

NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

NOVARTIS PHARMACEUTICALS
CORPORATION, NOVARTIS PHARMA
AG, and NOVARTIS INTERNATIONAL
PHARMACEUTICAL LTD.,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA,
INC.,

Defendant.

Hon. Dennis M. Cavanaugh

OPINION

Civil Action No. 05-CV-1887 (DMC)

DENNIS M. CAVANAUGH, U.S.D.J.:

This matter comes before the Court upon motion by Plaintiffs Novartis Pharmaceuticals Corp., Novartis Pharma AG and Novartis International Pharmaceutical Ltd (“Novartis”) for a preliminary injunction. Oral argument was heard on September 5, 2007. After carefully considering the submissions of the parties, and based upon the following, it is the finding of this Court that the preliminary injunction is **denied**.

I. BACKGROUND

Defendant Teva Pharmaceuticals USA, Inc. (“Teva”) was prepared to launch its generic famciclovir product on August 24, 2007 - the day the 30-month F.D.A. stay of approval expired. The release of Teva’s generic famciclovir product would infringe on Novartis’s U.S. Patent No. 5,246,937 (“the ‘937 patent”). The ‘937 patent is set to expire in September, 2010. Plaintiffs move for a preliminary injunction in order to prevent the launch of Teva’s generic product.

Teva submitted to the FDA an abbreviated new drug application (“ANDA”) pursuant to 21 U.S.C. § 355(j) seeking approval to manufacture, use and sell a generic version of famciclovir tablets. In its ANDA, Teva stated that the ‘937 patent is invalid and/or unenforceable. Subsequently, Plaintiff initiated the instant suit to obtain a permanent injunction restraining and enjoining Teva from engaging in the commercial manufacture, use or sale of famciclovir.

A. Parties

Novartis has sold Famvir® as an oral antiviral drug since 2001, generating over \$913 million in sales revenue in the United States. Famvir® is among the top five percent of prescription drugs in the U.S. market. (Lemieux Decl. ¶9.) The F.D.A. has approved Famvir® for the treatments of (1) acute herpes zoster (shingles); (2) genital herpes; (3) herpes labialis (cold sores); and (4) herpes simplex in HIV-infected patients. (Cudnik Decl., Ex. 2.) The Beecham scientists were the ‘937 patent inventors who created famciclovir - a key compound in Famvir®.

Teva produces several generic versions of patented drugs. Teva has developed a generic version of famciclovir, designed to offer the same treatment as Famvir®.

B. Structure of Famciclovir

Famciclovir is a “prodrug.” Prodrugs are pharmaceutical compounds that do not have the desired activity (in this case, antiviral effects), but are converted into the active compound when inside the body. The purpose of a prodrug is to increase the amount of active compound in the bloodstream after oral administration. This is also known as increasing the “absorption” or “bioavailability” of the active compound. (Broom Decl. ¶¶6, 58.)

Penciclovir is the active compound in famciclovir. Penciclovir is a member of the acyclic nucleosides group of compounds. Since the late 1970s, these compounds have been recognized as potential anti-mitotic or anti-viral agents. During that time period, Burroughs Wellcome scientists developed acyclovir, a synthetic acyclic nucleoside, that demonstrated selective inhibition of the herpes virus in humans. After that discovery, several medicinal chemists were motivated to work with acyclic nucleosides to further the antiviral properties of acyclovir. Several compounds resulted from this work, including ganciclovir (DHPG), FHBG, HBG, carba-iNDG and penciclovir.

C. Prior Art

Following the Burroughs Wellcome scientists' discovery of acyclovir, several scientists performed work and published articles regarding the effectiveness of acyclic nucleosides as antiviral agents. Several prior art references described penciclovir as an effective anti-viral agent, particularly useful for the treatment of infections caused by herpes. Teva contends that these prior art references, as a whole, made the development of famciclovir "obvious." These references included: (1) Greek Patent Application No. GR 80121 ("Greek '121 Application"), developed by the Beecham scientists that also developed famciclovir; (2) Astra's U.S. Patent No. 4,978,833 ("the '833 patent"); (3) Merck & Co.'s U.S. Patent. No. 4,845,084 ("the '084 patent"); and (4) an article published by Syntex Research (the "Tippie article"). However, in comparing the antiviral activity of penciclovir and ganciclovir, the Tippie article indicated that test results had shown penciclovir to be less active than ganciclovir. Several prior art references considered the toxicity of penciclovir: (1) the Greek '121 Application found that penciclovir was non-toxic in various cell cultures; (2) the '833 patent referenced tests that showed low toxicity of

penciclovir; and (3) the Tippie article noted that there may be problems with toxicity of penciclovir in humans. In addition, British patent application No. GB 2130204 (“GB ‘204 patent”) was another prior art reference. In this patent application, Burroughs Wellcome described making prodrugs of other acyclic nucleosides - acyclovir and ganciclovir.

D. Development of Famciclovir

Based on the prior art, the Beecham scientists knew (1) that penciclovir belonged to a group of compounds that had proven to be effective antiviral agents; (2) there might be toxicity problems with penciclovir; and (3) the group of compounds that penciclovir belonged to were generally poorly absorbed when dosed orally. Based on this prior art, several other pharmaceutical companies - Astra, Merck and Syntex - also researched penciclovir. Ultimately, the other pharmaceutical companies abandoned their research efforts with penciclovir. The Beecham scientists continued their work and succeeded in developing famciclovir.

Recognizing the absorption and bioavailability problems with penciclovir, the Beecham scientists developed a prodrug using penciclovir. At that time, making a prodrug was not new technology. In fact, the GB ‘204 patent described making prodrugs of other acyclic nucleosides - acyclovir and ganciclovir. Specifically, the GB ‘204 patent taught that the use of esters improves the bioavailability of a wide variety of compounds, including nucleosides. Throughout the Beecham scientists’ reports, there are several references to the Burroughs Wellcome’s GB ‘204 patent.

