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UNITED STATES DISTRICT COURT

FOR THE CENTRAL DISTRICT OF CALIFORNIA

SOUTHERN DIVISION

VALEANT PHARMACEUTICALS INTERNATIONAL, Plaintiff, v. MICHAEL O. LEAVITT, in his official capacity as Secretary of the U.S. Department of Health and Human Services, and ANDREW C. VON ESCHENBACH, M.D., in his official capacity as Commissioner of the Food and Drug Administration, Defendants.	NO. SA CV 08-00449-AG DEFENDANTS' OPPOSITION TO PLAINTIFF'S APPLICATION FOR A TEMPORARY RESTRAINING ORDER [REDACTED] No Hearing Scheduled Before the Honorable Andrew J. Guilford

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I. INTRODUCTION

At issue in this case is the approval by the Food and Drug Administration ("FDA") of a generic version of fluorouracil 5% (hereafter "5-FU"), a topical cream commonly used for treating multiple actinic keratoses ("AK"), a pre-cancerous skin growth caused by excessive sun exposure, and more rarely used to treat certain superficial basal cell carcinomas ("sBCC"). Plaintiff Valeant Pharmaceuticals International ("Valeant") manufactures the pioneer (or first) version of 5-FU and markets it under the brand name Efudex®. For over 35 years, Valeant has had a monopoly for this product, which it seeks to perpetuate with this lawsuit. However, FDA's decision to approve generic 5-FU is mandated by statute and falls squarely within the agency's scientific and technical expertise. Valeant's attempt to reverse this decision in order to preserve its own profits, while decreasing the availability of a low-cost, reliable, and safe pharmaceutical for treating serious conditions, should be rejected.

Because the alleged harm that Valeant will suffer if a TRO is not granted is minimal, and certainly no greater than what the generic manufacturer and proposed intervenor Spear Pharmaceuticals, Inc. ("Spear") will suffer if one is granted, the balance of harms does not weigh in Valeant's favor in this case. It is the government's understanding that Spear has already commercially launched its generic product, and granting the temporary or preliminary relief sought by Valeant would, in fact, alter the *status quo*. For these reasons, Valeant must establish a very strong likelihood of success on its claim that FDA's approval of generic 5-FU must be set aside – a burden Valeant has manifestly failed to meet. Contrary to Valeant's contentions, FDA approved generic 5-FU using appropriate bioequivalence standards and based upon a thorough and rigorous review of the scientific evidence. Thus, Valeant has no likelihood of success on the merits of its contention that Spear should have conducted an additional clinical trial to provide evidence of bioequivalence for sBCC.

Spear's application for approval of this generic product was pending before FDA for over three years – due in part to Valeant's submission to the agency of a citizen petition ("CP") which sought to block approval of Spear's product on the grounds that Spear should have conducted an additional clinical trial to show bioequivalence for sBCC. That petition, and this subsequent lawsuit, represent yet another instance in which a manufacturer of a pioneer drug product in fear of losing its lucrative monopoly has attempted to block generic competition by challenging the scientific basis upon which FDA has approved a generic drug product. *See, e.g.*, *Glaxo Group v. Leavitt*, AMD 06-469 (D. Md., Mar. 6, 2006) (Davis, J.) (unpublished opinion) (transcript attached)*; Schering Corp. v. FDA*, 51 F.3d 390 (3d Cir. 1995); *Schering Corp. v. Sullivan*, 782 F. Supp. 645 (D.D.C. 1992), *vacated as moot sub nom. Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993); *Somerset Pharms., Inc. v. Shalala*, 973 F. Supp. 443 (D. Del. 1997); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994). These challenges failed, as should this one. The courts in these cited cases have unequivocally held that scientific determinations as to the appropriate methodology required for approval of a generic drug product falls squarely within the broad discretion of the agency, which Congress has determined is in the best position to make such complex and technical scientific decisions.

In addition, Valeant has failed to establish that it would suffer irreparable harm in the absence of emergency injunctive relief – a critical prerequisite for the issuance of a TRO or other preliminary relief. REDACTED

Valeant is a large multi-national company with a product portfolio of some 350 brands and total revenues of close to $900 million. *See* http://www.valeant.com/aboutValeant/index.jspf; Valeant Pharmaceuticals International 2007 Annual Report at 110, 113, *available at*

http://www.valeant.com/fileRepository/investorRelations/annualReports/annual_07.pdf. Because only a small percentage of Valeant's worldwide sales revenues (about 8%) is derived from sales of all formulations of Efudex (cream and solution), and because Valeant will be sharing the market with Spear for only one of those formulations (cream), it will suffer virtually no injury at all, let alone irreparable injury, from the denial of a TRO or other preliminary injunctive relief pending resolution of this action on the merits. *See* Valeant Pharmaceuticals International 2007 Annual Report at 9, 110, 113, *available at* http://www.valeant.com/fileRepository/investorRelations/annualReports/annual_07.pdf. By contrast, every day that the marketing of generic 5-FU – whose performance FDA has found to be equivalent to Efudex – is halted, American consumers lose a less expensive alternative to a more costly drug, and FDA's mandate to approve generic products that meet statutory requirements is hampered. Moreover, when the alleged harm to Valeant is compared against that of Spear – whose product has been approved after meeting all statutory and regulatory requirements – the balance does not tip in Valeant's favor. For these reasons alone, Valeant's request for a TRO should be denied.

Indeed, Valeant's claim of harm is belied by its dilatory tactics in initiating this suit. FDA denied Valeant's citizen petition and approved Spear's application on April 11, 2008. Spear reportedly began commercially marketing its product that same day. Nevertheless, Valeant waited two full weeks to commence this action. It was not until the afternoon of Friday, April 25 that Valeant – with no prior notice to either FDA or Spear – suddenly raced into court with its eleventh-hour request for emergency relief.[1] And, as demonstrated below, Valeant offers no plausible

[1] Moreover, despite repeated requests, it was not until approximately 11:54 p.m. (EDT) on Saturday, April 26 that Valeant served complete, unredacted copies of its papers upon the government. Because Valeant's principal argument concerning the critical irreparable injury factor was redacted from the briefs and affidavits originally

justification to refute FDA's scientific and technical conclusion that Spear's application for generic 5-FU meets the statutory requirements for approval, or to undermine FDA's decision that it was not necessary to conduct an additional clinical trial for the sBCC indication.

For all of these reasons, as set forth more fully below, Valeant's motion for a TRO should be denied. At a minimum, the Court should afford the parties an adequate opportunity to fully brief the issues Valeant has raised. Indeed, any consideration of the merits of Valeant's claims must await the preparation and submission of the administrative record, without which defendants cannot fully respond to, and the Court cannot adequately consider, Valeant's allegations. The Court should therefore either deny Valeant's TRO outright and set a briefing schedule on its request for preliminary injunctive relief, or hold the motion in abeyance pending submission of the administrative record and full briefing by the parties.

