WINSTON & STRAWN LLP
Gail J. Standish (SBN: 166334)
e-mail: gstandish@winston.com
Peter E. Perkowski (SBN: 199491)
e-mail: pperkowski@winston.com
333 South Grand Avenue, 38th Floor
Los Angeles, California 90071-1543
Telephone: (213) 615-1700
Facsimile: (213) 615-1750

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
Steven Lieberman (admission *pro hac vice* pending)
Minaksi Bhatt (SBN: 151312 – reactivation pending)
Lisa N. Phillips (admission *pro hac vice* pending)
1425 K Street, N.W.
Washington, D.C. 20005
Telephone: 202-783-6040
Facsimile: 202-783-6031

Attorneys For Defendant-Intervenor
SPEAR PHARMACEUTICALS, INC.

UNITED STATES DISTRICT COURT

FOR THE CENTRAL DISTRICT OF CALIFORNIA

SOUTHERN DIVISION – SANTA ANA

VALEANT PHARMACEUTICALS INTERNATIONAL,

Plaintiff,

v.

MICHAEL O. LEAVITT, et al.,

Defendants.

and

SPEAR PHARMACEUTICALS, INC

Defendant-Intervenor.

Case No. 8:08-cv-00449-AG-AGR

The Honorable Andrew J. Guilford

MEMORANDUM OF POINTS AND AUTHORITIES OF SPEAR PHARMACUETICALS, INC. IN OPPOSITION TO VALEANT'S APPLICATION FOR A TEMPORARY RESTRAINING ORDER

Supporting Declarations of K.L. Spear and Minaksi Bhatt Filed Concurrently Herewith

Date: None set
Time: None set
Place: Room 10D

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MEMORANDUM OF POINTS AND AUTHORITIES

Defendant-Intervenor Spear Pharmaceuticals, Inc. ("Spear") respectfully submits this memorandum of points and authorities in opposition to the application of Valeant Pharmaceuticals International ("Valeant") for a temporary restraining order asking this Court to substitute its scientific judgment for that of the U.S. Food and Drug Administration ("FDA") and set aside the FDA's approval of the pharmaceutical product that Spear has been selling since April 11, 2008.

INTRODUCTION AND SUMMARY OF ARGUMENT

On April 11, 2008, the FDA approved Spear's Abbreviated New Drug Application ("ANDA") for a fluorouracil product bioequivalent to Valeant's Efudex product. Spear's ANDA had been pending before the FDA since January 2005. That same day, the FDA also denied Valeant's Citizen Petition, which had been pending before the FDA since December 2004.

Immediately following its receipt of FDA approval, Spear began selling its fluorouracil product. Declaration of Dr. K.L. Spear ("Spear Dec.") ¶ 19.

Valeant waited 14 days after the approval of Spear's application before filing its application for emergency relief with this Court.

This is the first time that the Valeant Efudex product has faced generic competition.

Valeant's lawsuit against the FDA seeking to set aside the approval of a competitive generic product is a fairly standard tactic that has been used for years by certain brand name pharmaceutical companies in an effort to block or delay generic competition. It is also a tactic that has met with virtually universal failure as court after court has held that the FDA's scientific determinations regarding the appropriate methodology required for approval of a generic drug product fall squarely within the broad discretion of the agency, and, therefore, enjoy special deference from a

reviewing court.[1] Valeant's application does not discuss any of those cases. As demonstrated below in Section II, in those cases, as in this one, the FDA's decisions were based on scientific determinations, and as a result, the FDA's evaluation "is entitled to a high level of deference from this court." Biovail Corp., 519 F. Supp. 2d at 47 (quoting Serono Labs., 158 F.3d at 1320) (internal quotations omitted); Allergan, Inc. v. Crawford, 398 F. Supp. 2d 13, 22 (D.D.C. 2005) (internal quotations and citation omitted). See also Zeneca, 213 F.3d at 170; Schering Corp., 51 F.3d at 399; Somerset Pharms., 973 F. Supp. at 453; Upjohn, 938 F. Supp. at 444; Bristol-Myers Squibb Co., 923 F. Supp. at 220; Fisons, 860 F. Supp. at 966-67.