The Beecham scientists employed various approaches to create famciclovir. (Pl. Br. at 10-13.) Initially, the Beecham scientists had poor results with their work on esters of penciclovir.

Through trial and error, however, the Beecham scientists ultimately synthesized several esters of penciclovir, finding that famciclovir proved to be more stable in the digestive system and would not be degraded prior to absorption. Famciclovir subsequently underwent preclinical and clinical testing.

Plaintiffs claim that the success of famciclovir was surprising and unexpected because the drug is metabolized in an effective manner to ensure that the production of penciclovir (the active compound) is maximized. Additionally, Plaintiffs claim that famciclovir had unexpected advantages over other acyclic nucleosides with respect to dosing and treating latent herpes virus in animal studies.

E. Patent Application Process

The '937 patent, issued on September 21, 1993, is the basic patent covering famciclovir, pharmaceutical compositions containing famciclovir and methods for treating viral infections, including herpes, with famciclovir. The '937 patent describes the compounds that are subject to the '937 invention and teaches how they have antiviral activity against herpes viruses.

Additionally, the '937 patent contains biological data showing the high oral absorption of famciclovir. The '937 patent claims specific to famciclovir - Claims 9, 14 and 15 through 19 - are the only claims at issue for purposes of this preliminary injunction motion.

The patent application and prosecution process for '937 was lengthy. Over the course of eight years, the U.S. Patent and Trademark Office ("PTO") rejected the '937 patent claims as obvious in light of GB '204 on eight separate occasions. (Koval Decl. Ex. 7.) Teva contends that the PTO ultimately approved the '937 patent because the applicants made a number of

misleading statements regarding the teaching of the “prior art as a whole.” (Koval Decl. Ex. 7 at Teva-fam005536, Teva-fam005589, Teva-fam005603, Teva-fam005614.) Throughout the prosecution, the ‘937 applicants repeatedly stated that the prior art as a whole taught away from the steps taken by the Beecham scientists. Additionally, certain prior art references were withheld and the applicants did not cite to allegedly relevant portions of references that were disclosed. Finally, throughout the patent prosecution, the applicants argued that the success of famciclovir was “unexpected” based on the prior art.

F. ISSUES PRESENTED

The two core issues on this motion are whether (1) the ‘937 patent is obvious; and (2) the ‘937 patent is enforceable. To determine whether the ‘937 patent is obvious, this court must determine whether the prior art taught that penciclovir was an obvious lead compound and whether it was obvious to create a prodrug of penciclovir. To determine the enforceability of the ‘937 patent, the court must assess whether the patent applicants engaged in inequitable conduct by stating that the “prior art as a whole” taught away from the approaches employed by the Beecham scientists and whether the withholding of particular prior art references was done to intentionally deceive the PTO.

II. STANDARD OF REVIEW

Federal Circuit law governs the standard for granting an application for a preliminary injunction of patent infringement. See Hybridtech, Inc. v. Abbott Labs., 849 F.2d 1446, 1451 n.12 (Fed. Cir. 1988). In determining whether to grant Plaintiffs’ requested injunctive relief, this Court must consider four factors: (1) Plaintiffs’ reasonable probability of success on the merits;

(2) irreparable harm; (3) the balance of hardships; and (4) the public interest. See Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 237 F.3d 1359, 1363 (Fed. Cir. 2001); Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1374 (Fed. Cir. 2006). “The court must balance these four factors, as their relative weight warrant, in service to the interest of justice.” Monsanto Co. v. McFarling, 302 F.3d 1291, 1297 (Fed. Cir. 2002). A preliminary injunction is a “drastic remedy that is not to be routinely granted.” Intel Corp. v. ULSI Sys. Tech., Inc., 995 F.2d 1566, 1568 (Fed Cir. 1993). Thus, to prevail on its application for a preliminary injunction, Plaintiffs must make a “clear” showing of likely success on the merits and irreparable harm. See Nutrition 21 v. U.S., 930 F.2d 867, 869-70 (Fed. Cir. 1991).

III. REASONABLE PROBABILITY OF SUCCESS ON THE MERITS

To succeed on its application for a preliminary injunction, Plaintiffs must show a reasonable likelihood of success on the merits, as determined in the context of the presumptions and burdens that would inhere at trial. See H.H. Robertson Co. v. United Steel Deck, Inc., 820 F.2d 384, 388-90 (Fed. Cir. 1987). Plaintiffs must show that the ‘937 patent is both valid and enforceable. Although Teva has the ultimate burden of proving invalidity and enforceability at trial, “at the preliminary injunction stage, because of the extraordinary nature of the relief, the *patentee* carries the burden of showing likelihood of success on the merits with respect to the patent’s validity.” Nutrition 21, 930 F.2d at 869 (emphasis in original).

_____ Every patent is presumed valid and enforceable, and this presumption exists at every stage of the litigation. See 35 U.S.C. § 282; Sanofi, 470 F.3d at 1375 (citing Canon Computer Sys., Inc. v. Nu-Kote Int’l Inc., 134 F.3d 1085, 1088 (Fed. Cir. 1998)). Thus, at trial, and for

consideration of Plaintiffs' preliminary injunction application, Defendant must overcome the presumption that Plaintiffs' '937 patent is valid and enforceable. Additionally, Defendant bears the burden of proof on the obviousness and inequitable conduct issues by clear and convincing evidence. See Oney v. Ratliff, 182 F.3d 893, 895 (Fed. Cir. 1999); Am. Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1358-60 (Fed. Cir. 1984). In the preliminary injunction context, Defendant bears the initial burden of producing evidence that raises a "'substantial question' concerning validity, [or] enforceability." Purdue, 237 F.3d at 1363. If Defendant satisfies this burden, then Plaintiffs must produce countervailing evidence demonstrating "that these defenses 'lack substantial merit.'" Id.; Sanofi, 470 F.3d at 1374.