II. STATEMENT OF FACTS

A. Statutory and Regulatory Background

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing a new drug application (NDA) containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. § 355(a), (b).

The Drug Price Competition and Patent Term Restoration Act of 1984 (known as the "Hatch-Waxman Amendments"), codified at 21 U.S.C. §§ 355 and 35 U.S.C. §§ 156, 271, 282, permits manufacturers to submit abbreviated new drug applications ("ANDAs") for approval of generic versions of approved drug products. 21 U.S.C. § 355(j). ANDA applicants generally need not submit clinical

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served, the government was severely prejudiced in its ability to evaluate and respond to Valeant's claim of harm.

data to demonstrate the safety and efficacy of the product, as in an NDA. Rather, an ANDA relies on FDA's previous findings that the product approved under the NDA is safe and effective. The FDCA sets forth in detail the information an ANDA must contain. *See* 21 U.S.C. § 355(j)(2)(A). The Hatch-Waxman Amendments were enacted to balance encouraging innovation in drug development with increasing the availability of lower cost generic drugs. *See* H.R. Rep. No. 98-857 (Part I), 98th Cong., 2d Sess. at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647-48; *see also, e.g.*, *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 139 (3d Cir. 1987).

Under the Hatch-Waxman Amendments, in order to obtain FDA approval, an ANDA must include information showing that the generic drug product is bioequivalent to the pioneer drug product. 21 U.S.C. § 355(j)(2)(A)(iv), (j)(4)(F); 21 C.F.R. §§ 314.127(a)(6)(i), 314.94(a)(7). A drug is considered to be bioequivalent if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug . . . ." 21 U.S.C. § 355(j)(8)(B)(i). For drugs not absorbed into the bloodstream (like Efudex), "the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(C).

The FDCA gives FDA significant discretion in determining appropriate methodologies to demonstrate bioequivalence, which FDA regulations define as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." 21 C.F.R. § 320.1(e). Although the FDCA does not require clinical studies for generic approvals, it has been FDA's policy to require a clinical study to demonstrate

bioequivalence for topical drugs such as 5-FU for which there is no suitable pharmacokinetic or pharmacodynamic endpoint, *i.e.*, the amount of active ingredient of the drug cannot be measured in the blood or urine. Chang Dec. Ex. A ("CP Response") at 5. To that end, FDA's regulations provide that applicants must conduct bioequivalence testing "using the most accurate, sensitive, and reproducible approach available among" the following approaches, in descending order of accuracy, sensitivity, and reproducibility: (1) in vivo or in vitro testing in humans measuring the concentration of the active ingredient in the blood; (2) in vivo testing in humans measuring urinary excretion of active moiety; (3) in vivo testing in humans measuring an appropriate active pharmacological effect of the active moiety over time; (4) clinical trials, especially for dosage forms intended for topical preparations; (5) in vitro tests acceptable to FDA that ensures human in vivo bioavailability; or (6) any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence. 21 C.F.R. § 320.24(b).

B. Factual Background

1. Valeant's NDA

Efudex is a topical cream for the treatment of multiple actinic keratoses ("AK") and superficial basal cell carcinomas ("sBCC"). In 1970, FDA approved Valeant's NDA (NDA 16-831) for Efudex Cream, 5%, and Solution, 2% and 5%, for the topical treatment of AK. AKs are pre-cancerous growths in the epidermis and may protrude into the upper dermis. AKs may progress to squamous cell carcinoma. In 1976, FDA approved Efudex Cream, 5%, and Solution, 5%, for the treatment of sBCC when conventional methods are impractical, such as with multiple lesions or difficult treatment sites.[2]

[2] As described in the label, the sBCC approval of Efudex is limited to use in specific circumstances. The labeling further states that safety and effectiveness of Efudex in other indications have not been established, and more specifically that Efudex has not been proven effective in other types of basal cell carcinomas (*i.e.*, non

2. Spear's ANDA

Spear submitted an ANDA (ANDA 77-524) for a generic version of 5-FU cream on December 22, 2004, which FDA approved on April 11, 2008. In order to be approved, Spear's product had to meet all requirements under 21 U.S.C. § 355(j), including showing that it was bioequivalent ("BE") to Efudex.

FDA required Spear to perform a clinical study to demonstrate BE because there is no suitable pharmacokinetic or pharmacodynamic endpoint for topical drugs such as 5-FU. FDA determined that a controlled clinical trial demonstrating BE between Spear's and Valeant's 5-FU for treatment of AK would also adequately establish BE for sBCC. FDA's regulation provides that such studies are particularly appropriate for demonstrating BE for topical products intended to deliver the active moiety locally, such as 5-FU. Spear's clinical study demonstrated not just that Spear's product was as effective in treating AK as Valeant's product, but also that Spear's active ingredient would be available to the site of action for both the AK and sBCC indications to a comparable extent as Valeant's product.

3. Valeant's Citizen Petition

On December 21, 2004, Valeant submitted a citizen petition to FDA that questioned the reliability of a single BE study in the treatment of AK, noting that Efudex Cream, 5%, is also approved for sBCC. Valeant submitted additional correspondence to the docket on October 21, 2005, April 3, 2006, and July 13, 2006. On November 7, 2006, Hogan & Hartson LLP submitted comments in support of the petition. The law firm of Rothwell, Figg, Ernst and Manbeck, P.C., submitted comments to the docket in opposition to the citizen petition on September 16, 2005, January 3, 2006, and May 5, 2006.

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superficial). Accordingly, it is not surprising that, as it appears from submissions to the Valeant citizen petition docket, the vast majority of prescriptions written for Efudex are for the AK indication.

FDA denied Valeant's petition on April 11, 2008, in a comprehensive, 11-page letter. That same day, FDA approved Spear's ANDA for generic 5-FU based upon the agency's determination that Spear's product met the statutory and regulatory requirements for approval set forth at 21 U.S.C. § 355(j). Two weeks later, on April 25, 2006, Valeant filed this suit for injunctive and declaratory relief pursuant to the Administrative Procedure Act ("APA"). Valeant claims that FDA's approval of Spear's ANDA for generic 5-FU was arbitrary, capricious, an abuse of discretion, and contrary to law and seeks, *inter alia*, a TRO compelling FDA to suspend approval of Spear's ANDA.

For the reasons set forth below, Valeant's TRO application should be denied.

