UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ORTHO-MCNEIL PHARMACEUTICAL, INC., Plaintiff and Counterclaim Defendant, v. MYLAN LABORATORIES INC. and MYLAN PHARMACEUTICALS INC., Defendants and Counterclaim Plaintiffs.	**DOCUMENT ELECTRONICALLY FILED** Civil Action Nos. 04-1689 and 06-757 (FLW) (TJB) Consolidated Cases

(REDACTED) PLAINTIFF'S BRIEF IN SUPPORT OF ITS MOTION FOR PRELIMINARY INJUNCTION

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Pursuant to Fed.R.Civ.P. 65(a), Plaintiff Ortho-McNeil Pharmaceutical, Inc. ("Ortho-McNeil")[1] respectfully submits this memorandum in support of its Motion for Preliminary Injunction against Defendants, Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. (collectively, "Mylan"). As discussed further below, a statutory 30-month stay is due to expire on September 9, 2006, after which Mylan could enter the market with its generic copy of Ortho-McNeil's patented TOPAMAX® drug. To preserve the status quo and to prevent irreparable and unrecoverable damage to Ortho-McNeil, Mylan should be preliminarily enjoined from marketing and/or selling its admittedly infringing product until after the issues raised in this litigation have been fully resolved. The Court also should preliminarily order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date for FDA approval of Mylan's topiramate products shall be a date which is not earlier than the date of expiration of Ortho-McNeil's U.S. Patent No. 4,513,006 ("the '006 patent").

PRELIMINARY STATEMENT

I. THE NATURE AND STAGE OF THE PROCEEDINGS

Ortho-McNeil filed this lawsuit to protect its rights under the '006 patent, pursuant to the Hatch-Waxman Act[2] upon being served with notice of Mylan's certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) indicating its intent to sell a generic knockoff of Ortho-McNeil's TOPAMAX® products before the '006 patent expires. Mylan's proposed tablets contain topiramate, the same patented active ingredient found in TOPAMAX®. Mylan's notice triggered Ortho-McNeil's obligation to file suit to preserve its patent grant of exclusivity. The

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[1] "Ortho-McNeil" as used herein also includes Ortho-McNeil's wholly-owned subsidiary, Ortho-McNeil Neurologics, Inc. ("Neurologics"), which actually makes and sells TOPAMAX® products. (*See* Declaration of Seth H.Z. Fischer in Support of Plaintiff's Motion for Preliminary Injunction ("Fischer Dec."), ¶ 2) (filed under seal).

[2] The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984), codified at 21 U.S.C. §§ 355, 360cc, and 35 U.S.C. §§ 156, 271.

filing of Ortho-McNeil's lawsuit gave rise to an automatic 30-month stay under the Act, preventing Mylan from marketing the drug before the expiration of the 30 months, or until September 9, 2006, approximately eight weeks from now. 21 U.S.C. § 355(j)(5)(B)(iii).

The Hatch-Waxman Act contemplates that, if the litigation will not be resolved before the expiration of the 30-month stay, a court may grant a preliminary injunction. *Id.* at subparagraph III and IV. Consequently, the Act authorizes entry of a preliminary injunction to prohibit the manufacture and sale of a generic product and to prevent the FDA from approving that product until after the court decides the issues of patent validity and infringement. *Id.*; *see also Zeneca Ltd. v. Pharmachemie B.V.*, 16 F.Supp.2d 112, 116 (D.Mass. 1998) (recognizing statutory authority for a preliminary injunction to maintain status quo after expiration of the 30-month stay). Indeed, courts have granted an injunction under essentially the same circumstances presented here. *See, e.g., Syntex (U.S.A.) LLC v. Apotex Inc.*, Dkt. No. C 01-02214 MJJ, 2006 WL 1530101, *1-*2 (N.D.Cal. June 2, 2006). Even when the 30-month stay is not implicated, courts will grant a preliminary injunction to prevent premature generic entry before the underlying patent issues can be resolved. *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*, 429 F.3d 1364 (Fed.Cir. 2005); *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.*, 235 F.Supp.2d 390 (D.Del. 2002).

Here, unless an injunction is entered before the statutory stay expires, Ortho-McNeil remains vulnerable to the launch of Mylan's topiramate tablets, which would cause Ortho-McNeil irreparable harm in depriving Ortho-McNeil of the benefits of its patent property. Ortho-McNeil will lose most of the market share for the topiramate drug, as well as most of the profits that a patent holder is entitled to pursue for the next two years while the patent remains in force, plus potentially another six month period of FDA exclusivity – through March 2009 – that

Ortho-McNeil would receive upon fulfillment of its agreement with the FDA to study the effects of topiramate in young children. [redacted] These devastating effects to Ortho-McNeil could never be cured simply by Mylan's payment of monetary damages or by entry of a permanent injunction after the fact.

II. SUMMARY OF ARGUMENT

Ortho-McNeil must establish that it is entitled to a preliminary injunction in view of the four equitable factors of (1) a likelihood of success on the merits; (2) irreparable harm; (3) the balance of hardships; and (4) the public interest. *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1446, 1451 (Fed.Cir. 1988); *Eli Lilly and Co. v. Premo Pharmaceutical Labs., Inc.*, 630 F.2d 120, 136 (3d Cir. 1980). Each factor must be weighed and measured against the others and against the form and magnitude of the relief requested. *Hybritech*, 849 F.2d at 1451. Here, all four factors favor Ortho-McNeil's motion.