A. Validity of '937 Patent: Obviousness Argument

Defendant argues that the '937 patent is invalid on obviousness grounds, claiming that the prior art taught how to make the claimed compound famciclovir and described the biological properties one could reasonably expect famciclovir to possess. To prevail on its obviousness argument, Defendant must demonstrate by clear and convincing evidence that:

the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

35 U.S.C. § 103(a). Obviousness is a question of law, Panduit Corp. v. Dennison Manufacturing Co., 810 F.2d 1561, 1566-67 (Fed Cir. 1987), based on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) the objective evidence, or "objective indicia," of nonobviousness. See Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18

(1966). Additionally, this court must also consider “objective indicia” of nonobviousness such as unexpected properties and commercial success. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 667 (Fed Cir. 2000). In chemical cases, such as this one, proper evaluation of an obviousness argument requires the court to look at the claimed invention as a “whole,” which includes a compound and all of its properties. See Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1448 (Fed Cir. 1984) (citing 35 U.S.C. § 103); In re Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963).

Recently, in KSR International Co. v. Teleflex Inc., the Supreme Court cautioned against (1) a rigid application of the teaching, suggestion and motivation (“TSM”) test, and (2) a rigid application of using an “obvious to try” analysis when there is pressure to solve a problem with “a finite number of identified, predictable solutions.” 127 S. Ct. 1727, 741-42 (2007). Instead, the Court advocated a “common sense” approach to determining obviousness. See id. at 1741-43. Specifically, the Court explained that “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining elements in the manner claimed.” Id. at 1742. The Court reasoned that, “if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” Id. at 1740. Even in light of the approach advocated by

KSR, this court is cautious in not using hindsight when considering Defendant's obviousness argument. Thus,

[i]n conducting an obviousness analysis, [a] factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.' This is because the genius of invention is often a combination of known elements that in hindsight seems preordained.

In re Omeprazole Patent Litig., No. MDL 1291, 2007 U.S. Dist. LEXIS 39670, at *400-01 (S.D.N.Y. May 31, 2007) (citation omitted) (quoting KSR, 127 S.Ct at 1742); see also Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138 (Fed. Cir. 1985).

Plaintiffs argue that KSR has limited applicability to this case because KSR involved mechanical arts. In Takeda Chemical Industries, Ltd v. AlphapharmPty., Ltd., however, the Federal Circuit discussed the effect of KSR on the TSM test in chemical compound cases. See No. 06-1329, 2007 WL 1839698, at *5 (Fed. Cir. Jun. 28, 2007). First, Takeda Chemical reaffirmed the test for *prima facie* obviousness of structurally similar compounds:

structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case for obviousness. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for a change in structure.

Id. at *4 (citing In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990)); In re Grabniak, 769 F.2d 729, 731-32 (Fed. Cir. 1985); In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995)). Next, the Federal Circuit noted that the "KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry" but found that "[a]s long as the test is not applied as a 'rigid and mandatory' formula, that test can provide 'helpful insight' to an

obviousness inquiry.” Id. at *5 (citing KSR, 127 S.Ct. at 1731). Finally, the Federal Circuit concluded that “in cases involving new chemical compounds,” like the instant case, “it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.” Id.

1. Prior Art: Penciclovir Was an Obvious Lead Compound

Plaintiffs argue that they have a strong likelihood of success on the merits because Defendant cannot prove that penciclovir was an obvious lead compound. Instead, Plaintiffs claim that penciclovir was one of many other acyclic nucleoside and non-nucleoside compounds that the prior art taught had some degree of promise as an antiviral agent. (Bartlett Decl., ¶¶64, 114, 118.) Additionally, Plaintiff argues that Defendant’s obviousness argument fails because it ignores the fact that the Beecham researchers were unsuccessful when they started with other lead compounds. (Jarvest Decl., ¶¶5-7.) Finally, Plaintiffs contend that one of the prior art articles - the Tippie article - suggested that penciclovir would not be the most effective lead compound and that it had possible toxicity problems. Plaintiffs further argue that more weight should be given to the Tippie article than all the other prior art references because it focused on only two compounds - ganciclovir and penciclovir - unlike the other prior art available in 1983 that focused on hundreds of other compounds.

In support of these positions, Plaintiffs rely heavily upon Takeda Chemical. In Takeda Chemical, the Federal Circuit found that where there were many potential lead compounds, the selection of one particular compound was not an obvious choice. See 2007 WL 1839698 at **7-8. In Takeda Chemical, the court stated that it should look at the “prior art as a whole” to

determine whether a person of ordinary skill in the art would select a compound as a lead. See id. at *6. The Federal Circuit considered whether the given compound was the most promising or whether it might have toxicity problems. See id. at **5-6.

Defendant agrees that the court should look at the prior art “as a whole,” and that the prior art instructs that penciclovir was an obvious choice for a lead compound. First, penciclovir was one of only five known acyclic nucleosides to have strong activity and low toxicity. In fact, four pharmaceutical companies, including Beecham, published their work with penciclovir and described its impressive properties. (Broom Decl. ¶¶30-51; Smee Rpt. ¶¶10, 27, 45.) Thus, selecting penciclovir was a matter of “ordinary skill and common sense.” KSR, 127 S.Ct at 1742.

This court finds Takeda Chemical factually distinguishable from the current case. In Takeda Chemical, the prior art disclosed “hundreds of millions” of potential compounds. See 2007 WL 1839698 at *5. Here, penciclovir was one of only a few compounds that would act as an effective lead compound. In its Reply Brief, Plaintiffs rebut this argument, stating that in 1985, the time the invention was made, there were many promising compounds, some of which were still being tested. (Suppl. Bartlett Decl. ¶3.) While this information is relevant, it fails to provide clear factual grounds upon which to conclude that this case is similar to the facts in Takeda Chemical. Furthermore, Plaintiffs failed to set forth any proof that the prior art revealed “hundreds of millions” of compounds from which the Beecham group might have selected a lead compound.