III. ARGUMENT

A. Valeant Has Failed to Show Any Likelihood of Success.

The ordinary standard for issuance of a TRO is basically the same standard used for a preliminary injunction. Injunctive relief is an extraordinary remedy of a drastic nature. Plaintiffs have the burden of proving their entitlement to such extraordinary relief. *Orantes-Hernandez v. Thornburgh*, 919 F.2d 549, 557-558 (9th Cir. 1990). The requirements for a preliminary injunction are discussed in *Stanley v. Univ. of S. Cal.*, 13 F.2d 1313, 1319 (9th Cir. 1994). Preliminary injunctive relief is available if a party meets one of two tests: "(1) a combination of probable success and the possibility of irreparable harm, or (2) serious questions are raised and the balance of hardships tips in its favor." *Arcamuzi v. Continental Air Lines, Inc.*, 819 F.2d 935, 937 (9th Cir. 1987). "These two formulations represent two points on a sliding scale in which the required degree of irreparable harm increases as the probability of success decreases." *Id.* Under both formulations, to prevail on its application for a temporary restraining order, plaintiff must demonstrate both a fair chance of success on the merits of its complaint, and a significant threat of irreparable harm. *Superior Servs. v. Dalton*,

851 F. Supp. 381, 384-385 (S.D.Cal. 1994); *see also Stanley v. Univ. of S. Cal.*, 13 F.2d at 1319 (a showing of a fair chance of success on the merits is an "irreducible minimum.")

A prohibitory injunction preserves the status quo. *Johnson v. Kay*, 860 F.2d 529, 541 (2d Cir. 1988). A mandatory injunction "`goes well beyond simply maintaining the status quo pendente lite [and] is particularly disfavored.'" *Anderson v. United States*, 612 F.2d 1112, 1114 (9th Cir. 1979) (quoting *Martinez v. Mathews*, 544 F.2d 1233, 1243 (5th Cir. 1976)). In this case, Valeant is seeking more than maintaining the status quo. On April 11, 2008, the FDA already approved an abbreviated new drug application ("ANDA") which was submitted by Spear under section 505(j) of the Federal Food, Drug, and Cosmetic Act ("Act"), 21 U.S.C. § 355(j), for a generic version of the EFUDEX (fluorouracil) Cream. *See* Ex. A at n.2, April 11, 2008 Letter, attached to the Request for Judicial Notice file herewith. The TRO sought by Valeant would require that the FDA undo its approval of Spear's application to produce a generic drug. Thus, Valeant seeks mandatory injunctive relief. This raises plaintiff's burden for obtaining injunctive relief even higher. When a party seeks mandatory injunctive relief that "goes well beyond maintaining the status quo pendente lite, courts should be extremely cautious about issuing a preliminary injunction." *Stanley v. Univ. of S. Cal.*, 13 F.3d at 1319 (quoting *Martin v. Int'l Olympic Comm.*, 740 F.2d 670, 675 (9th Cir. 1984)). When mandatory injunctive relief is requested, the district court should deny such relief unless the facts and law clearly favor the moving party. *Id.*

As discussed below, plaintiff has not demonstrated even a fair chance of success on the merits or irreparable injury. The facts and law do not favor the moving party. Accordingly, because Valeant has failed to meet the stringent standards for this extraordinary relief, this Court should deny Valeant's TRO application because plaintiff has not met the requirements for issuance of a TRO.

1. Valeant Has Not Shown Any Likelihood of Success on the Merits of Its Administrative Procedure Act Claim.

(a) FDA's Administrative Decision is Entitled to Deference.

FDA's administrative decisions are subject to review by the Court under the Administrative Procedure Act ("APA"), and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). Indeed, "'there is a presumption in favor of the validity of the administrative action.'" *Bristol-Myers*, 923 F. Supp. at 216 (quoting *Ethicon, Inc. v. FDA*, 762 F. Supp. 382, 386 (D.D.C. 1991)). The reviewing court must consider whether the agency's decision was based upon consideration of the relevant factors and whether there has been a clear error of judgment. *Overton Park*, 401 U.S. at 416. However, "under this narrow scope of review, '[t]he court is not empowered to substitute its judgment for that of the agency.'" *Bristol-Myers*, 923 F. Supp. at 216 (quoting *Overton Park*, 401 U.S. at 416). In applying the arbitrary and capricious standard, the court reviews the administrative record assembled by the agency and does not undertake its own fact finding. *See, e.g., Camp v. Pitts*, 411 U.S. 138, 142 (1973).

When, as here, an agency's decision is based on evaluation of scientific information within the agency's area of technical expertise, its decisions are traditionally accorded great deference. *Sw. Pa. Growth Alliance v. Browner*, 121 F.3d 106, 117 (3d Cir. 1997); *Bristol-Myers*, 923 F. Supp. at 216 (citing *Fed. Power Comm'n v. Fla. Power & Light Co.*, 404 U.S. 453, 463 (1972)). Courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'" *Troy Corp. v. Browner*, 120 F.3d 277,

283 (D.C. Cir. 1997) (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)); *see also Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992) ("The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise.")

Such deference has repeatedly been applied in cases under the FDCA. *See, e.g.*, *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) ("FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug . . . . We therefore defer to its reasonable findings."); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us."); *Tri-Bio Laboratories, Inc. v. United States*, 836 F.2d 135, 142 (3d Cir. 1987) ("in evaluating scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful consideration by this court").

(b) Courts Have Consistently And Specifically Held That FDA Has Broad Discretion When Making Drug Approval Determinations.

As already noted, the agency's scientific judgments are entitled to the highest level of deference; this is particularly so where Valeant challenges FDA's selection of the appropriate testing necessary to demonstrate that the conditions for approval have been met. See *Solite Corp. v. EPA*, 952 F.2d 473, 489-90 (D.C. Cir. 1991); *see also Nat'l Ass'n of Metal Finishers v. EPA*, 719 F.2d 624, 657 (3d Cir. 1983) ("the choice of scientific data and statistical methodology to be used is best left to the sound discretion of the [agency]"), *rev'd on other grounds*, 470 U.S. 116 (1985). Indeed, courts have repeatedly and consistently upheld FDA's scientific judgment in making BE determinations such as Valeant seeks to challenge in this case.

Schering, for instance, involved a challenge to an FDA regulation that pertained to methods of determining BE for non-systemically effective generic drugs (such as the 5-FU cream at issue here). Schering contended that the regulation impermissibly construed the statute by permitting FDA to determine BE by examining the availability of the drug at the site of application, rather than by examining absorption. 51 F.3d at 393. The court rejected this argument, however, finding "no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of ANDA approval." *Id.* at 399. As the court forcefully explained, "The FDA is the agency charged with implementing the Food, Drug, and Cosmetic Act as amended. Its judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us." *Id.*

Similarly, in *Bristol-Myers*, an innovator drug manufacturer sought a preliminary injunction against FDA's approval of a generic competitor, arguing that FDA had impermissibly determined BE based solely on *in vitro* testing rather than requiring both *in vivo* and *in vitro* testing as it had required in the past. 923 F. Supp. at 216. The court denied the preliminary injunction request, recognizing FDA's broad discretion in making BE determinations and holding that FDA may, "as part of its expertise and exercise of discretion, . . . waive certain testing procedures." *Id.* at 217. Noting that the case involved "the agency's scientific judgments concerning what testing methods are needed to establish bioequivalence," the Court explained: "While the 1984 amendments did make the bioequivalence requirement mandatory . . . there is nothing in the legislative history to indicate that Congress intended to restrict FDA's historical discretion to decide how that requirement would be met." *Id.* at 218 (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 649-50 (D.D.C. 1992).