1. Likelihood of success: The first factor favors Ortho-McNeil because Mylan's remaining defenses all lack substantial merit.

a. All of Mylan's primary defenses have already been finally resolved against Mylan in this case. When Mylan first notified Ortho-McNeil of Mylan's intention to market topiramate, Mylan was required to provide "a detailed statement of the factual and legal basis … that the patent is invalid or will not be infringed." 21 U.S.C. § 355(j)(2)(B)(iv)(II). Mylan gave Ortho-McNeil the required notice, but then Mylan completely abandoned the only defense identified in that notice – [redacted] (*See* Declaration of Eric L. Lohrenz in Support of

Plaintiff's Motion for Preliminary Injunction ("Lohrenz Dec."), Ex. I, Mylan's Notice of Paragraph IV Certification) (filed under seal). Next, Mylan filed a single summary judgment motion on whether the claim language covered Mylan's drug. The Court ruled that it did and so there is no question whether Mylan infringes the '006 patent. (*See* Dkt. Entry # 50). Third, Mylan accused Ortho-McNeil's inventor Dr. Maryanoff of "inequitable conduct and scientific fraud." This serious and baseless accusation also was resolved against Mylan as a matter of law. (*See* Dkt. Entry # 134).

b. Mylan is left with its entirely meritless obviousness and § 112 defenses that fail to address the proper questions under the law and are seriously lacking in evidentiary support. With respect to obviousness, Mylan's experts fail to offer any opinions that the topiramate compound or its use as an anticonvulsant would have been obvious from the prior art. Instead, they offer the entirely irrelevant opinions that if topiramate were already known, a person skilled in the art would know how to make it and also might suspect it might be a good anticonvulsant. Mylan's expert opinions are also legally and factually erroneous for other reasons that are discussed in detail below. None of Mylan's evidence can come close to carrying the heavy burden of proving obviousness by clear and convincing evidence. Mylan's defenses of non-enablement and indefiniteness also are meritless. As explained in Ortho-McNeil's summary judgment papers, Mylan cannot even raise a material fact issue regarding these defenses. Furthermore, because of its discovery delays, Mylan is precluded from offering any response to the expert opinions of Dr. Michael Privitera that the information disclosed in the '006 patent would allow one skilled in the art to determine an "anticonvulsantly effective amount" without undue experimentation. (Dkt. Entry #87, January 16, 2006 Order, at 3). Accordingly, Ortho-McNeil can demonstrate a likelihood of success on the merits of the remaining Mylan defenses.

2. **Irreparable harm:** The irreparable harm to Ortho-McNeil from Mylan's premature generic entry strongly favors granting a preliminary injunction. Not only would the marketing of Mylan's copycat generic drug eviscerate Ortho-McNeil's patent rights during the remaining two years that the '006 patent will be in force, [redacted] These injuries to Ortho-McNeil cannot be undone by the issuance of a permanent injunction after trial or by the mere payment of monetary damages.

3. **Balance of hardships:** This factor decidedly favors Ortho-McNeil. In contrast to the devastating harm to Ortho-McNeil that would result from Mylan's premature market entry, Mylan faces only minimal hardship, if any, from having to wait a brief additional period until Ortho-McNeil's claims are finally adjudicated on the merits. Mylan is not presently marketing topiramate products, and it has numerous other opportunities to expand its generic business.

4. **Public interest:** Lastly, the public interest also favors Ortho-McNeil's position. The patent system, which is critical to preserving this country's lead in technological innovation, would be significantly undermined if patents likely to be held valid and infringed were deprived of their statutory right of exclusivity. While in the short term the public may benefit from less expensive topiramate, that would come at the expense of inhibiting investment in research and development of patented pharmaceuticals. The Hatch-Waxman Act struck a balance that was intended only to provide a mechanism for removing patent protection for

meritless patents, while recognizing the value to the public of the patentholder's right to exclusivity. Thus, unless the likelihood of success is so weak that the Court can conclude that the patent-in-suit is likely meritless, the public interest factor should weigh in favor of maintaining the status quo. Otherwise, the careful balance struck by Congress in the Hatch-Waxman Act will be disturbed.

STATEMENT OF FACTS

III. THE DISCOVERY OF TOPIRAMATE AND GRANT OF THE '006 PATENT

In 1978, Dr. Bruce Maryanoff, a scientist at Ortho-McNeil's predecessor McNeil Laboratories ("McNeil"), started research that led to the discovery of a novel chemical compound now known as topiramate. This discovery was quite serendipitous: topiramate was actually an intermediate for other compounds that he was trying to synthesize at the time, as part of his work on a project involving a new approach to antidiabetic drugs. (Declaration of Bruce E. Maryanoff, Ph.D., in Support of Plaintiff's Motion for Preliminary Injunction ("Maryanoff Dec."), ¶ 3).

As an intermediate, topiramate had no expected utility except as a molecule that could be chemically modified in the hope of obtaining a target compound. (Maryanoff Dec., ¶ 3). Nonetheless, in 1979, Dr. Maryanoff had the presence of mind to isolate samples of topiramate from the synthesis process so that they could be submitted for evaluation in various ongoing pharmacological assays at McNeil. (*Id.*, ¶ 4). Another McNeil scientist, Dr. Joseph Gardocki, directed topiramate for evaluation as an anticonvulsant. In the course of that evaluation, Dr. Gardocki discovered that topiramate might have some anticonvulsant properties. (*Id.*, ¶ 4). Dr. Gardocki then directed further testing to confirm and characterize the nature of topiramate's anticonvulsant properties. (*Id.*, ¶ 5).