Additionally, Beecham's several failures with other lead compounds has no bearing on the obviousness issue. In KSR, the Supreme Court held that it would be obvious for one of ordinary skill to pursue a number of different options:

When 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 has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

127 S.Ct at 1742. In this case, the "prior art as a whole" would have motivated Beecham to pursue penciclovir as one of the "known options" within their "technical grasp." Specifically, a person of ordinary skill would have pursued working with acyclic guanine nucleosides like penciclovir - not other classes of compounds - because they had been proven very effective antiviral agents.

Finally, the Tippie article did teach away from penciclovir, but the "prior art as a whole" did not teach away from using penciclovir as a lead compound. Several other patents and patent applications taught that penciclovir was a potent antiviral agent. Additionally, one skilled in the art would have known that test results can vary. Moreover, Plaintiffs' position that the Tippie article is more persuasive or should be afforded more weight than the other art references is unsupported by any case law. Thus, it is evident that the prior art produced some conflicting results about the effectiveness and toxicity of penciclovir. The Tippie article should be weighed equally with the other prior art references. There are far greater references teaching that penciclovir would act as a powerful antiviral agent. Thus, the "prior art as a whole" did not "teach away" from using penciclovir as a lead compound.

2. Prior Art: Obviousness of Making an “Oral Version” of Penciclovir

Plaintiffs argue that they have a strong likelihood of success on the merits because Defendant cannot prove that the prior art indicated that penciclovir was poorly absorbed and that an oral version would be necessary. Plaintiffs claim that the prior art indicated that acyclic nucleosides generally do not absorb particularly well. (Bartlett Decl., ¶¶119-120.) Plaintiffs characterize Defendant’s reasoning as “hindsight” reasoning because the prior art would not have motivated one skilled in the art to choose penciclovir as a lead compound and to modify it into a prodrug.

Defendant relied heavily on the teachings of the GB ‘204 patent, which instructed how to improve the oral bioavailability of antiviral compounds that were almost identical to penciclovir. (Broom Decl. ¶¶61-64; Smee Rpt ¶¶34, 36, 41-42.) A person of ordinary skill in the art would have expected penciclovir to share the poor oral bioavailability of other acyclic nucleosides. As such, the GB ‘204 patent would have been one of the first resources that someone skilled in the art would have consulted because that patent instructs on how to improve the bioavailability of compounds similar to penciclovir. In fact, Beecham’s own documents demonstrate that Beecham copied the Burroughs Wellcome work shortly after it was published. (Koval Decl. Exs. 9-10.) A skilled artisan would have been motivated to combine the teachings of GB ‘204 regarding bioavailability and other prior art such that it was obvious to use penciclovir as a lead compound and to modify it into a prodrug. Further, Plaintiffs’ evidence indicates that the Beecham group was motivated to pursue that exact course. _____

3. Prior Art: It Was Obvious to Modify Penciclovir to Create the Prodrug Famciclovir

Plaintiffs set forth seven arguments explaining why it was not obvious to modify penciclovir to create the prodrug famciclovir. As set forth below, the bulk of these arguments are not persuasive and do not rebut Teva's arguments regarding obviousness.

First, Plaintiffs argue that there are "numerous possible substitutions" that could have been made at the 2-position and 6-position and "many different ester functions," and thus, the development of famciclovir was not obvious. In response, Teva contends that the existence of other possible substitutions has no relevance to the obviousness inquiry. As set forth in KSR, a skilled artisan need only have a reasonable expectation of success based on the prior art. See 127 S.Ct at 1741-42. Here, the 6-deoxy modification had proven to be several times more effective than any other substitutions. Thus, the 6-deoxy would have been one of the first options explored by one skilled in the art.

Second, Plaintiffs argue that it was "unknown" whether the modifications made to acyclovir, as described in GB '204, creating an effective prodrug, would have a similar effect on penciclovir. Teva argues that the obviousness inquiry does not ask whether a result is "unknown," but rather where there is a reasonable probability of success. Plaintiffs cannot rebut a defense of obviousness by "showing some degree of unpredictability in the art so long as there was a reasonable probability of success." Pfizer, Inc., 480 F.3d at 1364; see also In re O'Farrell, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

Third, Plaintiffs argue that the development of famciclovir was not obvious because the 6-deoxy acyclovir and 6-deoxy penciclovir "turned out to behave quite differently in the body."

(Pl. Br. at 25.) Defendant contends that this argument is “misleading and irrelevant.” (Def. Opp’n Br. at 26-27.) First, the result achieved by making the 6-deoxy modification is the same in both compounds: the prodrug is converted into the active compound by the body’s enzymes. Second, it does not matter that it was determined years after the relevant time period that a different enzyme was responsible for the conversion of 6-deoxy penciclovir. The prior art provided clear motivation to make the 6-deoxy modification.

Fourth, Plaintiffs argue that the development of famciclovir was not obvious because the prior art as a whole taught away from using ester functions on penciclovir. (Bartlett Decl. ¶¶128-133.) Specifically, Plaintiffs contend that the GB ‘204 did not provide any data on esters of the acyclic nucleosides. Defendant contends that the use of acetyl esters to enhance oral bioavailability of nucleosides is “ancient technology” that was exemplified in several prior art references, including GB ‘204. (Broom Decl. ¶¶72-74.) Defendant cites Plaintiffs’ own expert in support of this point: esterification is “one strategy that medicinal chemists may explore” and “had been applied in the field of nucleoside derivatives.” (Bartlett Decl. ¶128.) Additionally, Defendant contends that Plaintiffs’ argument that GB ‘204 does not provide data specifically for esters (as opposed to the 6-deoxy) is meritless because prior art teaching need not be that clearly articulated in terms of specific biologic data. This court agrees with Defendant that a skilled artisan would know that enhancing absorption was the only purpose for the ester modification described in GB ‘204.

Fifth, Plaintiffs argue that there were many different ester functions the Beecham inventors could have tried, and thus, Defendant’s obviousness argument is impermissibly based

on hindsight. While Defendant does not directly respond to this point, it is irrelevant to the obviousness inquiry because a skilled artisan would have a reasonable expectation of success with the acetate ester selected by Beecham.