In *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994), Fisons' request for a preliminary injunction against approval of generic competitors was also

denied. Like Bristol-Myers, Fisons contended that FDA could not waive *in vivo* testing to demonstrate BE for the inhaled product there at issue. The court held, however, that FDA had broad discretion in making BE determinations and could, "as part of its expertise or discretion in making that [BE] finding, . . . elect to waive certain testing procedures where the make-up of pioneer and generic products are similar in all pertinent ways." *Id.* at 865. Finding nothing in the statute or legislative history "that mandates that the FDA undertake a given methodology" in determining BE, *id.* at 866, the court concluded that FDA was free to exercise its discretion "based on a 'reasonable and scientifically supported criterion, whether [FDA] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs or dosage forms." *Id.* (quoting in part *Schering Corp. v. Sullivan*, 782 F. Supp. at 651); *see also Somerset Pharms., Inc. v. Shalala*, 973 F. Supp. 443, 453 (D. Del. 1997) ("measuring bioequivalence is a matter of scientific judgment, falling squarely within the FDA's discretion").

Most recently, in *Glaxo Group v. Leavitt*, AMD 06-469 (D. Md., Mar. 6, 2006) (Davis, J.) (unpublished), the court rejected a similar challenge to an FDA BE determination in which the manufacturer of Flonase sought to block the approval of a competing generic nasal spray. In an unpublished bench ruling, Judge Davis refused to enter preliminary injunctive relief, holding that FDA's approval of the generic nasal spray fell squarely within the agency's scientific and technical expertise and that FDA had used scientifically valid methods to determine BE between the generic and innovator products. *See* Transcript (attached hereto).

Courts have deferred to FDA's scientific judgment in other contexts as well. Indeed, Courts are especially reluctant to disturb FDA's drug approval decisions and have consistently rebuffed scientific challenges brought by innovator manufacturers seeking to enjoin the agency's approval of generic competitors. *See, e.g.*, *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1324 (D.C. Cir. 1998)

("FDA's 'judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.'") (quoting *Schering*, 51 F.3d at 399); *Warner Lambert Co. v. Shalala*, 202 F.3d 326, 328 (D.C. Cir. 2000) (affirming denial of preliminary injunction where innovator sought to overturn FDA approval generic competitor that did not have the same dosage form as innovator's product); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499-1500 (D.C. Cir. 1996) (upholding FDA determination that generic product did not need to have labeling identical to innovator).

In stark contrast to this unbroken line of decisions according deference to FDA's scientific judgments, Valeant cites only *one* case in which it claims that a court reversed FDA on a question of science. *See* Mem. at 11-12 (discussing *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484 (D.C. Cir. 1995) ("*A.L. Pharma I*"). In *A.L. Pharma I*, however, the court simply held that FDA had not adequately explained its decision approving the competitor, but more importantly, given the present posture of this case, it explicitly refused to vacate or enjoin the approval. 62 F.3d at 1492. Moreover, Valeant ignores the subsequent history of that case, which ultimately resulted in the D.C. Circuit affirming FDA's BE determination, albeit while remanding a second time for further explanation from the agency. *Alpharma v. Leavitt*, 460 F. 3d 1, 9 (D.C. Cir. 2006) ("*Alpharma II*"). The court refused to overturn the agency's approval of the ANDA at issue because, as in this case, "no significant harm would result from allowing the approval to remain in effect pending the agency's further explanation." *Id.* at 12 (quoting *A.L. Pharma I*, 62 F.3d at 1492).

Thus, even if, after full briefing on the merits, this Court were to find that FDA had failed in some significant way to explain its scientific decision so as to enable the Court to conclude that FDA's action was the "product of reasoned decisionmaking," *id.*, the proper course would be to remand the matter to FDA for further explanation – not to overturn the approval of Spear's 5-FU ANDA.

Because no "significant harm" will result from the approval and marketing of Spear's generic product, FDA's approval of Spear's ANDA should remain in place even if this Court should ultimately find FDA's explanation of its action on Valeant citizen's petition wanting. *Id.*

(c) FDA's Approval of Spear's 5-FU ANDA was Proper

In this case, FDA properly determined that Spear's ANDA met the conditions for approval, and FDA's determination that Spear's 5-FU product is bioequivalent to Efudex is supported by the record and by FDA's citizen petition response, as described below. Some of Valeant's arguments, however, raise issues that FDA believes will be best addressed by reference to the administrative record underlying Spear's ANDA approval and FDA's citizen petition response. Because FDA could not possibly compile its administrative record in the short period of time allotted for responding to Valeant's motion for a temporary restraining order, FDA seeks a schedule from this Court that will afford it a reasonable time-frame within which to assemble and submit the administrative record and more fully brief the matters here at issue.

(1) FDA's determination that Spear's 5-FU is bioequivalent to Efudex is not arbitrary and capricious.

(a) FDA required an appropriate clinical study to demonstrate bioequivalence.

As noted above, the FDCA grants FDA significant discretion in determining appropriate methodologies to demonstrate BE. Although the statute does not require clinical studies, it has been FDA's policy to require a clinical study to demonstrate BE for topical drugs such as 5-FU for which there is no suitable pharmacokinetic or pharmacodynamic endpoint, *i.e.*, the amount of active ingredient of the drug cannot be measured in the blood or urine. CP Response at 5. For such drugs, the FDCA allows FDA to "establish alternative, scientifically valid

methods to show BE if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(C).

In this case, consistent with 21 C.F.R. § 320.24(b)(4), FDA determined that a controlled clinical trial with BE endpoints demonstrating BE between Spear's and Valeant's 5-FU to treat AK would also adequately establish BE for sBCC. FDA's regulation provides that such studies are particularly appropriate for demonstrating BE for topical products intended to deliver the active moiety locally, such as 5-FU. Spear's clinical study demonstrated not just that Spear's product was as effective in treating AK as Valeant's product, *but was also evidence that Spear's active ingredient was available to the site of action for both the AK and sBCC indications to a comparable extent as Valeant's product, i.e.*, that Spear's product is BE to Valeant's product for both the AK and sBCC indications. As noted, the only issue in this case is the propriety of FDA's BE determination. FDA's reliance on that clinical trial is consistent with the FDCA, agency regulations, and agency precedent approving generic versions of other topical drugs with more than one indication based on clinical trials involving only one indication. *See, e.g.*, CP Response at 4 (noting FDA approval of generic topical corticosteroid drug products for multiple indications without requiring a BE test for every indication).