In September 1983, the inventors filed a patent application based on their work with topiramate and related compounds that also exhibited anticonvulsant activity. (Maryanoff Dec., ¶ 8). For their discoveries, they were granted the '006 patent in April 1985. (*Id.*, ¶ 8). Plaintiff Ortho-McNeil now owns the '006 patent, the patent at issue here. (Dkt. Entry #58, Final Pretrial Order, at 6, ¶ 12).

IV. THE DEVELOPMENT AND LAUNCH OF TOPAMAX® PRODUCTS

Following the discovery of topiramate and its anticonvulsant properties, the inventors sought the assistance of an independent scientific expert to conduct further anticonvulsant testing of topiramate in animals. (Maryanoff Dec., ¶ 6). That expert, Dr. Harvey Kupferberg from the National Institute of Neurological Diseases and Stroke (NINDS), was impressed by both the pharmacological profile of topiramate and its unique molecular structure. (Maryanoff Dec., ¶ 6; Declaration of Harvey Kupferberg, Ph.D., in Support of Plaintiff's Motion for Preliminary Injunction ("Kupferberg Dec."), ¶¶ 4-5). Consequently, the NINDS gave topiramate a high ranking for development as a treatment for epileptic seizures. (Kupferberg Dec., ¶ 5). Dr. Kupferberg's support for topiramate, together with the case assembled by the two inventors, led to a strong recommendation for clinical development of the drug by McNeil. Thus, preclinical development of topiramate was initiated in late 1983, and an Investigational New Drug (IND) application was filed with the FDA in June, 1986. (Maryanoff Dec., ¶ 7).

Thereafter, McNeil and later Ortho-McNeil invested substantial resources to conduct the clinical studies to demonstrate the safety and efficacy of topiramate as required by the FDA, and to shepherd the TOPAMAX® products through the regulatory process to obtain FDA approval. (*See* Declaration of Joseph Hulihan, M.D., in Support of Plaintiff's Motion for Preliminary Injunction ("Hulihan Dec."), ¶¶ 2,4). As a result of Ortho-McNeil's efforts, the FDA in December 1996 approved topiramate for use as adjunctive therapy (*i.e.*, in conjunction

with other drugs) in treating epilepsy; in August 2004, the FDA approved topiramate for use in preventing migraines; and, in June 2005, the FDA approved topiramate for use as initial monotherapy (*i.e.*, as a stand-alone drug) in treating epilepsy. (Hulihan Dec., ¶ 2). The '006 patent is included in the FDA's "Orange Book" listing of patents on active drug ingredients, as covering TOPAMAX® products and the active ingredient topiramate. (*See* Lohrenz Dec., Ex N).

Topiramate now has been used by millions of patients worldwide since it was first approved in the United Kingdom in 1995. (Hulihan Dec., ¶ 2). Clinical experience has shown topiramate to be a novel therapeutic agent offering significant benefits to a wide range of epilepsy and migraine patients (*id.*, ¶ 3), including the following:

- As an anticonvulsant, topiramate has multiple mechanisms of action that may contribute to its potent antiseizure activity. The expansive clinical development program for TOPAMAX® has documented the efficacy of topiramate in treating a broad spectrum of different seizure types, including seizures in patients for whom older antiepileptic drugs were not effective. (*Id.*, ¶ 4). In addition, topiramate is the only drug approved for primary generalized tonic-clonic seizures, and it is one of three products established to treat drop attacks associated with Lennox Gastaut syndrome in adults and children. (*Id.*, ¶ 4).

- As a migraine preventive, topiramate has been studied in the largest clinical development program to date for this indication. Topiramate has a rapid onset of action and significantly reduces migraine frequency. It also has been shown to have sustained efficacy for long-lasting protection against migraine attacks. (*Id.*, ¶ 5).

- Topiramate has very favorable pharmacokinetics for the above uses. Its long half-life permits less frequent dosing, thus increasing patient convenience. Topiramate also has minimal clinically significant drug interactions. Of particular relevance to migraine, which occurs predominantly in women of childbearing potential, is the lack of interaction with oral contraceptives at doses below 200 mg per day. (*Id.*, ¶ 6).

- Topiramate also has a favorable tolerability profile when used according to its recommended dosing and titration guidelines. The most common side effects seen with topiramate tend to occur early in therapy, and are either self-limited or respond to dosage adjustments. Unlike some other agents used to treat epilepsy or migraine, topiramate has not demonstrated adverse effects that would cause it to be contraindicated in special patient populations, such as those who are obese or who have diabetes. (*Id.*, ¶ 7).

Thus, topiramate affords new opportunities in the treatment of epilepsy and prevention of migraine that did not exist before the discovery and development of this drug. (*Id.*, ¶ 8).

V. THE IMPORTANCE OF TOPAMAX® PRODUCTS TO ORTHO-MCNEIL

Topiramate, now marketed by Ortho-McNeil under the TOPAMAX® brand, is an unquestionable commercial success. TOPAMAX® is the flagship product of Ortho-McNeil's Neurologics subsidiary, [redacted] and it also is one of the highest selling products for Ortho-McNeil's parent, Johnson & Johnson. (Fischer Dec., ¶ 9). Indeed, TOPAMAX® is identified as a "key product" in quarterly reports of sales and earnings published on the Johnson & Johnson web site for investors. (*Id.*, ¶ 9). [redacted]