Sixth, Plaintiffs argue that the development of famciclovir was not obvious because the “synergy” achieved by using the 6-deoxy and ester modifications with penciclovir was “wholly unexpected.” As Defendant noted, this argument is factually incorrect because GB ‘204 already described the 6-deoxy and acetyl ester modifications being used together on acyclic nucleosides to improve oral bioavailability.

Seventh, Plaintiffs argue that the development of famciclovir was not obvious because it had “unexpected” advantages over acyclovir and its prodrug, such as a convenient dosing schedule and superiority in treating latent herpes virus infections. (Bartlett Decl., ¶¶140-142, Exs. 26-31.) Plaintiffs note that Burroughs Wellcome’s work on a prodrug for acyclovir, as reflected in the GB ‘204 patent, was unsuccessful. Therefore, Plaintiffs claim that their success with famciclovir was particularly unexpected. If such findings were, in fact, unexpected, this court should consider it as objective indicia of nonobviousness. See Ruiz, 234 F.3d at 667. These findings, however, were expected: (1) based on the prior art, especially the success of ganciclovir, such results had previously been produced and were thereby not unexpected; (2) Novartis’ studies regarding “dosing advantage” are not persuasive because it does not do a head-to-head comparison of the various treatments (Broom Decl. ¶¶81-82; Smee Reply ¶¶9-10; Coen Reply, 5-6); (3) there is no evidence supporting a latency advantage for famciclovir over other drugs; and (4) these advantages are related to the invention because they are not benefits

achieved through modifications made to obtain famciclovir, but instead flow from the inherent properties of penciclovir (Broom Decl. ¶79; Smee Reply ¶¶4-6; Coen Reply p. 5).

B. Unenforceability of the '937 Patent: Inequitable Conduct

_____ Plaintiffs contend that they have a strong likelihood of success on the merits because Defendant cannot establish that the patent is unenforceable due to Plaintiffs' alleged inequitable conduct during the prosecution of the '937 patent. Patent applicants and other individuals substantively involved in the patent prosecution are held to the highest standards of honesty and candor. See 27 C.F.R. § 1.56(a) (2007); Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995); Norton v. Curtiss, 433 F.2d 779, 794 (C.C.P.A. 1970). Breach of the duty of candor and good faith during the patent application process can render a patent unenforceable. See Molins, 48 F.3d at 1178.

Defendant has offered ample evidence that the '937 patent is invalid on obviousness grounds. To prove inequitable conduct, Defendant must show by clear and convincing evidence (1) that the patent application omitted material information or misrepresented material facts; and (2) that the applicant did so with the intention of misleading or deceiving the patent examiner. See Monsanto Co. v. Bayer Bioscience N.V., 363 F.3d 1235, 1239 (Fed. Cir. 2004); Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1362-63 (Fed. Cir. 2003). For the first prong, information is considered material if there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the patent. See Digital Control Inc. v. Charles Mach. Works, 437 F.3d 1309, 1314-16 (Fed. Cir. 2006); Dayco Prods., 329 F.3d at 1363. The Federal Circuit has explained that the issue of "materiality" does not

center on whether the withheld information would have rendered the claims invalid; rather, materiality relates to whether it is a matter “within a reasonable examiner’s realm of consideration.” Merck & Co. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1421 (Fed. Cir. 1989). For the second prong, the court must have a factual basis for a finding of deceptive intent. See In re Hayes Microcomputer Prods., Inc. Patent Litig., 982 F.2d 1527, 1546 (Fed. Cir. 1992); Halliburton Co. v. Schlumberger Tech. Corp., 925 F.2d 1435, 1442 (Fed. Cir. 1991). However, intent to deceive need not be proven by direct evidence. See Frazier v. Roessel Cine Photo Tech. Inc., 417 F.3d 1230, 1235 (Fed. Cir. 2005). If Defendant satisfies these threshold showings, the court must then balance the equities to determine whether the patentee has committed inequitable conduct. See Monsanto, 363 F.3d at 1239.

In this case, Defendant satisfies the first prong of the inequitable conduct analysis on two grounds. First, the “prior art as a whole” taught away from using penciclovir was a material misrepresentation because Plaintiffs withheld material prior art references. Disclosing these prior art references would have contradicted the applicants’ argument that the “prior art as a whole” taught away from using penciclovir. Second, the applicants’ representations that penciclovir was “unexpectedly” less toxic than ganciclovir constituted a material misrepresentation based on previous patent applications. For the second prong, intent to deceive may be inferred because omission of such material information indicates a lack of good faith on the part of the applicants.

1. Withholding of Material Prior Art References

Defendant contends that the '937 patent applicants intentionally withheld six material prior art references:

- (1) the Larsson publication;
- (2) the '190 patent;
- (3) the '084 patent;
- (4) the '833 patent;
- (5) the Greek '121 application; and

Defendant contends that withholding these prior art references was misleading because all of these references undercut the applicants' argument that the "prior art as a whole" taught that methylene compounds, like penciclovir and DHBG, were not "effective" and "should not work" as antiviral agents. (App. B.) According to Defendant, these prior art references were material and would have been "within a reasonable examiner's realm of consideration" because they taught that penciclovir and DHBR would have strong antiviral activity. Thus, the prior art, including these references, allegedly did not teach away from the use of methylene compounds as antiviral agents.

