

Appeal No. 2007-1542

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**United States Court of Appeals**  
*for the*  
**Federal Circuit**

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

*Plaintiffs-Appellants,*

- v. -

TEVA PHARMACEUTICALS USA, INC.,

*Defendant-Appellee.*

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APPEAL FROM THE UNITED STATES DISTRICT COURT FOR  
THE DISTRICT OF NEW JERSEY IN CASE NO. 05-CV-1887,  
JUDGE DENNIS M. CAVANAUGH

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**PLAINTIFFS-APPELLANTS' REPLY  
IN SUPPORT OF ITS EMERGENCY MOTION**

ROBERT L. BAECHTOLD  
NICHOLAS N. KALLAS  
HUGH C. BARRETT  
SIMON D. ROBERTS  
FITZPATRICK, CELLA, HARPER & SCINTO  
30 Rockefeller Plaza  
New York, New York 10112  
(212) 218-2100

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*Attorneys for Plaintiffs-Appellants*

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## INTRODUCTION

Although both parties acknowledge that to prevail on this motion, Novartis must meet the Standard Havens requirements, Teva's opposition in essence would require, in this truncated procedure, that Novartis now demonstrate that this Court ultimately will reverse. While that indeed will be the ultimate result, all that is required of Novartis at this time is that it show a likelihood of success on appeal. That showing has been made. Indeed, all of the Standard Havens factors weigh in Novartis' favor.

The trial court expressed unfamiliarity and discomfort with the complex chemistry involved in this case,<sup>1/</sup> but nevertheless declined Novartis' offer to provide live expert and fact witnesses, a normal and advisable precaution in cases with the serious consequences presented here. See Sims v. Greene, 161 F.2d 87, 88 (3d Cir. 1947) ("If witnesses are not heard [in a preliminary injunction motion,] the trial court will be left in the position of preferring one piece of paper to another."); All Care Nursing Serv., Inc. v. Bethesda Mem'l Hosp., Inc., 887 F.2d 1535, 1539 (11th Cir. 1989) (trial court erred in deciding a preliminary injunction motion without an evidentiary hearing and in affording the parties only thirty minutes apiece for oral presentations). Instead, the trial court heard only 90

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<sup>1/</sup> See September 5, 2007 Transcript at 27, submitted with Novartis' Reply.

minutes of argument before summarily denying the motion as soon as that argument ended.

Informed only by “pieces of paper”, the trial court unfortunately accepted arguments from Teva that were superficial and out of touch with what the contemporaneous documents said and what had happened in the real world.<sup>2/</sup> Then, although it cited Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368 (Fed. Cir. 2006), the trial court never acknowledged the virtually identical facts presented there that led to the grant -- and this Court’s affirmance -- of a preliminary injunction.

As demonstrated in its opening brief and below -- and as will be more fully articulated in the briefing of the appeal itself -- the trial court’s preliminary injunction denial was based on clear legal and factual errors, and amounted to an abuse of its discretion. Teva’s opposition on this motion engages in the same dissembling, the same disregard for real world facts, and the same distortion of the prosecution record which misled the court below.

**A. FAMCICLOVIR WAS NOT OBVIOUS**

Teva’s theoretical obviousness argument is litigation inspired and could only have been constructed by hindsight. For example, the GB ‘204

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<sup>2/</sup> See Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1544 (Fed. Cir. 1984) (“...patent cases should not be mere games played with pieces of paper called references and the patent in suit. Lawsuits arise out of the affairs of people, real people facing real problems.”)

reference was no road map to success. The deoxy modification did not even solve the bioavailability problems faced by its authors because it produced a toxic metabolite with acyclovir, the very compound that GB '204 described. (Bartlett Decl. ¶ 126).

Moreover, the trial court's finding that GB '204 teaches that esters enhance absorption lacks factual support. Indeed, the authors of GB '204 explicitly said, in a different scientific publication, that esters showed "no significant improvement in absorption after oral dosing." (Bartlett Decl. ¶¶ 129, 132-33; Bartlett Decl. Exh. 24). But in the real world, neither modification alone -- the 6-deoxy modification nor the ester modification -- gave the '937 inventors satisfactory results for penciclovir, and there was even strong disagreement within Beecham whether there was any point in trying them in combination. (Bartlett Decl. ¶ 79; Bartlett Decl. Exh. 17).

The lower court's legal conclusion that a prior art teaching "need not be that clearly articulated in terms of specific biologic data" (Decision, 16), further highlights its failure to appreciate the real world significance of Teva's key reference. From that starting point, the trial court then concluded that even though the GB '204 reference contained no data on the bioavailability of esters, it nevertheless taught that esters enhanced the absorption of the compounds -- acyclovir and ganciclovir -- described in that reference (Decision, 16-17) and

made “successful” prodrugs. But there simply was no record evidence to support that erroneous conclusion.