VI. MYLAN'S INFRINGEMENT

Not surprisingly, the commercial success that TOPAMAX® achieved with Ortho-McNeil's nurturing has prompted Mylan and others to want to copy it. (*See* Lohrenz Dec., Ex. K). On December 24, 2001, Mylan filed an Abbreviated New Drug Application ("ANDA") seeking the FDA's approval to market its topiramate tablets. (Dkt. Entry #58, Final Pretrial Order, at p. 8, ¶ 26). Mylan received tentative approval from the FDA on April 23, 2003. (*Id.* at p. 9, ¶ 28). While Mylan initially was content to wait until the '006 patent expired before obtaining final approval to market its topiramate tablets, that changed in or around March 2004, when Mylan amended its ANDA to request FDA approval to market its topiramate tablets before the '006 patent expired. (*See id.*, ¶ 29). Ortho-McNeil responded by filing the present lawsuit in

order to protect its exclusive rights under the '006 patent. (*Id.*, ¶ 31; *see also* Lohrenz Dec. Ex. B, Complaint).

Mylan admittedly infringes the '006 patent under the claim construction adopted by the Court. Following a *Markman* hearing, the Court issued a Memorandum Opinion on claim construction holding that "the plain language of Claim 1 … may be properly construed to expressly claim topiramate." (Dkt. Entry #49, Mem. Opinion, at 20). In view of this claim construction, Mylan stipulated that "the proposed manufacture, use and sale of Mylan's topiramate product would infringe claims 1, 2, 4, 5, 6, 7, 8, 11 and 12 of the '006 patent," subject to Mylan's remaining defenses. (*See* Dkt. Entry #58, Final Pretrial Order at 10, ¶ 33).

VII. THE IMPENDING EXPIRATION OF THE STATUTORY STAY

Under the Hatch-Waxman Act, a patent holder cannot file suit until the generic company files an ANDA, or an amendment to its ANDA, seeking to market a generic copy of a patented drug prior to patent expiration. Once suit is filed, a 30-month stay is automatically entered which prevents the generic company from marketing its drug before the stay expires. 21 U.S.C. § 355(j)(5)(B)(iii). In this case, the 30-month statutory stay is set to expire on or about September 9, 2006. (*Id.*; *see also* Lohrenz Dec. Ex. C, Mylan Patent Amendment (specifying dates on which notices of Mylan's Paragraph IV Certification were received)) (filed under seal). Unless Ortho-McNeil's motion is granted, the FDA may at any time after that date convert its tentative approval of Mylan's ANDA to a final approval, clearing the way for Mylan to enter the market with a generic copy of Ortho-McNeil's TOPAMAX® tablets.

Because Ortho-McNeil is likely to prevail at trial, and because introduction of Mylan's generic product will irreparably harm Ortho-McNeil, Mylan should be enjoined from marketing its proposed topiramate tablets until the remaining issues in this case are resolved.

ARGUMENT

VIII. ALL FOUR PRELIMINARY INJUNCTION FACTORS WEIGH IN FAVOR OF ORTHO-MCNEIL'S MOTION.

As summarized above and explained further below, Ortho-McNeil's motion should be granted because the four preliminary injunction factors – likelihood of success on the merits, irreparable harm, balance of hardships, and the impact on the public interest – all favor Ortho-McNeil.

A. Ortho-McNeil Is Likely To Succeed On The Merits.

The first factor requires Ortho-McNeil to establish a "reasonable probability of eventual success" on the merits of its allegations that at least one claim of the '006 patent is infringed and not invalid.[3] *H.H. Robertson Co. v. United Steel Deck, Inc.*, 820 F.2d 384, 387 (Fed.Cir. 1987). As explained below, Ortho-McNeil is highly likely to succeed in demonstrating these propositions.

1. Mylan Admittedly Infringes The '006 Patent Under The Court's Claim Construction.

The Court has determined, following a *Markman* hearing, that "the plain language of Claim 1 … may be properly construed to expressly claim topiramate." (Dkt. Entry #49, Mem. Opinion, at 20). Mylan admittedly infringes claims 1, 2, 4-8, 11 and 12 of the '006 patent under this claim construction. (Dkt. Entry #58, Final Pretrial Order, at 10, ¶ 33).

2. Mylan's Obviousness Defense Lacks Substantial Merit.

The '006 patent is presumed valid and Mylan bears the ultimate burden of proving invalidity by clear and convincing evidence. 35 U.S.C. § 282; *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1365 (Fed.Cir. 2001). To demonstrate a likelihood

[3] Mylan also had asserted that the '006 patent was unenforceable due to inequitable conduct, but the Court dismissed Mylan's inequitable conduct defense after granting Ortho-McNeil's motion for partial summary judgment. (*See* Dkt. Entry #134, at 21).

of success, Ortho-McNeil must show Mylan's invalidity defenses "lack[] substantial merit" in light of these presumptions and burdens. *Tate Access Floors, Inc. v. Interface Architectural Resources, Inc.*, 279 F.3d 1357, 1365 (Fed.Cir. 2002) (citations omitted). Because of the presumption of validity, "if [Mylan] fails to identify any persuasive evidence of invalidity, the very existence of the patent satisfies [Ortho-McNeil's] burden on validity." *Purdue Pharma*, 237 F.3d at 1365.

Here, Mylan's obviousness arguments lack substantial merit in view of findings that the Court has already made in dismissing Mylan's inequitable conduct defense, and in view of the fatally flawed opinions of Mylan's experts, Dr. Laurens Anderson and Dr. Claudiu Supuran. Strong evidence of secondary considerations further confirms the non-obviousness of the '006 patent claims.

a. The Court's Prior Findings Show That Mylan's Obviousness Defense Lacks Substantial Merit.