Plaintiffs' position is that the applicants were under no obligation to disclose the prior art references cited by Defendant because such references were cumulative. The Federal Circuit has stated that "a reference need not be provided to the examiner if it is merely cumulative to or less material than other references before the examiner." Upjohn Co. v. MOVA Pharm. Corp., 225 F.3d 1306, 1312 (Fed. Cir. 2000). "Materiality is not considered in a vacuum, but is based upon the overall degree of similarity between the omitted reference and the claimed invention in light of the other prior art before the examiner." Highway Equip. Co., Inc. v. FECO, Ltd., No. C03-

0076, 2005 WL 1843469, *9 (N.D. Iowa Jul. 27, 2005) (citing Baxter Int'l Inc. v. McGaw, Inc., 149 F.3d 1321 (Fed. Cir. 1998)). Nevertheless, when there is a question about whether a prior art reference would be cumulative or repetitive, “[i]t is axiomatic that ‘[c]lose cases should be resolved by disclosure, not unilaterally by applicant.’” Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1257 (Fed. Cir. 1997) (quoting LaBounty Mfg., Inc. v. U.S. Int'l Trade Comm'n, 958 F.2d 1066, 1076 Fed. Cir. 1992)). The applicants in this case, however, elected to withhold and not disclose several references that, arguably, presented such a “close case.”

The first two references, the Larsson publication and the ‘190 patent, both disclose the DHBG compound. Nevertheless, Plaintiffs contend that this was not a material withholding, but was cumulative because other references before the Patent Examiner disclosed DHBG, namely the Ericson and Oberg references. (Bartlett Decl. ¶¶154-155; Cudnik Decl., Ex. 7.) Disclosure of the Ericson and Oberg references, however, did not render the Larsson publication and the ‘190 patent cumulative. Even though all of these references - both the articles and the patents - disclose DHBG, “the applicants directed the patent examiner’s attention only to selective quotations regarding the different compound, HBG and said nothing about DHBG or the fact that it was a methylene compound.” (Def. Opp’n Br. at 35.) In Molins PLC v. Textron, Inc., the Federal Circuit noted that “‘burying’ a particularly material reference in . . . a multiplicity of other references can be probative of bad faith.” 48 F.3d at 1184. Further, the Federal Circuit instructed that, where a long list is submitted, the references of most significance should be highlighted. See id. In sum, the additional references to the Larsson publication and the ‘190

patent disclosing DHBG would have been material to a reasonable examiner assessing whether the prior art as a whole taught away from methylene compounds.

The third, fourth and fifth references - the '084 patent, the '833 patent and the Greek '121 application - disclose penciclovir. Plaintiffs argue that withholding these references did not constitute inequitable conduct because the Tippie article disclosed penciclovir and compared its antiviral activity to another compound. (Pl. Br. at 30 n.13.) Disclosure of the Tippie article, however, did not render the other patent references cumulative, even though the Tippie article also discloses penciclovir. An important distinction between the Tippie article and the other references is that the Tippie article only speculates about the "possibility" of penciclovir having toxicity whereas the withheld patents and patent applications all demonstrate penciclovir's lack of toxicity, and its strong potency. On this basis, the applicants materially misrepresented the prior art "as a whole."

The parties dispute whether including the '833 patent, the '190 patent, the '084 patent and the Greek '121 application would have been cumulative because the Patent Examiner was aware of these prior art references. First, these prior art references were disclosed in another co-pending patent application involving the same applicants as the '937 application. (Pl. Br. at 30 n. 13.) Second, the applicants had in-person conferences with the Patent Examiner regarding both applications in which the '190 patent was discussed. Third, the '084 patent was located in the official file history of the '937 patent application (apparently placed there by the Patent Examiner). Finally, the European counterpart to the Greek '121 application was before the Patent Examiner and was cited in the '937 patent. These arguments are not persuasive because

they do not directly respond to the inequitable conduct inquiry. Such evidence does not show that the '937 applicants did not intentionally withhold material references with the intent to deceive.

2. Alleged Misrepresentations to USPTO

The applicants engaged in inequitable conduct because they made affirmative misrepresentations to the patent examiner, specifically the applicants' representations regarding the toxicity of penciclovir. Relying on the Boyd declaration, Plaintiffs represented to the patent examiner that penciclovir was "unexpectedly" less toxic than ganciclovir. This was a misrepresentation because the applicants' own Greek application, as well as the withheld Astra '833 patent, stated that penciclovir was not toxic. This misrepresentation was material because it pertained to patentability. See Rohm & Hass Co. v. Crystal Chem. Co., 772 F.2d 1556, 1571 (Fed. Cir. 1983). According to Novartis' own expert, the examiner relied upon the applicants' toxicity argument in allowing the '937 patent to issue. (Koval Decl. Ex. 7 at TEVA-fam005812; Bartlett Decl. ¶105.)

_____ Plaintiffs argue that additional evidence was set forth to show that these discoveries were, in fact, surprising. Specifically, Plaintiffs cite the Tippie article as evidence that penciclovir appeared to have toxicity problems. This argument is unavailing because it does not respond to Defendant's argument that the Tippie article was contrary to the prior art as a whole, which tended to indicate that the results of penciclovir should not have been surprising. The applicants' heavy reliance on the Tippie article is arguably misleading because the article disregarded excluded prior art references showing that penciclovir's toxicity problems could be reduced.

3. Intent to Deceive

Plaintiffs' primary argument regarding the second prong, whether there was an intent to deceive the USPTO, is that Defendant lacks any evidence to support this argument. Defendant does not claim to have any direct evidence of the applicants' intent to deceive the patent examiner. Instead, Defendant argues that intent to deceive may properly be inferred from the applicants' withholding of material prior art references and by the applicants' material affirmative misrepresentations. Defendant emphasizes that courts have noted that direct evidence of deceitful intent is rare. Thus, Defendant argues that this court must evaluate the applicants' overall conduct to assess the applicants' conduct. See Paragon Podiatry Lab., Inc. v. KLM Labs., Inc., 984 F.2d 1182, 1189-90 (Fed. Cir. 1993).

Where a patentee knew or should have known that withheld information is material, then the patentee will have great difficulty in establishing subjective good faith sufficient to overcome an inference of intent to mislead. See Critikon, Inc., 120 F.3d at 1257. In this case, it is evident, and Plaintiffs do not dispute, that the applicants acted intentionally. Plaintiffs do not claim that the prior art references were unintentionally withheld, but instead that these withholdings were not material. The withheld information was material, so it may also be inferred that the applicants had an intent to deceive the patent examiner. See Bruno Indep. Living Aids v. Acorn Mobility Servs. Ltd., 394 F.3d 1348, 1354 (Fed. Cir. 2005).

