduced to practice when the inventor (1) constructed an embodiment . . . that met all the limitations and (2) determined that the invention would work for its intended purpose. Reduction to practice occurs if the claimant had possession of the subject matter of the [claim] and that it was shown or known to work for its intended purpose.
> . . .
> Generally there must be some demonstration of the workability or utility of the claimed invention. This must show that the invention works for its intended purpose beyond a probability of failure but not beyond a possibility of failure.

Helsinn, 855 F.3d at 1371-72 (citations omitted).

Helsinn does not dispute the basic facts of its transactions with another pharmaceutical company, MGI: prior to the critical date, the two companies entered into both a licensing agreement as well as a supply and purchase agreement, giving MGI the right to commercialize a palonosetron drug product. Helsinn also agrees that it conducted a phase 3 trial, called "PALO-99-03," which examined the safety and efficacy of 0.25 mg and 0.75 mg doses of palonosetron for the treatment of CINV. The data from the study was unblinded on January 2, 2002, and preliminary results were compiled by January 7, 2002. Helsinn contends, however, that, prior to the critical date of January 30, 2002, it did not know that 0.25 mg of palonosetron reduces the likelihood of delayed CINV:

> Thus, even though preliminary data numerically indicated that more patients receiving 0.25 mg palonosetron were free from emesis in the delayed phase than those receiving ondansetron (id. ¶ 49 (reporting, for example, 75.0%-86.6% confidence interval for 0.25 mg palonosetron and 58.6%-72.6% for ondansetron in the ">24-48 hour" time period)), it could not have been concluded from that data alone that palonosetron, as opposed to, for example, variations between the patient groups, caused this difference.

(Pl.'s Br. 16-17.)

In support of its assertion that, even after examining the preliminary results of PALO-99-03, it did not know whether 0.25 mg palonosetron reduced the likelihood of delayed

CINV, Helsinn points to the statements of Dr. Calderari, a named inventor on the '094 patent. (Calderari Dec. ¶¶ 37, 38.) Dr. Calderari states:

> 37. After reviewing the PALO-99-03 preliminary results in January 2002, I recall that neither I nor Helsinn's palonosetron project team members knew whether 0.25 mg palonosetron was reducing the likelihood of delayed CINV. Since ondansetron had not been shown to prevent delayed CINV, the project team did not know, at least in the January 2002 time period, whether this preliminary data alone could be interpreted as 0.25 mg palonosetron having some therapeutic effect in the delayed CINV phase. For example, the project team knew that a certain percentage of patients receiving chemotherapy would not experience emesis even if they received no antiemetic. I recall that we and our consultants also found it "puzzling" that patients receiving 0.75 mg palonosetron, a three-times higher dose, appeared to be experiencing more emesis than patients receiving 0.25 mg palonosetron in the preliminary results for PALO-99-03. (Ex. 43 at HELSN0119995.) Consistent with this view, in Helsinn's cover letter to the FDA attaching the PALO-99-03 preliminary results, only the "acute CINV" data was discussed, and the "Proposed Indication" was not yet modified to include "delayed CINV." (Ex. 7 at HELSN0379824-25.)

(Calderari Dec. ¶ 37.) Helsinn also contends that neither of the two phase 2 CINV studies demonstrated that 0.25 mg palonosetron was effective in controlling delayed CINV.

Helsinn also points to evidence of skepticism about the usefulness of 0.25 mg palonosetron to treat delayed CINV, contending that this demonstrates that the invention of claim 4 was not ready for patenting. This argument does not correctly apply Federal Circuit law. "This must show that the invention works for its intended purpose beyond a probability of failure but not beyond a possibility of failure." Helsinn, 855 F.3d at 1372. Applying this standard, the presence of skepticism – such as might accompany a belief in the possibility of failure – does not necessarily negate a finding of reduction to practice. Under Federal Circuit law, it is not skepticism that negates a finding of reduction to practice but a belief in the probability of failure.