FDA's approval decision, as explained in the CP response, focused on the most important factors that could affect the availability of the active ingredient at the site of action. First, FDA concluded that both conditions for which 5-FU is indicated have the same site of action: the epidermis and the upper dermis. FDA thus rejected Valeant's contention that the site of action for treating AK and sBCC differed because the two conditions occurred in different layers of the epidermis, noting that the epidermis is only 0.06 to 0.8 millimeters thick, and that Valeant had presented no evidence to support the conclusion that if the formulation provided

the active ingredient to one layer of the epidermis, it would not also be available in the other layer. CP Response at 6-7. Valeant does not appear to challenge that determination in this case.

Second, FDA explained that the epidermal layers were often thickened with AK, but not for sBCC. Thus, FDA concluded that if topical 5-FU penetrated the skin to treat AK, it would also penetrate the skin to treat sBCC, "which usually involves a compromised stratum corneum," *i.e.*, an epidermal layer that would be more easily penetrable. *Id*. at 8.

As part of this analysis, FDA determined that certain differences in formulation for these 5% topical 5-FU products can reasonably be concluded not to affect the amount of active ingredient that is made available to the site of drug action:

> Both the reference Efudex (5-FU) Cream, 5%, and Efudex Solution, 5%, have been approved for the treatment of AK and sBCC. These products have combined labeling, which provides no restrictions on the use of one 5% formulation or the other to treat these conditions. Thus, the presumption is that they may be used interchangeably to treat either condition. This argues against some critical formulation issue that could meaningfully affect the ability of these topical 5-FU products to deliver drug to the site of action for the approved uses.

Id. In other words, because Valeant's approved Efudex solution and cream, which have very different formulations, can be used interchangeably to treat both AK and sBCC, FDA recognized that the precise formulation of a 5% product is not a critical factor in efficacy (and thus BE), particularly once BE for use in treating AK has been shown through comparative clinical trials. *Id.*; *see also id.* at 10 (noting that sBCC clinical studies in reference drug pooled the data together for the 5% solution and 5% cream). FDA focused on other factors that were critical for determining whether a clinical trial for AK would also establish BE for sBCC: the

site of action, and whether the differences in indication would result in any significant difference between the amount of drug available to the active site. Here, FDA properly concluded that, to the extent that the differences in indication could result in different availability of the active ingredient at the site of action, a BE test for AK (for which topical delivery of the drug to the site of action was potentially more difficult because of thickening) would adequately ensure that, if a study demonstrated BE for treating AK (and thus similar bioavailability), it would provide assurance that the active ingredient would also penetrate the skin sufficiently to treat sBCC. *Id.* at 8.

Third, FDA addressed Valeant's argument that BE had to be shown using the most difficult-to-treat condition. FDA explained that:

> The ideal clinical endpoint bioequivalence study should be conducted in the indication which will be the most sensitive in discriminating formulation differences. The optimal indication is generally one with the least variability in the disease state and expected course of disease and for which the recommended duration of treatment is the same for all patients. This is often, but not necessarily, the most difficult-to-treat condition. Furthermore, the shortest duration of treatment for which a significant treatment effect is expected is likely to be the most discriminatory, since extending the duration of therapy may result in a higher probability of success for all study groups and less ability to differentiate between products.

Id. at 10.

Because the recommended treatment duration for AK is 2 to 4 weeks, and for sBCC is at least 3 to 6 weeks, FDA concluded that "[t]he sBCC indication may not be the indication that is most sensitive in discriminating formulation differences between 5-FU products," particularly in view of the excellent success rates for treatment of both AK and sBCC. *Id.* In addition, FDA observed that

formulation did not appear to be "especially significant in evaluating the efficacy of 5-FU in the treatment of sBCC" based on the pooling of data for 5-FU solution and 5-FU cream in the reported clinical studies for sBCC. *Id.* For all of these reasons, as stated: "[t]he agency concludes an AK bioequivalence study is sufficient to establish that the generic topical 5-FU formulation will be available in the epidermis and the upper dermis to act on both AK and sBCC lesions to an extent that is comparable to Efudex Cream." *Id.*

(2) Valeant's challenge to FDA's approval lacks merit.

Valeant argues that FDA's decision to require a BE test for AK – and not for sBCC – is arbitrary and capricious because clinical trials have not been able to detect the amount of active ingredient necessary to effectively treat AK, citing FDA's discussion of a study in which a 0.5% cream was found to be as effective as a 5% cream in treating AK. Mem. at 4 (citing CP Response at 8). Valeant further argues that greater levels of 5-FU are necessary to treat sBCC, and thus a BE test for AK does not establish BE for sBCC.

Valeant's argument is fatally flawed, however, because it depends on the proposition that formulation is critical for assessing BE for 5-FU, as well as unsupported speculation that sBCC requires significantly more active ingredient for efficacy. Under Valeant's theory, if treating sBCC requires a greater amount of active ingredient than AK (a proposition that is not supported by the record), there is a *hypothetical possibility* that Valeant's formulation of the product provides the required amount for treating both indications, but Spear's formulation of the product does not. Thus, while Spear's formulation may show BE in treating AK, it would not necessarily be bioequivalent for treating sBCC. Therefore (in Valeant's view), Spear must conduct an additional clinical trial to establish BE for sBCC.

FDA, however, has concluded that formulation differences are not critical for assessing 5-FU BE of 5% topical products for these indications. As explained

above, FDA's conclusion is based in part on the fact that Efudex 5% cream is used interchangeably with Efudex 5% solution, the labeling on those two products provides no restrictions on the use of the type of formulation for treating those conditions, and the approval of both Efudex 5% solution and Efudex 5% cream for sBCC was based on pooled results from studies using the two different formulations. CP Response at 8, 10. "This argues against some critical formulation issue that could meaningfully affect the ability of these topical 5-FU products to deliver drug to the site of action for the approved uses." *Id.* at 8. Morever, and as will be more apparent when FDA files an administrative record in this case, FDA did not find the differences in inactive ingredients between Spear's and 5-FU's formulations to be significant.

Valeant has pointed to nothing credible in the record to establish that sBCC requires a greater amount of active ingredient for successful treatment. Valeant states that FDA "admits" that "[s]ignificantly more fluorouracil is needed to combat cancer than to treat sun-damaged skin" based on FDA's statement in the approved labeling for Efudex, which is sold in both 2% and 5% concentrations: "Only the 5% strength is recommended." Mem. at 4-5. Notwithstanding Valeant's assertion, however, FDA's finding that the 5% strength is effective for treating sBCC is not an affirmative determination that other strengths are not effective for treating sBCC. Thus, no record evidence supports Valeant's argument that FDA has "admitted" that more active ingredient is required to treat sBCC than AK, nor has that fact been conclusively determined.