IV. IRREPARABLE HARM

_____ Plaintiffs argue that monetary damages are insufficient to make Plaintiffs whole if their application for a preliminary injunction is denied. The principal value of a patent is the statutory right to exclude. See Hybritech, 849 F.2d at 1456-57 (cited in Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 98 F. Supp. 2d 362, 398 (S.D.N.Y. 2000), aff'd 237 F.3d at 1363). On this basis, Plaintiffs contend that loss of its statutory right to exclude constitutes a loss that cannot be compensated later by money damages.

The Federal Circuit has repeatedly held that patentees are entitled to a presumption of irreparable harm when the patentee successfully showed a reasonable likelihood of success on the merits regarding patent infringement. See Pfizer, Inc. v. Teva Pharms, USA, Inc., 429 F.3d 1364, 1381 (Fed Cir. 2005) (recognizing presumption of irreparable harm when patent is infringed upon); Purdue Pharma, 237 F.3d at 1363 (holding that showing of reasonable likelihood of success on merits in patent case entitles patentee to presumption of irreparable harm). In eBay Inc. v. MercExchange, L.L.C., the Supreme Court held that, on an application for a permanent injunction, a finding of patent infringement does not give rise to a presumption of irreparable harm. See 126 S. Ct. 1837, 1841 (2006). Subsequently, courts have disputed whether eBay should be extended to preliminary injunction applications involving patents. Compare Sun Optics, Inc. v. FGX Int'l., Inc., No. 07-137, 2007 WL 2228569, *1 (D. Del. Aug. 2, 2007) (noting that allowing presumption of irreparable harm to attach on preliminary injunction application after showing of likelihood of success on merits appears inconsistent with eBay); Chamberlain Group, Inc. v. Lear Corp., No. 05-3449, 2007 WL 1017751, *5 (N.D. Ill. Mar. 30,

2007) (extending holding of eBay to preliminary injunctions); Abbott Labs. v. Andrx Pharms. Inc., 452 F.3d 1331, 1347 (Fed. Cir. 2006) (holding that plaintiff had not established likelihood of success on merits and is “no longer entitled to a presumption of irreparable harm”). eBay poses the question whether, on preliminary injunction applications, a presumption of irreparable harm attaches after the patentee has proven a likelihood of success on the merits. This court relies upon eBay’s broader holding that, on motions for injunctions, courts should not apply categorical rules and presumptions. See 126 S.Ct. at 1840-41; see also Sun Optics, Inc., 2007 WL 2228569 at *1. eBay instructs that, in patent cases, this court should not depart from traditional equity principles that adhere in motions for injunctive relief. See id. Since this court is not satisfied that Plaintiff has established a likelihood of success on the merits, they are not entitled to a presumption of irreparable harm. A review of all of the foregoing facts and arguments leads this court to conclude that Plaintiff will not suffer irreparable harm if their application is denied.

A. Market Share and Price Erosion

Plaintiffs argue that they will suffer irreparable harm by Defendant flooding the market with its generic famciclovir product. Specifically, Plaintiffs claim that they will suffer irreparable harm in the form of (1) lost market share to the lower priced generic product; and/or (2) price erosion in an attempt to maintain its market share. In ANDA cases involving the potential entry of a generic drug, some courts have recognized these types of injuries as the kind of irreparable harm that is necessary to support preliminary injunctive relief. See Purdue, 237 F.3d at 1368; Sanofi, 470 F.3d at 1382-83; Glaxo Group Ltd. v. Apotex, Inc., 64 F. Appx. 751, 756 (Fed. Cir. 2003).

Both loss of market share and price erosion are economic harms and are compensable by money damages. First, the court should not be swayed by the fact that money damages may be difficult to calculate: “neither the difficulty of calculating losses in market share, nor speculation that such losses might occur, amount to proof of special circumstances justifying the extraordinary relief of an injunction prior to trial.” Nutrition 21, 930 F.2d at 871. Specifically, in the context of generic competition in the pharmaceutical industry, some courts have held that loss of market share is a compensable economic injury. See Abbott Labs., 452 F.3d at 1347-48; Eli Lilly & Co. v. Am. Cyanamid Co., 82 F.3d 1568, 1578 (Fed. Cir. 1996); Novartis Corp. v. Teva Pharms. USA, Inc., No. 04-4473, 2007 U.S. Dist. LEXIS 42163 (D. N.J. Jun. 11, 2007). In addition, Plaintiffs’ price erosion claims are purely speculative because Plaintiffs’ expert does not cite an example of a branded pharmaceutical suffering price erosion in response to generic competition. Instead, “[h]istorically, pharmaceutical companies have maintained or even increased prices on brand product when faced with generic competition.” (Def. Opp’n Br. at 38 (citing Leffler Decl. ¶32.)). Any economic harm that Plaintiffs might incur is not irreparable because Defendants can pay whatever damages may arise and satisfy any reasonable judgment awarded to Plaintiffs if Plaintiffs ultimately prevail at trial.

B. Suspension of Clinical Research

Additionally, Plaintiffs argue that their clinical research will be disrupted by a premature launch of Defendant’s generic famciclovir. Plaintiffs argue that they are committed to invest large sums of money to investigate the effects of Famvir® treatment on the African American population and to conduct pediatric clinical trials. These research opportunities would allegedly

be lost if Defendants are allowed to launch the generic product. (Pl. Br. at 34-35) (citing Sanofi, 470 F.2d at 1382-83; Pharmacia & Upjohn Co. v. Ranbaxy Pharms., Inc., 274 F. Supp. 2d 597, 614, aff'd, 85 F. App's 205 (Fed. Cir. 2003)) (supporting proposition that discontinuing of clinical trials establishes irreparable harm). This argument is “attenuated” and lost clinical research does not constitute irreparable harm. (Def. Opp'n Br. at 38-39) (citing Novartis, 2007 U.S. Dist. LEXIS 42163, at *92.) Specifically, Plaintiffs have not demonstrated that a temporary reduction in revenue from Famvir®, a relatively small product for a multibillion dollar company, would cause research investments to be withdrawn.