Helsinn argues that the facts here are similar to those in In re Omeprazole Patent Litig. v. Apotex Corp., 536 F.3d 1361, 1375 (Fed. Cir. 2008), in which the Federal Circuit affirmed the

district court's finding that, in the absence of the completion of phase 3 trials, the invention had not been reduced to practice. Omeprazole, however, establishes no bright line rules, and, in the context of an appeal of a final judgment, applied a different legal test: the challenger to the patent's validity "bore the burden of demonstrating by clear and convincing evidence that the phase III formulation had been reduced to practice before the testing began." Id. at 1373. The Federal Circuit simply found no clear error in the district court's determination that the challenger had not proven reduction to practice by clear and convincing evidence.[2] The standard on this motion is different: Teva need not prove invalidity at this juncture by clear and convincing evidence. Instead, to defeat the motion for a preliminary injunction, Teva must raise a substantial question of validity that Helsinn does not show lacks substantial merit.

Teva argues that, even if the Federal Circuit's decision is not found to be preclusive, "[t]he same evidence considered by the Federal Circuit in invalidating the '219 patent shows that using palonosetron to treat delayed CINV was ready for patenting. . . before the critical date." (Defs.' Opp. Br. 20.)

Teva points to the following evidence in support of its contention that claim 4 was reduced to practice before the critical date: 1) the 2010 declaration submitted to the PTO (the "2010 Declaration"); 2) certain press releases; and 3) the phase 3 trial results available in January, 2002.

The 2010 Declaration is dated August 23, 2010 and signed by Sergio Cantoreggi, Enrico Braglia, and Riccardo Braglia. (Creasey Dec. Ex. 2 at DTX-0287-0479-482.) The Declaration

[2] Moreover, the Helsinn panel expressly distinguished Omeprazole: "this case is not like *Omeprazole*." Helsinn, 855 F.3d at 1375.

was filed as part of U.S. Patent Application No. 11/129,839. (Id. at DTX-0287-0479.) The Declaration states that it pertains to the invention of a claim directed to, in brief, "a method of treating chemotherapy or radiotherapy-induced acute and delayed emesis in an adult human for five days . . . comprising administering to said human a single dose of a treatment-effective amount of about 0.25 mg of palonosetron . . . without administering any further palonosetron during said five-day period." (Id. at ¶ 11, DTX-0287-0480.) The declarants aver that they had conceived the invention, conducted clinical trials to test it, and reduced it to practice "before November 16, 2001." (Id. at ¶¶ 2-3, DTX-0287-0479) (emphasis added). The Declaration clearly states that it applies to both acute and delayed CINV. (Id. at ¶¶ 14-17, DTX-0287-0481.)

In reply, Helsinn argues that Dr. Cantoreggi spoke Italian and "was mistaken in his understanding of the United States legal term 'reduced to practice.'"[3] (Pl.'s Reply Br. 7.) Helsinn offers no evidence to support the assertion that Dr. Cantoreggi did not understand what he was signing. Indeed, the formatting of the document itself suggests that it was drafted by an expert in patent prosecution in the USPTO. Helsinn also argues that "it was not possible for Helsinn to have known whether 0.25 mg palonosetron could treat delayed CINV before November 16, 2001." (Pl.'s Reply Br. 7.) In support, Helsinn points to the evidence already discussed, particularly the Carderari declaration. The Calderari declaration and the Cantoreggio declaration do indeed contradict each other on a number of key points.

Teva also points to two press releases issued by Helsinn. One press release, dated April

[3] It is worth noting that Helsinn, in its reply, does not dispute the meaning of the words that Dr. Cantoreggi signed his name to but, instead, suggests that he did not understand what he was signing. At oral argument, counsel for Helsinn admitted that Dr. Cantoreggi had been assisted by U.S. patent counsel.