On May 30, 2006, the Court granted Ortho-McNeil's motion for summary judgment dismissing Mylan's inequitable conduct defense. (*See* Dkt. Entry # 134, Opinion, at 21). In granting Ortho-McNeil's motion, the Court also addressed issues going to the very heart of Mylan's obviousness defense, specifically, whether Mylan had any evidence to show that a person of ordinary skill in the art would have had a motivation to make topiramate. To establish a threshold showing – called a "*prima facie* case" – that a chemical compound like topiramate is obvious, Mylan must show that the prior art *suggests the claimed compound* to someone skilled in the art, not merely that such a person would know how to make the compound if he or she set out to do so. *In re Deuel*, 51 F.3d 1552, 1559 (Fed.Cir. 1995) ("There must, however, still be prior art that *suggests the claimed compound* in order for a *prima facie* case of obviousness to be

made out.... A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out.") (emphasis added).

Here, the Court's opinion dismissing Mylan's inequitable conduct defense includes findings which establish that Mylan *cannot* show that someone skilled in the art would have had a motivation to make topiramate. The Court found no such motivation in the Jenkins and Shuman references on which Mylan's Dr. Anderson relies, concluding that those references "could not have supported a prima facie case of obviousness." (Dkt. Entry # 134, at 19-20) (underline in original). The Court also found Dr. Supuran's obviousness opinion based on the compound acetazolamide to be of "dubious" value, because he "assumes that one reasonably skilled in the art arrived at topiramate *by chance*, and does not appear to deal with whether or not one reasonably skilled in the art would be *motivated* to make topiramate based on acetazolamide or the acetazolamide testing." (*Id.* at 14, n.7) (emphasis in original).

Moreover, Prof. Samuel Danishefsky, an expert in organic chemistry and the synthesis of new drugs, confirms that Mylan's experts have completely failed to identify any evidence at all to show a motivation to make or use the claimed invention. (Declaration of Prof. Samuel J. Danishefsky in Support of Plaintiff's Motion for Preliminary Injunction ("Danishefsky Dec."), ¶¶ 5-8, 12-15, 19). Dr. Danishefsky explains that neither Dr. Anderson nor Dr. Supuran have performed a proper obviousness analysis, and that under a proper analysis, the invention claimed in the '006 patent would not have been obvious. (*Id.*, ¶¶ 16-19).

Thus, in view of the Court's findings and other evidence showing that Mylan cannot establish a motivation to make or use topiramate, Mylan's obviousness defense lacks substantial merit. *Deuel*, 51 F.3d at 1559; *In re Rouffet*, 149 F.3d 1350, 1355 (Fed.Cir. 1998).

b. Dr. Anderson Improperly Equates Dr. Maryanoff With A Person Of Ordinary Skill And Uses Dr. Maryanoff's Own Work To Reconstruct The Invention.

Mylan's obviousness defense also lacks substantial merit in view of Mylan's reliance on Dr. Anderson's erroneous obviousness analysis. Dr. Anderson's analysis includes at least two crucial errors, as discussed at length in the briefs in support of Ortho-McNeil's motion *in limine* to exclude the testimony of Mylan's experts. (*See* Dkt. Entry # 93, at 13-14; Dkt. Entry # 116 at 3-7). Specifically: (1) Dr. Anderson erroneously bases his obviousness analysis on the perspective of one of the inventors, Dr. Maryanoff, rather than the perspective of someone of ordinary skill; and (2) Dr. Anderson improperly relies on a hindsight reconstruction of Dr. Maryanoff's invention. (*See* Lohrenz Dec. Ex. D, Anderson Report at ¶¶ 11,12,16,17; *see also* Danishefsky Dec., ¶ 6). As explained in Ortho-McNeil's briefs, Congress and the Federal Circuit long ago rejected any approach that relies on the inventor's own work to show that an invention would have been obvious. *See Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed.Cir. 1986) (finding legal error in district court's obviousness determination that relied too heavily on the alleged opinion of an inventor); *see also Life Technologies, Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed.Cir. 2000) ("the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute"). The Federal Circuit instead requires that the patent challenger "must show reasons that the skilled artisan confronted with the same problems as the inventor and *with no knowledge of the claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed." *Rouffet*, 149 F.3d at 1357 (emphasis added).

Contrary to this requirement, Dr. Anderson merely recites what Dr. Maryanoff himself did, without considering whether those actions would have been obvious to a person of ordinary skill in the art. Specifically, Dr. Anderson states:

- "*Dr. Maryanoff became interested in the possibility of preparing inhibitors* of the enzyme fructose bisphosphatase (FBPase) .... *He thought such inhibitors might be useful* in controlling the level of blood sugar (glucose) in diabetic patients ...."

- "*Dr. Maryanoff suggested that the desired inhibitory properties might be present* in fructose derivatives having sulfamate groups ... in place of one or both of the phosphate groups ... of the natural substrate of FBPase."

- "*In his examination of the literature ..., Dr Maryanoff found* that two American research groups had generated adenosine 5'-sulfamates by reacting protected adenosine derivatives with sulfamoyl chloride."

- "*As a reactant for the preparation of his target compound, Maryanoff selected* the well-known derivative 2,3:45-di-O-isopropylidenefructopyranose ...."

(Lohrenz Dec. Ex. D, Anderson Report at ¶¶ 11,12,16,17 (emphasis added)).