Nor is this TRO application the only tactic Valeant has used in an effort to delay generic competition. As discussed below in Section C, Congress has recognized that the Citizen Petition process has been used by certain pharmaceutical companies for the improper purpose of delaying FDA approval of generic products, as evidenced by the recent introduction, passage and enactment into law on September 27, 2007 of amendments to the Federal Food, Drug, and Cosmetic Act directing the FDA not to

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[1] See, e.g., Zeneca, Inc. v. Shalala, 213 F.3d 161 (4th Cir. 2000) (ANDA approval upheld based on the FDA's scientific assessment and application of its express regulations); Warner-Lambert Co. v. Shalala, 202 F.3d 326 (D.C. Cir. 2000) (ANDA approval upheld based on FDA's determinations and regulations regarding the definition of a "dosage form"); Serono Labs. v. Shalala, 158 F.3d 1313 (D.C. Cir. 1998) (ANDA approval upheld based on FDA's determination that in vitro testing was sufficient to demonstrate bioequivalency); Schering Corp. v. FDA, 51 F.3d 390, 399 (3d Cir. 1995) (ANDA approval upheld because, although bioequivalence is required by statute, Congress did not intend "to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of ANDA approval"); Biovail Corp. v. FDA, 519 F. Supp. 2d 39, 47 (D.D.C. 2007) (ANDA approval upheld based on the FDA's "scientific research and judgment" regarding the generic drug's safety and effectiveness and determination that the proposed labeling was proper); Somerset Pharms. v. Shalala, 973 F. Supp. 443, 453 (D. Del. 1997) (ANDA approval upheld based on the FDA's wide discretion in what types of testing are required to demonstrate bioequivalence); Upjohn Co. v. Kessler, 938 F. Supp. 439, 444 (W.D. Mich. 1996) (denying request for a preliminary injunction prohibiting the FDA from approving applicant's ANDA based on the FDA's safety analysis and determinations); Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 220 (D.D.C. 1996) (ANDA approval upheld based on the FDA's wide discretion regarding the type of testing required to demonstrate bioequivalence); Fisons Corp. v. Shalala, 860 F. Supp. 859 (D.D.C. 1994) (ANDA approval without submission of certain in vivo testing upheld).

delay approval of ANDAs based on the filing of a Citizen Petition. See Food and Drug Administration Amendments Act of 2007 § 914(a), 21 U.S.C. § 355(q).

Here, two weeks after the FDA approved the Spear ANDA, and two weeks after Spear began selling its generic equivalent to Efudex cream, Valeant requests that this Court second-guess the reasoned and well-articulated scientific determination reached by FDA after more than **three years** of consideration. Efudex cream was first approved in 1970 and until Spear launched its product on April 11, 2008, U.S. consumers have never had a true generic alternative to that product. Spear respectfully requests that this Court recognize Valeant's real purpose here – to further hamper Spear's efforts to bring an economical generic alternative to the public – and that Valeant's application for a TRO be denied.

Valeant's discussion of the scientific merits is also seriously misleading. In the very first page of its brief, Valeant defines actinic keratosis ("AK") simply as a "form of sun-damaged skin." Valeant Br. at 1. Valeant uses this false and misleading definition in an effort to trivialize the clinical trial that the FDA found to be scientifically acceptable. In fact, the American Academy of Dermatology describes actinic keratosis as "cutaneous neoplasms. . .on sun damaged skin. These premalignant lesions are usually a consequence of long-term solar radiation . . . actinic keratosis must be treated to prevent their conversion to squamous cell carcinoma." See Spear Dec. ¶ 9, Ex. 2.

Valeant also omits from its TRO brief the fact that 98% of Efudex prescriptions are written for patients having AK, not sBCC. Spear Dec. ¶ 11. Indeed, in its brief, Valeant describes Efudex as "the top selling topical treatment for patients with a form of skin cancer called superficial basal cell carcinoma" and says that it "is also approved to treat" AK (Valeant Br. at 1), suggesting that sBCC is the principal approved medication. In fact, Valeant's own FDA-approved product label rebuts this. The Efudex product label states that Efudex "is recommended for the topical treatment of multiple actinic or solar keratosis. In the 5% strength it is also useful in the

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treatment of superficial basal cell carcinomas when conventional methods are impractical. . ." Spear Dec. ¶ 7, Ex. 1.