10, 2001, announced the execution of the agreements with MGI and stated: "The extended half-life of palonosetron as compared to the other agents and the results of phase 2 trials assessing efficacy beyond 24 hours differentiates palonosetron from the three currently marketed 5-HT_3 antagonists indicated for CINV." (Creasey Dec. Ex. 6 at 1-2.) A second press release, dated January 16, 2002, announced that patient treatment in the phase 3 clinical trial program had been completed and data analysis was underway. (Creasey Dec. Ex. 3.) Describing the phase 3 trial, the press release stated:

> Based on the extended half-life of Palonosetron and the results of a Phase 2 trial, the efficacy of Palonosetron in the Phase 3 trial is being assessed over Day 2 through Day 5 following treatment . . .
>
> "The half-life of other available 5-HT(3) receptor antagonists ranges from approximately five to nine hours, whereas Palonosetron has a plasma elimination half-life of nearly 40 hours," notes Dr. John MacDonald, senior vice president of Research and Development at MGI. "The activity seen with Palonosetron in the Phase 2 trial, coupled with its safety profile observed to date, led to the initiation of a Phase 3 program to assess the ability of the drug to provide prolonged protection against CINV with a single dose."

(Id.) The press release statements support the the inference that, even before the phase 3 trial was begun, the inventors had obtained evidence from the phase 2 trial that encouraged them to further investigate palonosetron's efficacy for treating delayed CINV.

In reply, Helsinn points to this statement by Teva's own expert, Dr. Fruehauf: "It is also not disputed that Helsinn's phase II studies were not specifically designed to assess efficacy for delayed CINV." (Fruehauf Dec. ¶ 74 n.9.) This point confuses the time frame of interest: even if the inventors had no idea that palonosetron would reduce delayed CINV *before* the phase 2 trials, at issue here is what they knew *after* the phase 2 trials, not before.

Teva also points to the preliminary phase 3 data in Helsinn's possession prior to the

critical date, which showed that 74.1% of patients treated with palonosetron 0.25 mg showed a response during the entire delayed-onset period. (Creasey Dec. Ex. 8 at DTX-0264-0009.) Teva contends that these results demonstrated that the invention works for its intended purpose beyond a probability of failure. The parties dispute what inferences a skilled artisan could have reasonably made from the preliminary data. Teva's expert opined that a skilled artisan would have been able to examine the preliminary data "and conclude that palonosetron was effective at treating delayed emesis." (Fruehauf Dec. ¶ 69.) Helsinn's expert disagreed.[4] (Saab Reply Dec. ¶ 25.) This disputed point seems likely to be resolved by a battle of the experts at trial.

It appears probable to this Court that Helsinn's success on the merits of this invalidity challenge will turn on the determination of the date on which the inventors knew that "the invention works for its intended purpose beyond a probability of failure but not beyond a possibility of failure." Helsinn, 855 F.3d at 1372. At this point, this Court need not conclusively determine whether, before the critical date, the inventors knew that the invention worked to treat

[4] The Court notes, however, that Dr. Saab's reasoning is not persuasive. Dr. Saab asserts: "Because up to 70% of patients receiving moderately emetogenic chemotherapy will not get emesis even if they are not given any antiemetic, probability-wise, it is possible that none of those patients needed 0.25 mg palonosetron to avoid emesis." (Saab Reply Dec. ¶ 25 n.60.) The preliminary phase 3 data showed that, in the 24-120 hour period overall, 74.1% of patients in the palonosetron .25 mg group were emesis-free, and that, for days 2-5 individually, the percentage of emesis-free patients ranged from 81.5% to 92.6%. (Creasey Dec. Ex. 8 at DTX-0264-0009.) It is difficult to credit the assertion that, given a difference of 10-20% between the treatment group and what would be expected from a control group, a skilled artisan would not have suspected that palonosetron .25 mg worked to treat delayed CINV beyond a probability of failure. Moreover, at several points during oral argument, Helsinn's counsel characterized the ocansetron 32 mg treatment group as a "placebo." If Helsinn's counsel is correct, a skilled artisan might have compared the Day 2-5 palonosetron .25 mg emesis-free percentage (74.1%) to the Day 2-5 ocansetron 32 mg emesis-free percentage (55.1%) and inferred that the preliminary phase 3 results showed that palonosetron .25 mg had demonstrated that it works for its intended purpose beyond a probability of failure.

delayed CINV beyond a probability of failure but not beyond a possibility of failure. At this juncture, this Court need only determine whether Teva has raised a substantial question about this issue, which Helsinn has not shown lacks substantial merit. This Court finds that Teva has done so: the record before this Court contains several pieces of evidence which, considered together, support a substantial challenge to the validity of the '094 patent under the on-sale bar.