Thus, Dr. Anderson "simply takes the inventor's disclosure as a blueprint for piecing together prior art to defeat patentability--the essence of hindsight." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 13771-72 (Fed.Cir. 2000). As a result, Dr. Anderson's obviousness opinion cannot support a substantially meritorious obviousness defense.

c. Dr. Supuran's Opinion That Claims 6-8 Would Have Been Obvious Is Fatally Flawed.

Claims 6-8 of the '006 patent are directed to anticonvulsant applications of the chemical compositions described in the other claims. (*See* Lohrenz Dec. Ex. A, '006 patent, claims 6-8). Mylan's obviousness defense for these claims lacks substantial merit for the additional reason that Mylan relies on the fatally flawed obviousness opinion of Dr. Supuran to support that defense. Dr. Supuran focuses on what he calls "the two most salient features" of topiramate's structure, namely, the sulfamate moiety (*i.e.*, the $-OSO_2NH_2$ group) and a lipophilic organic scaffold (the rest of the topiramate molecule). (Lohrenz Dec. Ex. E, Supuran Report, ¶ 14). Dr. Supuran asserts that these features would have made it *obvious to test* topiramate for biological activity. (Lohrenz Dec. Ex. E, Supuran Report, ¶15). Mylan gains nothing from Dr. Supuran's opinion, which is based on an approach that is both legally and factually incorrect.

On the law, Dr. Supuran relies on an erroneous obviousness standard. The obviousness statute requires a showing that the differences between the patented invention and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. §103. Dr. Supuran relies instead on an "obvious to test" standard that was specifically rejected by a predecessor court of the Federal Circuit. As that court explained, "'obvious to test' is a very different thing from obviousness of an invention." *In re Ehringer*, 347 F.2d 612, 618 (CCPA 1965) (reversing rejection of claims on obviousness grounds).

On the facts, Dr. Supuran mistakenly assumes that the features of topiramate's structure would have been "apparent" during the relevant time period of 1978-79. (Lohrenz Dec. Ex. E, Supuran Report, ¶15). Topiramate was unknown at that time, however, and Dr. Supuran could point to nothing in the prior art that would have led a person of ordinary skill in the art to topiramate in order to test it. (Lohrenz Dec. Ex. F, Supuran Dep. Tr. at 125:5-10, 131:22-135:3). Thus, contrary to Dr. Supuran's assumption, the features of topiramate would *not* have been apparent during the relevant time period because the compound itself was not available.

Consequently, Mylan's defense that claims 6-8 of the '006 patent would have been obvious lacks substantial merit for these additional reasons.

d. Secondary Considerations Confirm The Nonobviousness Of The Claimed Subject Matter.

Strong evidence of secondary considerations further demonstrates the nonobviousness of topiramate. Such secondary considerations are often the most probative evidence in the record. *Gambro Lunda AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579 (Fed.Cir. 1997). Here, the secondary considerations include unexpected results, skepticism of experts, commercial success, copying and industry recognition. For example:

Unexpected results: Topiramate's excellent anticonvulsant properties are unexpected, and could not have been predicted from the fact that it is a sulfamate of a sugar derivative. (Kupferberg Dec., ¶ 4). Topiramate also unexpectedly exhibits enhanced properties compared to known anticonvulsant sulfonamide compounds like acetazolamide, including topiramate's surprisingly different anticonvulsant mechanisms of action and the lack of tolerance to its anticonvulsant effects after long-term use. (Declaration of Michael D. Privitera, M.D., in Support of Plaintiff's Motion for Preliminary Injunction ("Privitera Dec."), ¶ 7).

Skepticism of experts: Dr. Harvey Kupferberg is a much-honored expert in the field of antiepileptic drug development with 30 years of experience in the Epilepsy Branch at NINDS. (Kupferberg Dec., ¶ 1). When he was first shown topiramate's structure, Dr. Kupferberg was extremely skeptical that it would exhibit any anticonvulsant activity at all, because he felt that too much of the compound's molecular weight (38%) was made up of oxygen. (*Id.*, ¶ 5). The fact that topiramate works as an effective anticonvulsant notwithstanding Dr. Kupferberg's initial skepticism is powerful evidence of nonobviousness. *United States v. Adams*, 383 U.S. 39, 52 (1966); *Environmental Designs, Ltd. v. Union Oil Co. of California*, 713 F.2d 693, 697-98 (Fed.Cir. 1983).

Commercial success: TOPAMAX® products, containing the active ingredient topiramate, are a commercial success for the reasons already stated in Section V above, and as further explained in the declaration of Seth Fischer filed herewith. (*See* Fischer Dec., ¶¶ 4-9).

Copying: At least eight companies have copied topiramate by submitting ANDAs for different topiramate formulations. (Lohrenz Dec., ¶¶ 12-13). All but two of these have respected the validity of the '006 patent and have not submitted paragraph IV certifications challenging the infringement or validity of the '006 patent. (*See id.*, ¶ 13).

Industry recognition: Dr. Bruce Maryanoff, one of the co-inventors of the '006 patent, has received numerous awards for his discovery of and subsequent work on topiramate. These awards have included the R.W. Johnson Medal for Research & Development in 1997; the American Chemical Society Award in Industrial Chemistry in 2003; and the "Heroes of Chemistry 2000 Award," also from the American Chemical Society, which was bestowed upon "chemical innovators who have promoted global human welfare." (Maryanoff Dec., ¶ 9).

Given the strong secondary considerations, presumption of validity and lack of a substantially meritorious obviousness defense, Ortho-McNeil is likely to succeed on the merits.