STATUTORY AND REGULATORY BACKGROUND

Valeant's motion for a temporary restraining order relates to the statutory provisions of the Federal Food, Drug, and Cosmetic Act (the "FDCA") and the agency regulations that pertain to approvals of new drug applications ("NDAs" or "innovator" drugs) and abbreviated new drug applications ("ANDAs"). See 21 U.S.C. § 301 et. seq. (2005).

Under the FDCA an NDA must contain, among other things, clinical studies demonstrating that the drug is safe and effective. See 21 U.S.C. § 355(b)(1). The procedures for obtaining FDA approval of generic drugs are set forth in the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98- 417, 98 Stat. 1585, 21 U.S.C. § 355(j) (the "Hatch-Waxman Amendments"). In the Hatch-Waxman Amendments, Congress recognized the strong public interest in stimulating generic competition for brand-name patented drugs immediately upon expiration of relevant patents and created a streamlined procedure for the FDA to approve generic drugs more quickly. "Congress sought to get generic drugs into the hands of patients at reasonable prices – fast." In re Barr Labs., Inc., 930 F.2d 72, 76 (D.C. Cir. 1991).

As part of the streamlined generic drug approval process mandated by Congress, ANDAs do not have to include separate clinical data showing safety and efficacy of the drug, but instead may rely on the safety and efficacy data in the corresponding innovator NDA. In order to obtain the FDA's approval, an ANDA must demonstrate, *inter alia*, that the generic drug is "bioequivalent" to the corresponding innovator drug. See 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.R.F. §§ 314.127(a)(6)(i), 314.94(a)(7).

Bioequivalence is established by proving that "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," for drugs that are absorbed into the blood stream. See 21 U.S.C.

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§ 355(j)(8)(B)(i). For drugs that are not absorbed into the bloodstream, such as topical ointments (including Efudex), Congress has expressly given the FDA authority to "establish alternative, scientifically valid methods to show bioequivalence." See 21 U.S.C. § 355(j)(8)(C). Under this statutory provision, the FDA has the authority to permit an ANDA applicant to use any methods the FDA deems appropriate for the determination of bioequivalence of non-systemic drugs as long as the "the alternative methods are expected to detect a significant difference between the [generic] drug and the listed drug in safety and therapeutic effect." Id.

The provision of the FDCA granting FDA express authority to develop alternative methods of establishing bioequivalence for non-systemic (i.e., locally-acting) drug products like Efudex was enacted by Congress as part of The Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 ("MMA"). See 21 U.S.C. 355(j)(8)(C). This amendment codified the approach set forth in the FDA's regulation regarding the determination of bioequivalence for drugs not intended to be absorbed into the bloodstream, as well as the nearly two decades old practice with respect to these types of drugs. 21 C.F.R. § 320.24(b)(6).

Prior to commencing clinical testing to support an ANDA submission, a prospective applicant can communicate with the FDA and agree to "the parameters and design . . . of a bioavailability and bioequivalence stud[y] of a drug." 21 U.S.C. § 355(j)(3)(C). The plan agreed to cannot be changed unless "a substantial scientific issue essential to determining the safety and effectiveness of the drug has been identified after the testing has begun." 21 U.S.C. § 355(j)(3)(C)(ii).

FACTUAL BACKGROUND

A. Efudex (Fluorouracil Cream, USP 5%)

Efudex, fluorouracil cream, USP 5%, was first approved in 1970. Declaration of Alexandra Coles ("Coles Dec."), ¶ 3. Moreover, the patents applicable to the active ingredient in Efudex expired long ago. Since its approval date over thirty-five years

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ago, and the expiration of the applicable patents more than thirty years ago, until Spear's April 11, 2008 approval, there has never been a third party generic alternative to this product.

Valeant is an international pharmaceutical company with 2007 annual sales totaling nearly $786 million. See Declaration of Minaksi Bhatt in Support of Spear's Opposition to Valeant's Application for a Temporary Restraining Order ("Bhatt Dec."), Ex. 3 at p. 8. Valeant's annual sales of Efudex in 2007 were $71.7 million, less than 10 percent of its total company revenue. Id.

According to the Efudex package insert, the product is approved for and "indicated" in the treatment of actinic keratosis ("AK") and is also "useful" in the treatment of superficial basal cell carcinoma ("sBCC") when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. Spear Dec. ¶ 17. AK is a lesion on the epidermis, the outer layer of the skin, that is considered the earliest visually detectable stage in the development of skin cancer. Spear Dec. ¶ 8. sBCC is a skin cancer, also localized in the epidermis. Spear Dec. ¶ 10. Like AK, sBCC is usually caused by chronic sun exposure. Id.