Rather than focusing on formulation, given the interchangeability of the 5% solution and cream formulations for treating both AK and sBCC, FDA focused its BE determination on the factors that it considered significant for determining whether there was a "significant difference between the drug and the listed drug in safety and therapeutic effect," as the statute requires. 21 U.S.C. § 355(j)(8)(C). Those factors, as described above, include determination of the site of drug action

and any differences in ability of the drug to reach that active site based on the indication – and Valeant does not seriously challenge any of those conclusions in this case. Rather, Valeant speculates that slight differences in inactive ingredient formulation between two creams *could* be significant, despite the fact that FDA has already concluded that major differences between cream and solution formulations are not significant for purposes of effectiveness, and thus are not expected to be significant for BE. Valeant's speculation – unsupported by any evidence in the record – does nothing to undermine the deference due the agency's approval in this case, and does not justify the extraordinary relief that Valeant seeks.

Moreover, as described above, FDA properly concluded that the AK BE test would adequately discriminate between the effectiveness of the Spear and Valeant formulations and provide sufficient evidence by which the agency could conclude that "the generic topical 5-FU formulation will be available in the epidermis and the upper dermis to act on both AK and sBCC lesions to an extent that is comparable to Efudex cream." CP Response at 10. Valeant challenges that conclusion by arguing that the AK BE test cannot distinguish even a 10-fold difference between formulations, based on a study cited by FDA in the citizen petition response that concluded that a 0.5% cream was as effective as a 5% formulation.[3] Mem. at 5. In that discussion, FDA cites the 0.5% /5% study in the context of explaining that, for AK, the stratum corneum is often thickened – and hence "could provide a greater barrier to cutaneous penetration of topical 5-FU than the compromised stratum corneum in sBCC." CP Response at 8. Based on the overall discussion of studies involving AK treatment, FDA could conclude that,

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[3] Valeant raises what it characterizes as an independent argument that FDA relied on "false and contradictory" assertions regarding whether an AK BE test would be able to detect a significant difference between the generic and brand drugs. Mem. at 6-7. That argument is essentially the same as Valeant's claim that FDA's reliance on the AK BE test is arbitrary and capricious, and thus will not be separately addressed here.

to the extent that there were any barriers to reaching the active site, those barriers were more significant for AK than for sBCC, and thus a BE test for AK would provide assurance that there would also be sufficient skin penetration to treat sBCC. FDA's discussion of the 0.5% - 5% study is *not* an admission that a BE test for AK cannot adequately distinguish between formulations. FDA believes that this point will be further clarified to the Court when FDA files the administrative record.[4]

(3) FDA's decision is consistent with its regulations.

Valeant argues that FDA's decision violates its own regulations because, in Valeant's view, a BE test for AK is not the most "accurate, sensitive, and reproducible approach available," as required by 21 C.F.R. § 320.24(a). Mem. at 5. To the extent that Valeant challenges FDA's reliance on a BE test only for the AK indication, FDA disagrees, for all of the reasons set forth in the citizen petition response and described above. FDA made clear in its citizen petition response why it selected a BE test for AK rather than for sBCC, and why FDA believed that such a test would be adequately sensitive to allow the agency to conclude that the active ingredient would be bioavailable to the site of action to act on both AK and sBCC lesions comparably to Efudex. CP Response at 10. Moreover, this is precisely the type of issue for which FDA, as the agency entrusted to implement the FDCA, should be accorded particular deference.

Valeant also argues that FDA has an additional burden to allow only the

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[4] To the extent that FDA will be relying on the record instead of the four corners of the citizen petition response in defending its approval decision in this case, it bears noting that the agency is fully empowered to approve a drug even before issuing a response to a citizen petition when a petition has been filed. *See Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 162 (D.D.C. 2006) (denying plaintiff's motion for a temporary restraining order requiring FDA to rule on a citizen petition before approving a generic application). FDA stands behind its drug approval decision here based on the record that will be made available to this Court as soon as practicable, even independently of FDA's reliance on the citizen petition response.

most "rigorous" clinical trials because FDA's regulations make clear that clinical trials are the "least accurate" of the different methods used to demonstrate BE. Mem. at 6 n.7 (citing 21 C.F.R. § 320.24(b)(4)). Notably, however, FDA's regulation makes clear that any of the methodologies set forth in paragraph (b) are "acceptable," 21 C.F.R. § 320.24(b), and that, even though clinical trials are the "least accurate" of the general approaches, such trials are particularly appropriate for showing BE for topical drugs, such as 5-FU. Thus, Valeant can get no traction by arguing that FDA must require an additional clinical trial simply because clinical trials may not be the best methodology for showing BE for other types of drugs. Rather, as set forth in the citizen petition response, FDA properly chose to rely on clinical trial data to demonstrate BE for the AK indication, as appropriate for topical drugs such as 5-FU. That method is fully "acceptable" to demonstrate BE in accordance with FDA's regulations, and FDA's reliance on that method provides no basis for turning the marketplace on its head pending further briefing.

(4) FDA properly considered Valeant's submissions to the record.

Valeant asserts that "FDA also failed to consider significant information and expert testimony bearing on the accuracy, sensitivity, and reproducibility of the BE testing that it relied upon in connection with Spear's ANDA." Mem. at 7. Specifically, Valeant contends that FDA has violated its duties under the APA by not addressing three expert statements that Valeant submitted to the citizen petition docket. *Id.* at 8.

FDA need not specifically acknowledge each expert who submitted information to FDA in its citizen petition response, particularly where, as here, FDA has provided a reasoned explanation for its decision. *See Tourus Records, Inc. v. DEA*, 259 F.3d 731, 737 (D.C. Cir. 2001) (nothing more than a "brief statement" is necessary, as long as the agency explains "why it chose to do what it did."). Regardless, and contrary to Valeant's assertion, FDA did consider the

general arguments presented by Valeant's three experts. For example, FDA specifically referenced the declaration of Howard I. Maibach, MD, in its citizen petition response, and referred to Dr. Maibach's view that there are little data on the amount of active ingredient delivered to AK or sBCC action sites. CP Response at 7 n.26. FDA rejected D. Maibach's view that a comparative clinical study carried out on individuals with AK would not support a finding of BE for sBCC, for all of the reasons stated in the response. *Id.* at 8-10. Similarly, FDA addressed Valeant's general argument, as presented in Dr. Tran's declaration, regarding the site of action of AK vs. sBCC, and concluded that the site of action (epidermis) did not affect the BE analysis. *Id.* at 6-7. FDA also addressed the general argument, as presented in Dr. Fisher's declaration, that AK clinical trials may not be sensitive enough to detect differences between the generic and brand products. As described above, FDA determined that AK was in fact the appropriate indication to use for determining BE because AK treatment is of a shorter duration and because both indications have an excellent success rate. *Id.* at 10. Moreover, to the extent that the declarations may have raised specific issues that are not addressed in the CP response, many of those issues were in fact considered by FDA in the underlying administrative record, which FDA will provide to this Court as soon as it is feasible. Thus, FDA's approval decision, as reflected in the citizen petition response and the record, adequately accounts for the voluminous submissions and arguments raised by Valeant in the citizen petition proceeding.