C. Goodwill

____ Finally, Plaintiffs claim irreparable harm based on lost goodwill. Plaintiffs argue that if injunctive relief is delayed and Defendant floods the market with its lower priced generic drug, customers will grow accustomed to lower prices for famciclovir. Plaintiffs further argue that these customers will harbor ill-will towards them when the price for famciclovir rises if the generic drug later becomes unavailable on the market. (Pl. Br. at 35) (citing Sanofi-Synthelabo v. Apotex, No. 02-2255, 2006 U.S. Dist. LEXIS 65127, at *72 (S.D.N.Y. Aug. 31, 2006)); Sanofi, 470 F.3d at 1382-83; Syntex (USA) LLC v. Apotex Inc., No. 01-2214, 2006 U.S. Dist. LEXIS 34608, at *8-9 (N.D. Cal. May 18, 2006)). This argument, however, is “purely speculative.” (Leffler Decl., ¶37.)

V. BALANCE OF HARDSHIPS

_____Plaintiffs emphasize that a preliminary injunction preserves the status quo and, thus, there is minimal hardship to the accused infringer because the product is not yet on the market. See PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1567 (Fed. Cir. 1996)); Impax Labs, Inc. v. Aventis Pharms., Inc., 235 F. Supp. 2d 390, 396 (D. Del. 2002); Glaxo, 64 F. App's at 756; Abbott Labs v. Sandoz, Inc., No. 05-5373, 2007 Dist LEXIS 28185, *92 (N.D. Ill. Apr. 16, 2007). Additionally, Plaintiffs argue that any injury to Defendant would be self-inflicted, and would be purely monetary, easily calculated and fully protected by an injunction bond. Defendant contends, however, that granting the preliminary injunction would cause Defendant to lose profits it might have earned on sales of generic famciclovir during this period. Additionally, granting the preliminary injunction harms the public because the public will never recover the amount it overpaid for Famvir®. This, however, is not preserving the status quo.

VI. PUBLIC INTEREST

Plaintiffs argue generally that the public interest is favored by protecting patent holders' limited right to exclude other competitors. Enforcing intellectual property rights of innovator pharmaceutical companies is an essential component of efforts to discover new, useful compounds. Plaintiffs argue that the profits generated from a patent are utilized in part to fund research and development costs, which are an essential component of drug discovery. See Eli Lilly & Co. v. Premo Pharm. Labs., Inc., 630 F.2d 120, 137 (3d Cir. 1980); Ortho Pharm Corp. v. Smith, 15 U.S.P.Q. 2d 1856, 1863 (E.D. Pa. 1990); Sanofi, 470 F.3d at 183-84; Pfizer, 429 F.2d at 1382; Pharmacia, 274 F. Supp. 2d at 614. Defendants, however, argue that the public interest

is served by making lower-cost drugs available to consumers. Both parties present valid arguments on this issue. The motion is ultimately decided based on the other parts of the analysis.

Plaintiffs have a difficult burden. “The court must balance the[] four factors, as their relative weight warrant, in service to the interest of justice.” Monsanto Co. v. McFarling, 302 F.3d 1291, 1297 (Fed. Cir. 2002). A preliminary injunction is a “drastic remedy that is not to be routinely granted.” Intel Corp. v. ULSI Sys. Tech., Inc., 995 F.2d 1566, 1568 (Fed Cir. 1993). Thus, to prevail on its application for a preliminary injunction, Plaintiffs must make a “clear” showing of likely success on the merits. See Nutrition 21 v. U.S., 930 F.2d 867, 869-70 (Fed. Cir. 1991). Although Defendant has the ultimate burden of proving invalidity and enforceability at trial, “at the preliminary injunction stage, because of the extraordinary nature of the relief, the *patentee* carries the burden of showing likelihood of success on the merits with respect to the patent’s validity.” Nutrition 21, 930 F.2d at 869 (emphasis in original). Plaintiffs needed to show that the ‘937 patent is both valid and enforceable. Plaintiffs’ failed to establish a reasonable probability of success on the merits because of the obviousness of the ‘937 patent. Furthermore, Plaintiffs failed to establish irreparable harm. Both loss of market share and price erosion are economic harms and are compensable by money damages. The court is not swayed by the fact that money damages may be difficult to calculate: “neither the difficulty of calculating losses in market share, nor speculation that such losses might occur, amount to proof of special circumstances justifying the extraordinary relief of an injunction prior to trial.” Nutrition 21, 930 F.2d at 871. Specifically, in the context of generic competition in the pharmaceutical industry,

courts have held that loss of market share is a compensable economic injury. See Abbott Labs., 452 F.3d at 1347-48; Eli Lilly & Co. v. Am. Cyanamid Co., 82 F.3d 1568, 1578 (Fed. Cir. 1996); Novartis Corp. v. Teva Pharms. USA, Inc., No. 04-4473, 2007 U.S. Dist. LEXIS 42163 (D. N.J. Jun. 11, 2007). Any economic harm that Plaintiffs might incur is not irreparable because Defendants can pay damages to satisfy any reasonable judgment awarded to Plaintiffs if Plaintiffs ultimately prevail at trial.

VII. CONCLUSION

For the reasons stated, it is the finding of this Court that Plaintiffs' motion for a preliminary injunction is **denied**. An appropriate Order accompanies this Opinion.

S/ Dennis M. Cavanaugh
Dennis M. Cavanaugh, U.S.D.J.

Date: Sept. 6, 2007
Orig.: Clerk
cc: Counsel of Record
The Honorable Mark Falk, U.S.M.J.
File