The trial court also omitted any consideration of perhaps the most important real world event -- while it correctly noted that four research-based pharmaceutical companies had investigated penciclovir, three of those companies ultimately abandoned their work on that compound. (Decision, 4). The three sophisticated research groups that investigated penciclovir were all searching for an effective and profitable HSV drug. Nevertheless, those companies failed to follow what Teva now says was the clear route to famciclovir, and none ever developed any oral nucleoside drug sufficiently safe and effective to treat the most common HSV viruses. These real world events, all of which demonstrated that famciclovir was not obvious, were ignored below.

Thus, Teva’s “evidence” below was nothing more than a handful of references that had no significant impact in the real world, coupled with the hindsight opinions of litigation experts -- none of whom did, at the relevant time, the things they later told the court were obvious.<sup>3/</sup> The decision below cannot be sustained on self-serving, self-contradictory, hindsight-driven opinions.

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<sup>3/</sup> The most blatant example is Teva’s expert Dr. Smee who actually experimented with penciclovir, dropped it and then devoted his efforts to other compounds, none of which ever attained the prominence in the real world that famciclovir did.

The trial court also clearly erred on the law of chemical obviousness. Relying on a single sentence from Pfizer v. Apotex, 480 F.3d 1348, 1364 (Fed. Cir. 2007), -- to the effect that the inventor's expectation of success need only be "reasonable, not absolute" -- the trial court erroneously concluded that any chemical modification taught in the prior art could be predictably applied to a new molecule. Thus, the lower court found that these inventors merely had to use the modifications for acyclovir suggested in GB '204 -- a different compound than penciclovir -- to ensure success. That simplistic approach failed to appreciate the unpredictability of chemical modifications and their resulting effects on the human body. Indeed, the unpredictability of even slight modifications in chemical structures was clearly demonstrated here by the fact that the modifications disclosed in GB '204 turned out to be commercially fruitless. The impact of unpredictability, of course, is one of the basic tenets of non-obviousness. Takeda Chem. Industries, Ltd. v. Alphapharm Pty, Ltd., No. 06-1329, 2007 U.S. App. LEXIS 15349 (Fed. Cir. 2007). Equating the use of teachings in the chemical prior art to "obvious" results on new compounds was clear error -- of law and fact.

Teva is wrong when it argues that this Court, in Pfizer, 480 F. 3d 1348, found a chemical modification obvious under facts similar to those here. First, the "salt" invention in Pfizer -- amlodipine besylate -- had nothing to do with "bioavailability" whatsoever. The modification from one salt form to the other

was done to aid in processing, e.g., to prevent sticking to the tablet machine. Second, the modification from one salt to the other did not affect the pharmacological -- i.e., therapeutic -- properties of amlodipine. That compound had already been shown to be clinically effective, and the only issue was finding a salt that would improve tableting. Id. at 1368, 1371.

The chemical modifications in this case -- like those in Takeda -- are nothing like the type in Pfizer. The modifications here and in Takeda involve the true unpredictability of chemical modifications and their affect in the human body.

Teva attempts to close the factual gap between Pfizer and this case by asserting that penciclovir too was a “proven antiherpes drug”. It never was. At most, it was one of several compounds that had a degree of anti-HSV or anti-herpes activity that was significantly lower than ganciclovir (had not been compared to acyclovir) and that no one had ever developed or even proposed as an effective candidate, much less an established drug.

**B. THERE WAS NO INEQUITABLE CONDUCT**

With regard to the antiviral activity of methylene compounds, the applicants simply told the Examiner the truth -- methylene compounds are less active than their oxygen analogs. No evidence suggests the contrary. And, the applicants did not hide or obscure the antiviral activity of penciclovir. The Examiner was given the Tippie article that disclosed the activity of that compound

against HSV and herpes virus in animals -- the most reliable tests. Teva's so-called "concealed" references show nothing more than what Tippie disclosed.

Nor did the applicants mislead the Examiner by "burying" information in a particular reference and pointing the Examiner only to other parts of the reference. Thus, the trial court (Op., 21-22) erred in relying on Molins PLC v. Textron, Inc., 48 F.3d 1172, 1184 (Fed. Cir. 1995), which is factually distinguishable. Molins involved the improper "burying" of a critical prior art reference within large bundles of other references. Id.

Here, the applicants cited the critical prior art and discussed the portions relevant to the "prosecution dialog" -- i.e., the discussion regarding ether/methylene analogs. (Bartlett Decl. ¶ 154-55; Cudnik Decl. Exh. 7). And, of course, the Examiner was free to reach his own conclusions about this art in front of him. Akzo N.V. v. U.S. Int'l Trade Comm'n, 808 F.2d 1471, 1482 (Fed. Cir. 1986).

As to intent, the trial court improperly inferred an intent to deceive because no one testified that the omission of the references in question was inadvertent. But, there was no evidence that anyone consciously determined not to cite the references (indeed the evidence was to the contrary), and the piling of inferences on inferences does not satisfy Teva's burden of proving intent by clear and convincing evidence. See Purdue Pharma L.P. v. Boehringer Ingelheim

GmbH, 237 F.3d 1359, 1363 (Fed. Cir. 2001); In re Metoprolol Succinate Patent Litigation, 2007 U.S. App. LEXIS 17463, \*24-25 (Fed. Cir. 2007).