B. Mylan's § 112 Defenses Lack Substantial Merit.

Mylan next asserts that claims 6-8 of the '006 patent are invalid under 35 U.S.C. § 112, for lack of enablement and indefiniteness with respect to the term "anticonvulsantly effective amount." Ortho-McNeil already has provided several reasons why Mylan's § 112 defenses lack substantial merit, in the reply brief and supplemental reply brief in support of Ortho-McNeil's motion for summary judgment dismissing those defenses. (*See* Dkt. Entry ## 74, 138). Ortho-McNeil respectfully directs the Court to those briefs and the supporting materials referenced therein.

In addition, Mylan's § 112 defenses also lack substantial merit based on the supplemental expert opinion of Dr. Michael Privitera, which Ortho-McNeil was permitted to submit as a result of Mylan's belated disclosure of the bases for its § 112 defenses. (*See* Dkt. Entry #87, at 1-2). According to Dr. Privitera, clinical practitioners of ordinary skill in the art during the late 1970s and early 1980s would have known how to use the information disclosed in the '006 patent to determine an "anticonvulsantly effective amount" without undue or extensive experimentation. (Privitera Dec., ¶ 11). Moreover, in Dr. Privitera's opinion, the dosage information in the '006 patent is accurate and provides practitioners with proper direction to

conduct clinical studies, as demonstrated by the results of numerous clinical trials that found topiramate to be an effective anticonvulsant at dosages covering virtually the entire range that the patent discloses. (*Id.*, ¶¶ 12-14).

Not only do these opinions demonstrate beyond doubt that the '006 patent meets the requirements of § 112, but Mylan is precluded by Court order from offering any new evidence to rebut them. (*See* Dkt. Entry #87, at 3). Consequently, Mylan's § 112 defenses lack substantial merit and fail to raise any obstacle to Ortho-McNeil's likelihood of success on the merits.

IX. ORTHO-MCNEIL WILL BE IRREPARABLY HARMED IF MYLAN IS NOT ENJOINED FROM MARKETING ITS GENERIC COPY OF TOPAMAX®.

With Ortho-McNeil having shown a strong likelihood of success on the merits, the next factor considers the harm to Ortho-McNeil if Mylan is not preliminarily enjoined from infringing the '006 patent. Here, the harm stemming from Mylan's premature launch of a generic version of topiramate tablets would be extensive and irreparable. If no injunction is entered and Mylan launches its generic knockoff before the '006 patent expires, Ortho-McNeil will lose essentially the entire value of the last two years of the '006 patent term, plus an additional six months of FDA exclusivity that Ortho-McNeil would have received for studying topiramate's effects in pediatric patients. Such irreparable harm, in conjunction with Ortho-McNeil's clear showing of infringement and validity, weighs heavily in favor of the issuance of an injunction.

The effects of Ortho-McNeil's premature loss of its exclusive patent rights clearly will be catastrophic and beyond repair. [redacted]

[redacted] (*Id.*, ¶ 13). Based on industry experience and historical precedent, the lost sales, market share and profits would be permanent and irreparable. (*Id.*, ¶ 18). [redacted] there is a significant chance that Mylan – whose most recent fiscal year earnings before taxes were only $275 million – would lack the resources to compensate Ortho-McNeil for its injury. (Lohrenz Dec. Ex. G, Mylan 10-K, at 26).

But the harm to Ortho-McNeil does not end there. [redacted]

[redacted]

In addition, as mentioned above, Ortho-McNeil has started studies, requested by FDA, into the use of TOPAMAX® to treat children of ages 1-24 months. (Fischer Dec., ¶ 30). If the FDA accepts these studies, Ortho-McNeil would normally be entitled to a six-month period of market exclusivity beyond the expiration of the '006 patent. (*Id.*, ¶ 30). The purpose of this exclusivity is to encourage pharmaceutical companies, such as Ortho-McNeil, to conduct the expensive and time-consuming research necessary to determine whether or not certain drugs are appropriate for use in children. (*Id.*, ¶ 30). [redacted] (*Id.*, ¶ 31). Again, this loss would be cataclysmic and uncompensable.

For all of these reasons, Ortho-McNeil would be irreparably harmed if Mylan were permitted to launch its generic topiramate tablets before the present dispute is resolved. *See, e.g., Glaxo Group Ltd. v. Apotex Inc.*, 64 Fed.Appx. 751, 756, 2003 WL 1918246, at *4 (Fed.Cir. April 22, 2003) (affirming grant of preliminary injunction enjoining marketing of generic antibiotic drug; in finding irreparable harm, the Federal Circuit noted the "unquestionable loss of [Glaxo's] patent right" and evidence showing that generic entry would adversely affect Glaxo's price, profit and market share); *Pharmacia & Upjohn Co. v. Ranbaxy*

Pharmaceuticals, Inc., 85 Fed.Appx. 205, 214, 2003 WL 23016042 at *7 (Fed.Cir. Dec. 23, 2003) (upholding grant of preliminary injunction, including finding of irreparable harm based on "loss of the remaining relatively short life of the patent, irretrievable price and market erosion for the patented product, loss of current research opportunities resulting from loss of funding, … the speculative nature of damage assessments[,] and the difficulty of pursuing collection of that award ….").[4] Consequently, the second factor also favors granting Ortho-McNeil's motion for a preliminary injunction.