The most significant piece of evidence is the Cantoreggi declaration. It is clear that the Cantoreggi declaration, signed not only by Dr. Cantoreggi but also by Messrs. Braglia, both of whom were principals at Helsinn at various points, is an admission by a party to this case: the signers were serving as official representatives of Helsinn in its dealings with the PTO. It is clear that the Cantoreggi declaration was submitted to the PTO as a calculated decision by Helsinn and had been given careful thought. Under these circumstances, it is wholly appropriate for the Court to consider the admission, which expressly includes the subject matter of the '094 patent,[5] as being probative on the issue of reduction to practice.

Were the Cantoreggi declaration the only evidence showing reduction to practice before the critical date, this Court might hesitate to conclude that Teva has raised a substantial question of validity, but there is additional supporting evidence. The two cited press releases support finding a reduction to practice. Also, the fact that Helsinn designed and executed a phase 3 study in which treatment of delayed CINV was a target of study (even if of secondary importance) shows that Helsinn had a basis for believing that palonosetron would work for the treatment of delayed CINV. As the parties both stated at oral argument, phase 3 studies are

[5] The Cantoreggi declaration states that "we submit this declaration to establish that [the inventors] had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV." (Creasey Dec. Ex. 2 at DTX-0287-0479.)

expensive and are not undertaken lightly. Lastly, although the experts disagreed about what the preliminary phase 3 results, obtained before the critical date, demonstrated, on this record, this Court is persuaded that the preliminary phase 3 results, at a minimum, strongly suggest that palonosetron .25 mg works for its intended purpose (treatment of delayed CINV) beyond a probability of failure. This Court finds that the evidence, at this juncture, provides substantial support for a finding that, prior to the critical date, the inventors knew that the invention worked for its intended purpose beyond a probability of failure but not beyond a possibility of failure. Teva has succeeded in raising a substantial question of the validity of claim 4 of the '094 patent, and Helsinn has not shown that it lacks substantial merit.

The Federal Circuit has held:

> As this court explained in *New England Braiding Co. v. A.W. Chesterton Co.*, the trial court "does not resolve the validity question, but rather must . . . make an assessment of the persuasiveness of the challenger's evidence, recognizing that it is doing so without all evidence that may come out at trial." 970 F.2d 878, 882-83 (Fed. Cir. 1992). Instead of the alleged infringer having to persuade the trial court that the patent is invalid, at this stage it is the patentee, the movant, who must persuade the court that, despite the challenge presented to validity, the patentee nevertheless is likely to succeed at trial on the validity issue.

Titan Tire, 566 F.3d at 1377.

Because Teva has succeeded in raising a substantial question of the validity of claim 4 of the '094 patent, and Helsinn has not shown that it lacks substantial merit, Helsinn has failed to show that it will likely withstand this challenge to the validity of the '094 patent. Helsinn has thus failed to demonstrate a likelihood of success on the merits. Under Federal Circuit law, "[a] preliminary injunction should not issue if the accused infringer raises a substantial question concerning either infringement or validity." Metalcraft of Mayville, Inc. v. Toro Co., 848 F.3d 1358, 1364 (Fed. Cir. 2017). Helsinn's application for a preliminary injunction will be denied.

For these reasons,

IT IS on this 30th day of January, 2018 hereby

ORDERED that Plaintiff's motion for a preliminary injunction (Docket Entry No. 52) is **DENIED**.

s/ Stanley R. Chesler
Stanley R. Chesler, U.S.D.J.