Over 98% of the prescriptions written for Efudex® are used for patients with AK, not with sBCC. Id. ¶ 11.

B. Spear's ANDA For Fluorouracil Cream, USP 5%

For ANDAs with multiple uses, the FDA requires that only one indication need be studied to prove bioequivalence. During the fluorouracil product's development phase, beginning in June 1999, Spear consulted directly with the FDA in an effort to ensure that the clinical trial performed in support of the proposed ANDA was correctly designed and would be performed in accordance with the rigorous standards required. Spear Dec., ¶ 12. Because Efudex is used overwhelmingly for AK, Plaintiffs proposed a clinical trial in the treatment of AK, and the FDA agreed that such a trial would prove bioequivalence to the brand product with respect to both indications, AK and sBCC. Id.

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After the preliminary clinical study plan was approved, and, the specified studies were completed, Spear submitted its Abbreviated New Drug Application ("ANDA") on January 6, 2005. Spear Dec. at ¶ 13. The ANDA has been reviewed by the FDA's Bioequivalence Division and its statistical staff with respect to the Chemistry, Labeling and Clinical Trial information. Id. at ¶ 14. Moreover, as a result of the Citizen Petition filed by Valeant, the ANDA has been through an even more rigorous secondary statistical review, and Spear and Valeant together filed with the FDA a total of seven submissions in connection with the Citizen Petition. Spear Dec. ¶ 15.[2] Review of the Spear ANDA took 39 months, 22 months more than the average approval time for ANDA's. Id.

C. The Citizen Petition Process

Congress has recognized that the Citizen Petition process has been used by certain pharmaceutical companies for the improper purpose of delaying FDA approval of generic products, as evidenced by the recent introduction, passage and enactment into law on September 27, 2007 of amendments to the Federal Food, Drug, and Cosmetic Act directing the FDA not to delay approval of ANDAs based on the filing of a Citizen Petition. See Food and Drug Administration Amendments Act of 2007 § 914(a), 21 U.S.C. § 355(q). Remedying past abuse of the Citizen Petition process was a primary motivation for passage of the legislation, as evidenced by the following comments from the legislative history related to legislation before Congress at the time. From legislative history of the Citizen Petition Fairness and Accuracy Act of 2007 – introduced on January 4, 2007:

> • "The legislation I introduce today . . . targets one particularly pernicious practice by brand name drug companies to impede or block the marketing of generic drugs - abuse of the FDA citizen petition process." 153

[2] During the consideration of Valeant's citizen petition, Valeant made four submissions, and Spear made three submissions, to the FDA.

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Cong. Rec. S64 (daily ed. Jan. 4, 2007) (statement of Sen. Kohl).

• "While this citizen petition process was put in place for a laudable purpose, unfortunately in recent years it has been abused by frivolous petitions submitted by brand name drug manufacturers (or individuals acting on their behest) whose only purpose is to delay the introduction of generic competition." 153 Cong. Rec. S64 (daily ed. Jan. 4, 2007) (statement of Sen. Kohl).

• "Indeed, brand name drug manufacturers often wait to file citizen petitions until just before the FDA is about to grant the application to market the new generic drug solely for the purpose of delaying the introduction of the generic competitor for the maximum amount of time possible. This gaming of the system should not be tolerated." 153 Cong. Rec. S65 (daily ed. Jan. 4, 2007) (statement by Sen. Kohl).

• "Of the 21 citizen petitions for which the FDA has reached a decision since 2003, 20 -- or 95 percent of them -- have been found to be without merit. Of these, ten were identified as "eleventh hour petitions," defined as those filed less than 6 months prior to the estimated entry date of the generic drug. None of these ten "eleventh hour petitions" were found to have merit, but each caused unnecessary delays in the marketing of the generic drug by months or over a year. . . " 153 Cong. Rec. S65 (daily ed. Jan. 4, 2007) (statement by Sen. Kohl).

In addition, FDA officials have acknowledged that there is a problem. For example, FDA's Chief Counsel Sheldon Bradshaw has stated that "Sometimes,

stakeholders try to use this mechanism to unnecessarily delay approval of a competitor's products . . . [we've] already seen several examples of citizen petitions designed not to raise timely concerns with respect to legality or timeliness of the drug application, but rather to delay approvals by compelling the agency to consider arguments raised in the petition." Bhatt Dec., Ex. 4.