X. THE BALANCE OF HARDSHIPS DECIDEDLY FAVORS THE GRANTING OF INJUNCTIVE RELIEF.

The third factor balances the hardships to Ortho-McNeil from denying the present motion against the hardships to Mylan from granting the motion. *Hybritech*, 849 F.2d at 1457. Here, the balance tips distinctly in favor of Ortho-McNeil. The harm to Ortho-McNeil would be catastrophic and irreparable, as just explained. In contrast, when Mylan sought to introduce its infringing products here, it was well aware of the '006 patent from the FDA's Orange Book and its own Paragraph IV Certifications. (*See* Lohrenz Dec. Exs. I & J, Mylan's Notices of Paragraph IV Certification) (Ex. I has been filed under seal). Thus, to the extent Mylan's hardship results from its obligation to stop infringing Ortho-McNeil's patent, Mylan can only blame itself. *Rubbermaid Comm'l Prods., Inc. v. Contico Int'l, Inc.*, 836 F.Supp. 1247, 1258 (W.D.Va. 1993) (defendant's "knowing entrance into a risky venture lays much of the harm at its own doorstep"). As the Federal Circuit explained, "[o]ne who elects to build a business on a product found to infringe cannot be heard to complain if an injunction against continuing infringement destroys the business so elected." *Windsurfing Int'l, Inc. v. AMF Inc.*, 782 F.2d 995, 1003 n.12 (Fed.Cir. 1986).

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[4] Although the *Glaxo* and *Pharmacia* cases are not citable as precedent, the Federal Circuit's guidance, nevertheless, is instructive here.

The hardship to Mylan also is minimal here because granting Ortho-McNeil's motion for preliminary injunction will only leave Mylan in the same position as it was before the litigation, *i.e.*, excluded from the market for topiramate products. Any such hardship is further mitigated because this case is presently ready for trial. Thus, Ortho-McNeil's claims can be fully adjudicated on the merits within a matter of months, leaving ample time for Mylan to enter the market before the '006 patent expires in September 2008, in the event that Mylan ultimately should prevail in this litigation. *See Impax Labs.*, 235 F.Supp.2d at 396 (finding that balance of hardships tips in patentee's favor where infringer had not yet entered the market and the hardship to the alleged infringer would be only temporary).

In addition, Mylan has numerous other possible income sources and investment alternatives while it awaits resolution of the present case on the merits. According to a Mylan press release dated May 9, 2006, "Mylan currently has one of the most robust pipelines in the Company's history, with approximately 60 [ANDAs] pending before the [FDA], representing approximately $47.0 billion in calendar year 2005 brand sales." (Lohrenz Dec. Ex. H, 5/9/06 Press Release, at 1). Mylan also reported that, during its most recent fiscal year, it received 16 application approvals from the FDA, consisting of 11 final ANDA approvals, four tentative ANDA approvals and one supplemental ANDA approval for a new product strength. (Lohrenz Dec. Ex. G, Mylan 10-K, at 6). Mylan anticipates even further generic product opportunities over the next five years, during which a large number of high-value branded pharmaceutical patents are expected to expire, corresponding to U.S. annual brand sales of approximately $72.0 billion. (*Id.*) Thus, even if the Court grants the injunction requested by Ortho-McNeil, Mylan has many other opportunities to grow its generic business.

For all of these reasons, the balance of hardships decidedly favors Ortho-McNeil.

XI. THE PUBLIC INTEREST FAVORS ISSUANCE OF THE INJUNCTION TO PRESERVE ORTHO-MCNEIL'S PATENT RIGHTS.

Patents promote the constitutional public policy interest of advancing the progress of the useful arts. U.S. Const., art. 1, § 8, cl. 3. The patent laws are designed to strike a delicate balance between the need to promote technical advances through the inventive process and to preserve unimpeded competition in the marketplace. *Sears Roebuck & Co. v. Stiffel Co.*, 376 U.S. 225, 230-31 (1964). Thus, the public interest favors protecting valid patent rights. *See, e.g., H.H. Robertson*, 820 F.2d at 391; *Lilly v. Premo Pharmaceutical*, 630 F.2d at 138 ("Premo's claim that the public interest would be served by permitting it to enter the cephalexin market and sell at a lower price than currently offered by Eli Lilly is contrary to Congress' purposes in enacting the patent laws. … Instead, Congress has determined that it is better for the nation in the long-run to afford the inventors of novel, useful, and nonobvious products short-term monopolies on such products than it is to permit free competition in such goods.").

There is no question that the public interest will be served here by granting a preliminary injunction. In addition to the harm to the public interest stemming from the violation of Ortho-McNeil's patent rights, Mylan's launch of its generic topiramate tablets will [redacted]

[redacted]

On the other hand, there is no "critical public interest that would be injured by the grant of preliminary relief." *Hybritech*, 849 F.2d at 1458. Nothing in the Hatch-Waxman Act alters this conclusion. As the Federal Circuit recently explained, the Hatch-Waxman Act has not eliminated the exclusionary rights conveyed by pharmaceutical patents in favor of making more generic drugs available to the public, nor does the Act encourage or excuse infringement of valid pharmaceutical patents. *Pfizer v. Teva*, 429 F.3d at 1382. Thus, the mere fact that Mylan wishes to sell a lower-priced generic product "does not justify infringing a patent," nor does it make such an infringement in the public interest. *Id.*

Accordingly, the public interest also favors granting a preliminary injunction.

CONCLUSION

For all the foregoing reasons, Ortho-McNeil respectfully requests that the Court grant its motion for a preliminary injunction. In particular, Ortho-McNeil requests that Mylan be preliminarily enjoined from marketing and/or selling its topiramate products pending the entry of judgment in this litigation, and that the Court preliminarily order the effective date for FDA approval of Mylan's topiramate products to be a date which is not earlier than the date of expiration of the '006 patent.

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