2. Valeant Has Not Shown Any Likelihood of Success Under the Mandamus Act.

Valeant asserts claims under the Mandamus Act, 28 U.S.C. § 1361. Compl. at 4, ¶ 9. Valeant has failed to satisfy the standards required for a grant of mandamus. The Mandamus and Venue Act provides district courts with jurisdiction over "any action in the nature of mandamus to compel an officer or

employee of the United States or any agency thereof to perform a duty owed to the plaintiff." 28 U.S.C. § 1361. Courts have consistently recognized that "the remedy of mandamus is a drastic one, to be invoked only in extraordinary situations." *Allied Chemical Corp. v. Daiflon, Inc.*, 449 U.S. 33, 34 (1980); *Barron v. Reich*, 13 F.3d 1370, 1374 (9th Cir. 1994); *Stang v. IRS*, 788 F.2d 564, 565 (9th Cir. 1986). Accordingly, a writ of mandamus is appropriate only when "(1) the plaintiff's claim is 'clear and certain'; (2) the defendant official's duty to act is ministerial, and 'so plainly prescribed as to be free from doubt'; and (3) no other adequate remedy is available." *Barron v. Reich*, 13 F.3d at 1374; *Fallini v. Hodel*, 783 F.2d 1343, 1345 (9th Cir. 1986). Furthermore, even if plaintiff is able to meet these requirements, it is well-established that mandamus "is to be granted only in the exercise of sound discretion." *13th Regional Corp. v. U.S. Dept. of Interior*, 654 F.2d 758, 760 (D.C. Cir. 1980) (citing *Whitehorse v. Illinois Central R.R. Co.*, 349 U.S. 366 (1955)). "Thus the case must be found by a court to be clear and compelling on both legal and equitable grounds for a writ to issue." *13th Regional Corp.*, 654 F.2d at 760.

In the instant action, Valeant has simply failed to establish that the FDA owes it a "ministerial" duty. Valeant is unable to point to any language in the Act or elsewhere that requires defendants to withdraw the FDA's final approval of Spear's application to produce a generic drug. *See 13th Regional Corp.*, 654 F.2d at 760; *Independence Mining Co., Inc. v. Babbitt*, 105 F.3d 502, 508 (9th Cir. 1997). The FDA's actions in this case have been reasonable and justified, and do not involve a nondiscretionary, ministerial duty.

Moreover, the facts in this case do not warrant the drastic remedy of mandamus. *See In Re Barr Laboratories, Inc.*, 930 F.2d 72, 74 (D.C. Cir. 1991) (declining to exercise equitable powers even where a ministerial duty has been withheld). Accordingly, Valeant has not shown any likelihood of success under the Mandamus Act.

3. Valeant Has Not Shown Any Likelihood of Success For Declaratory Relief.

Valeant asserts claims for declaratory relief under 28 U.S.C. §§ 2201-2202. Compl. at 4, ¶ 9. Valeant's request for declaratory relief is meritless. *See Samuels v. Mackell*, 401 U.S. 66, 73 (1971) (The Supreme Court found that where a federal officer is the defendant "the discretionary relief of declaratory judgment is . . . the practical equivalent of specific relief such as injunction or mandamus.") "Such equivalence of effect dictates an equivalence of criteria for issuance." *Id*. Therefore, plaintiff must still meet the injunctive relief requirements to warrant declaratory relief. In the instant action, as stated above, plaintiff has failed to show any likelihood of success for injunctive relief, and therefore, plaintiff has not shown any likelihood of success on plaintiff's claim for declaratory relief.

B. Valeant Has Failed to Show That it Will Suffer Irreparable Harm Absent Preliminary Injunctive Relief.

Not only has Valeant failed to establish a likelihood of success on the merits of its claims, it has failed to demonstrate that it will suffer irreparable harm absent injunctive relief or that the balance of hardships tips in its favor. Courts insist that only *irreparable* harm justifies the issuance of a preliminary injunction. *Hughes Network Systems v. Interdigital Communications Corp.*, 17 F.3d 691, 694 (4th Cir. 1994). Indeed, "[t]he *sine qua non* of granting any preliminary injunctive relief is a clear and convincing showing of irreparable injury to the plaintiff." *Experience Works, Inc. v. Chao*, 267 F. Supp. 2d 93, 96 (D.D.C. 2003). Irreparable injury is a "very high standard." *See Varicon Int'l v. OPM*, 934 F. Supp. 440, 447 (D.D.C. 1996); *Bristol-Myers*, 923 F. Supp. at 220. The injury alleged must be certain, great, actual, and imminent, *Wisconsin Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985), and it must be "more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff." *Mylan v. Thompson*, 139 F. Supp. at 27

(quoting *Gulf Oil Corp. v. Dept. of Energy*, 514 F. Supp. 1019, 1026 (D.D.C. 1981)).

As the Ninth Circuit has explained, "[a] plaintiff must do more than merely allege imminent harm sufficient to establish standing; a plaintiff must *demonstrate* immediate threatened injury as a prerequisite to preliminary injunctive relief." *Caribbean Marine Servs. Co., Inc. v. Baldrige*, 844 F.2d 668, 674 (9th Cir. 1988) (emphasis in original); *see also Colorado River Indian Tribes*, 776 F.2d at 849 (Ninth Circuit has "long since determined that speculative injury does not constitute irreparable injury") (quoting *Goldie's Bookstore, Inc. v. Superior Court*, 739 F.2d 466, 472 (9th Cir. 1984)). Additionally, preliminary injunctive relief may only be granted when the moving party has demonstrated a significant threat of irreparable injury, irrespective of the magnitude of the injury. *See Big Country Foods, Inc. v. Board of Educ.*, 868 F.2d 1085, 1088 (9th Cir. 1989).

It is well settled that mere economic loss in and of itself does not constitute irreparable harm. *Wisconsin Gas*, 758 F.2d at 674; *Mylan Pharms., Inc. v. Thompson*, 207 F. Supp. 2d 476, 485 (N.D. W. Va. 2001); *Boivin v. US Airways, Inc.*, 297 F. Supp. 2d 110, 118 (D.D.C. 2003); *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d at 42; *Bristol-Myers*, 923 F. Supp. at 220. "Mere injuries, however substantial, in terms of money, time and energy necessarily expended" are inadequate. *Wisconsin Gas*, 758 F.2d at 674 (quoting *Virginia Petroleum Jobbers Ass'n v. FPC*, 259 F.2d 921, 925 (D.C. Cir. 1958)); *Colorado River Indian Tribes*, 776 F.2d at 850. Even irrecoverable economic loss does not rise to the level of irreparable harm unless the financial injury is so great as to "cause extreme hardship to the business, or even threaten destruction of the business." *Gulf Oil*, 514 F. Supp. at 1025; *see also Experience Works*, 267 F. Supp. 2d at 96 ($21.1 million reduction in funding is serious financial blow, but one frequently faced by other similar entities, and not an economic loss that threatens survival of the business); *Sociedad Anomia Vina Santa Rita v. Dep't of Treasury*, 193 F. Supp. 2d

6, 14 (D.D.C. 2001) ("financial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business").