**C. NOVARTIS WILL BE IRREPARABLY HARMED**

The trial court's conclusions on irreparable harm resulted from clear errors of law and abuse of its discretion. This Court's Sanofi decision is binding precedent establishing the proper analysis for irreparable harm, and compelling the opposite result from that reached here. The failure to follow that precedent was both an error of law and abuse of discretion because the showing of irreparable harm, both in Sanofi and here, was based upon:

- Testimony by a renowned economist, MIT Prof. Hausman, that (1) irreversible price erosion would occur absent an injunction (470 F.3d at 1382; Hausman Decl. ¶¶ 21-24 and Reply Decl. ¶¶ 14-15, 20, 22); (2) generic entry would result in the branded company offering increased discounts and rebates (470 F.3d at 1382; Hausman Decl. ¶¶ 21-24); and (3) generic entry would result in loss of preferred formulary tier status (470 F.3d at 1382; Hausman Decl. ¶¶ 11-13, 21-24).
- Evidence establishing (1) potential discontinuation of clinical trials (470 F.3d at 1381, 1383; Lemieux Decl. ¶¶ 13, 40; Hausman Decl. ¶ 25)<sup>4/</sup>; and (2) potential loss of goodwill due to generic entry (470 F.3d at 1381, 1383; Lemieux Decl. ¶ 41, Lemieux Reply Decl. ¶ 3).<sup>5/</sup>

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<sup>4/</sup> Teva's assertion that Novartis can fund clinical trials with funds generated from sources other than Famvir®, ignores the basic economic principle that when risk and uncertainty increase (as caused by Teva's generic entry), a rational business decision maker will greatly decrease investment in "sunk costs" like R&D, which cannot be recovered if a product fails. (Hausman Reply Dec. ¶ 23).

<sup>5/</sup> Teva attempts to distinguish Sanofi as affirming the grant, rather than the denial of a preliminary injunction. That is a distinction without a difference, since the point is that Sanofi established the irreparable harm analysis to be applied here.

Moreover, the irreparable harm record is even stronger here than in Sanofi because Novartis offered additional compelling evidence establishing:

- Likely irreversible loss of market share. (Hausman Decl. ¶¶ 15-20).
- No generic launch yet, which had occurred in Sanofi. (Hausman Reply Decl. ¶ 8).
- While the Sanofi product had no direct competing alternatives, Famvir® competes with Valtrex® and generic acyclovir, making the competitive interaction considerably more complex. (Hausman Decl. ¶¶ 17-20 and Reply Decl. ¶ 9).

The lower court also clearly erred and abused its discretion by effectively failing to even consider the balance of hardships (Decision at 29), which Teva did not seriously dispute below. (Leffler Decl. ¶ 38 (Teva’s economist)). Indeed, as the only generic that challenged the ‘937 patent, Teva (prior to the lower court’s decision, and Teva’s precipitous launch), was assured of receiving 180 days marketing exclusivity if it ultimately succeeds at trial. Thus, the only conceivable harm to Teva was a delay in the benefit of this marketing exclusivity (i.e., the time value of money), which is calculable, compensable and far outweighed by the harm to Novartis. (Lemieux Decl. ¶ 43).

Moreover, Teva’s present harm arguments deserve no weight -- all relate to circumstances of its own making. Despite notice of this motion, Teva chose to proceed with an immediate “at risk” launch with full knowledge that Novartis would seek a temporary injunction from this Court, an action that can only bespeak Teva’s concern that the decision below will be reversed by this

Court.<sup>6/</sup> See Sanofi, 470 F.3d at 1383 (Apotex’s harms were “almost entirely preventable” and the result of its calculated “at risk” launch).<sup>7/</sup>

**D. CONCLUSION**

Novartis respectfully requests that this Court maintain the injunction entered against Teva on September 7, 2007 until the conclusion of the appeal.

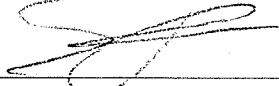
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<sup>6/</sup> Having launched, Teva complains of potential loss of its 180 days of marketing exclusivity, but, of course, that is wholly self-inflicted, and not an “entitlement” absent a judgment in Teva’s favor. Also, Teva now frets over the unproven possibility that Novartis may launch a competitive authorized generic. Novartis represented below, before Teva’s “at risk” launch, that Novartis would maintain the status quo as long as Teva did so. (Lemieux Reply Decl. ¶2).

<sup>7/</sup> Teva’s complaints about the hardships of a recall should similarly be rejected. Teva’s launch, which frustrates and flaunts this Court’s ability to provide fully effective relief, should justify a recall order.

Dated: September 12, 2007

Respectfully submitted,



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Robert L. Baechtold  
Nicholas N. Kallas  
Hugh C. Barrett  
Simon D. Roberts  
Fitzpatrick, Cella, Harper & Scinto  
30 Rockefeller Plaza  
New York, New York 10112  
(212) 218-2100

Counsel for Appellees  
Novartis Pharmaceuticals Corporation  
Novartis Pharma AG  
Novartis International Pharmaceutical Ltd.

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