Other federal agencies also recognize the potential for abuse in the citizen petition process and proposed ways in which to prospectively prevent it. Jon Leibowitz, FTC Commissioner, has stated that "where the cost of filing an improper petition is trivial compared to the value of securing even a brief delay in a rival's entry, there's certainly an **incentive to misbehave**." Bhatt Dec., Ex. 5 (emphasis added). Thus, the potential for abuse – and indeed, the actual abuse – by brand companies to delay generic entry using the citizen petition process, was recognized by the legislature, the FDA and other governmental agencies, and led to the enactment of the Food and Drug Administration Amendments Act 2007. See 21 U.S.C. §355(q).

D. The FDA's Denial Of Valeant's Citizen Petition And Approval Of Spear's ANDA

On December 21, 2004, Valeant filed a citizen petition asking the FDA not to approve any ANDA for a generic fluorouracil cream, 5% USP product, unless the applicant demonstrated bioequivalence in **both** AK and sBCC, or, in sBCC. Valeant's Br. at Ex. B.

The FDA, on April 11, 2008, denied Valeant's citizen petition and approved Spear's ANDA. Spear Dec., ¶¶ 15-16; Exs. 3-4. In its response to the citizen petition, the FDA set forth detailed reasoning and scientific evidence, as well as statutory and regulatory standards, supporting its conclusions on each of Valeant's arguments. Spear Dec., Ex. 4, pp. 5-11.[3] Specifically, the FDA (1) agreed with Valeant's

[3] The FDA's scientific determinations including the following:

FDA p.4: "For these products, FDA has determined that it is not necessary to test for bioequivalence in every clinical indication."

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argument that a sponsor of a generic topical 5-FU cream must conduct at least one comparative clinical study to establish bioequivalence to Efudex Cream (Spear Dec., Ex. 4, pp. 5-6); (2) disagreed with Valeant's argument, including the supporting expert testimony of Dr. Khanh P. Tran, that AK and sBCC occur at different sites of action (Id. at pp. 6-7); and, (3) disagreed with Valeant's argument, including the supporting expert testimony of Drs. Howard Maibach and Dennis M. Fisher, that topical delivery of the generic cream in AK patients could not predict its bioequivalence and/or effectiveness in treating sBCC (Id., pp. 7-10). In its ruling, the FDA set forth Valeant's argument, including any relevant supplemental evidence it had submitted during the citizen petition process, discussed the evidence it considered with respect to that issue, and then offered a reasoned explanation of the conclusion it reached. Consistent with that extensive analysis, the FDA also approved the Spear ANDA on April 11, 2008. Spear Dec., Ex. 3.

Spear began selling its generic flurouracil cream on that same day. Spear Dec. ¶ 19.

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FDA p.5 para 1: "The choice of which study design to use is based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug."

FDA p.7 first para: "Therefore, the site of action for a topical product to treat each of these conditions is the epidermis and the upper dermis."
FDA p.8 par 3: "We conclude that if a topical 5-FU formulation penetrates the skin to treat AK, which often involves a thickened stratum corneum, then that formulation would also penetrate the skin to treat sBCC, which usually involves a compromised stratum corneum."

FDA p.9 second para: "In light of these factors, and the absence of scientific evidence to the contrary, the 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."

FDA p. 10 second para: ". . . the recommended treatment duration of AK is 2 to 4 weeks ... For BCC ... at least 3 to 6 weeks, ... Therefore, a comparative study in the treatment of sBCC is likely to be less discriminatory in detecting a difference between products."

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ARGUMENT

I. THE APPLICABLE LEGAL STANDARDS

A. Review Of Agency Action

The Administrative Procedure Act governs review of the FDA's administrative decisions by the Court. See 5 U.S.C. § 706(2)(A). Such decisions can only be overturned if they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." Id. Under the APA, "[t]he ultimate standard of review is a narrow one. The court is not empowered to substitute its judgment for that of the agency." Zeneca, Inc., 213 F.3d at 167 (citation omitted). See also Bristol-Myers Squibb Co., 923 F. Supp. at 216.