Notwithstanding this well-established doctrine, economic loss is precisely the type of harm that Valeant alleges it will suffer in the absence of a TRO. *See* Mem. at 14.

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Valeant is a large, multi-national company with product sales exceeding $785 million in 2007 and total revenues of more than $872 million. *See* Valeant Pharmaceuticals International 2007 Annual Report at 110, 113, available at http://www.valeant.com/fileRepository/investorRelations/annualReports/annual_07.pdf; *see also* http://www.valeant.com/aboutValeant/index.jspf. Furthermore, Valeant is by no means a one-product company. *Cf. Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 29 (D.D.C. 1997) (recognizing injury to one-product line company). Valeant markets more than 350 products in over 100 countries, with some 3,000 employees worldwide. *See* http://www.valeant.com/aboutValeant/index.jspf. REDACTED only a small percentage of Valeant's worldwide revenues (about 8%) are actually derived from sales of Efudex.

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there is no reason to expect that those sales would be eliminated, or even materially reduced, considering that Valeant will continue to market its own "generic" version of Efudex (both cream and solution) in competition with Spear and because Valeant will be sharing the market with Spear for only one of those formulations (cream). Indeed, Valeant's irreparable harm analysis fails to take into account or even acknowledge the fact that, in apparent anticipation of competition with generics, Valeant already markets its own "authorized generic" version of Efudex (*i.e.*, "unbranded" 5-FU that is "identical to the branded products except for the use of the brand name"). Coles Dec. at ¶ 5. The impact of generic Efudex competition can hardly constitute irreparable harm in view of both the minimal impact of lost Efudex sales on Valeant's total sales picture and the fact that Valeant

will compete with Spear in the generic market as well, thus minimizing any potential loss of market share.

Valeant further asserts, without any support, that it will face injury to its reputation among patients and physicians if Spear's generic product is substituted for Efudex and it fails to provide the expected relief. Mem. at 13-14. Valeant speculates that patients will associate Efudex with any substandard experience with Spear's product, to the detriment of Valeant's reputation. Valeant has offered no evidence to suggest that Spear's generic 5-FU product will fail to provide the expected relief, however, and FDA's determination that Spear's 5-FU is bioequivalent to Efudex is directly contrary. Nor has Valeant offered any evidence to suggest that users would associate Spear's generic product with Valeant's Efudex. Valeant's speculative claim of reputational marketplace injury thus does not meet the standard of irreparable harm. *See Bristol-Myers*, 923 F. Supp. at 221 (rejecting Bristol's allegation that its reputation would suffer if a generic were approved, noting that there was nothing in the record to support such a claim). *Somerset*, 973 F. Supp. at 455 (rejecting Somerset's claim that its reputation would be harmed if patients were injured by generic products, noting that Somerset had "offered little more than a bare assertion" in support of this claim). *See also Direx*, 952 F.2d at 812 ("the required irreparable harm must be neither remote nor speculative, but actual and imminent").

Finally, any financial harm that Valeant may suffer in the absence of preliminary injunctive relief will be matched, if not exceeded, by the financial harm that generic manufacturer Spear will suffer by being wrongfully deprived of its right to market a competing generic product during the period that the TRO is in effect. *See Serono*, 158 F.3d at 1326; *Bristol-Myers*, 923 F. Supp. at 221; *see also Glaxo v. Heckler*, 623 F. Supp. 69, 71 (E.D.N.C. 1985) ("Glaxo cannot show that any injury it suffers without a decree outweighs Lilly's injury suffered by issuance of such a decree"). For all of these reasons, Valeant cannot meet its burden of

establishing that it will suffer irreparable injury in the absence of a TRO or that the balance of hardships weighs in its favor.

C. The Balance fo Harms Weighs Against Entry of a TRO.

Considerations of harm to others and the public interest – the third and fourth TRO factors – likewise militate strongly against Valeant's request for emergency injunctive relief. Indeed, Valeant has made no showing that any harm it would suffer in the absence of a TRO outweighs the potential harm to other parties or to the public. Although FDA has no commercial stake in the outcome of this litigation, FDA is the government agency charged with implementing the statutory scheme governing the approval of generic drugs. As such, FDA's interest coincides with the public interest. *Serono*,158 F.3d at 1326; *Mylan Pharmaceuticals, Inc. v. Shalala*, 81 F. Supp. 2d at 41-45.

Valeant argues that FDA will suffer no harm if a TRO issues because the agency took over three years to approve Spear's ANDA and it would not therefore be harmed by the entry of a brief, 10-day restraining order. Mem. at 15. Valeant's argument, however, ignores the fact that the agency has already determined pursuant to its statutory authority that Spear's generic 5-FU product is bioequivalent to Valeant's product, and satisfies the statutory criteria for approval, and that the product is being marketed. A TRO in these circumstances would therefore *alter* the *status quo* by forcing FDA to suspend its approval of an already *approved* ANDA – a step that would also upset ongoing commercial transactions among Spears and its distributors, as well as pharmacists, doctors, and patients. Indeed, a court-ordered suspension of a lawfully approved drug is qualitatively very different from any delay in market entry pending FDA's review of an ANDA. Whereas the review period for an ANDA ensures the public of the integrity of the drugs that are approved, suspending the approval of a lawfully approved generic drug would thwart Congress's generic drug approval scheme and FDA's lawful implementation of that scheme and directly undermine the public interest in the

availability of safe, effective, and affordable generic alternatives to brand name drugs.

Valeant's argument that Spear would not be harmed by the entry of a TRO is equally misconceived. Mem. at 15. Valeant maintains that Spear, like FDA, would suffer no hardship during the brief pendency of a TRO because Spear's ANDA was pending before the agency for years and, according to Valeant's understanding, Spear has not yet begun marketing its product. Contrary to Valeant's understanding, however, Spear represents that it began marketing its product on April 11, the day it received FDA approval. The entry of a TRO suspending Spear's 5-FU approval in such circumstances would obviously have seriously adverse consequences for both Spear and the consuming public. In these circumstances, the balance of harms plainly weighs against the entry of interim injunctive relief, and Valeant's motion for a TRO should therefore be denied.

IV. CONCLUSION

Plaintiff's TRO application should be denied for all of the foregoing reasons.

DATED: April 28, 2008.

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