Moreover, given that the scientific determinations at issue are within the agency's area of expertise, and "interpreting its own statute and regulations," the reviewing court is "particularly deferential." Pfizer, Inc. v. Shalala, 1 F. Supp. 2d 38, 45 (D.D.C. 1998). 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) (internal quotations and citation omitted). That is, 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 [a reviewing Court]." Schering Corp., 51 F.3d at 399. See also Zeneca, Inc., 213 F.3d at 170.

B. Standards On A TRO Application

To be entitled to issuance of a temporary restraining order, Valeant must "demonstrate [] either a combination of probable success on the merits and the possibility of irreparable injury or that serious questions are raised and the balance of hardships tips sharply in his [its] favor." Save Our Sonoran, Inc. v. Flowers, 408 F.3d 1113, 1120 (9th Cir. 2005) (emphasis in original) (citation omitted). "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. (citations omitted). "Under any formulation of the test, the moving party must demonstrate a significant threat of irreparable injury." Arcamuzi v. Continental Air Lines, Inc., 819 F.2d 935, 937 (9th Cir. 1987) (emphasis added) (citation omitted). See also Whittier College v. ABA, No. 07-1817, 2007 U.S. Dist. LEXIS 43707, at *16 (C.D. Cal. May 7, 2007). Injunctive relief "is a drastic and extraordinary remedy that should not be granted unless the movant, by a clear showing, carries the burden of persuasion." Avila v. Stearns Lending, Inc., No. 08-0419, 2008 U.S. Dist. LEXIS 31813, at *2 (C.D. Cal. Apr. 7, 2008) (Guilford, J.).

As Valeant recognizes, the purpose of a TRO is "to maintain the status quo." Valeant Br., at p. 8, line 17. However, because Valeant requests that the FDA suspend approval of the Spear ANDA, **which would require that Spear halt sales of the generic product that it has been selling since April 11, 2008**, Valeant is actually seeking a mandatory injunction that would alter the status quo. Requests for immediate relief which alter "the status quo are viewed with hesitancy and carry a **heavy burden of persuasion**." 3570 E. Foothill Blvd., Inc. v. City of Pasadena, 912 F. Supp. 1257, 1260 (C.D. Cal. 1995) (emphasis in original) (citation omitted). Thus, "[w]hen a mandatory preliminary injunction is requested, the district court should deny such relief 'unless the facts and law clearly favor the moving party.'" Stanley v. Univ. of S. Cal., 13 F.3d 1313, 1320 (9th Cir. 1994), cert. denied, 528 U.S. 1022 (1999) (citation omitted).

As set forth below, Valeant's arguments fall far short of meeting the required standard in order to obtain the relief it seeks, and, therefore, its application should be **denied**.

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II. VALEANT HAS NOT ESTABLISHED A LIKELIHOOD OF SUCCESS ON THE MERITS

A. Valeant's Failure To Establish Likelihood Of Success On The Merits Precludes Grant Of A TRO.

As described below, because each of Valeant's arguments requires the Court to substitute its own judgment for that of the decisions made by the FDA on scientific and medical issues, an area uniquely within the FDA's expertise, Valeant is not able to establish even a fair likelihood of success on the merits of its claims.

B. The FDA's Scientific Determinations, Such As That Spear Demonstrated Bioequivalence, Are Entitled To A High Level Of Deference.

As an initial matter, the courts have uniformly held that the FDA's scientific determinations are entitled to a high level of deference from a reviewing court. See cases cited in footnote 1. This deference is particularly appropriate when a court is reviewing the FDA's bioequivalence determinations.[4] Id.

For more than a decade, courts have held that the determination of bioequivalence and what specific tests are required to demonstrate it, are within the FDA's area of specific expertise, and, as such, deserve a high level of deference from a reviewing court. For example, in Fisons Corp. v. Shalala, the court was presented with an issue as to whether the FDA's regulation permitting waiver of *in vivo* testing to demonstrate bioequivalence in certain circumstances was proper. Fisons Corp., 860

[4] Similar determinations have been made by reviewing courts examining the FDA's decisions regarding whether a drug is safe and effective. See Henley v. FDA, 77 F.3d 616, 620 (2d. Cir. 1996) (FDA's refusal to amend labeling on oral contraceptives based on contradicting animal and human studies upheld by the reviewing court as a "product of agency expertise."); Upjohn Co., 938 F. Supp. at 444 (FDA's decision not to require an applicant seeking approval to market the innovator's drug as an over the counter product to satisfactorily complete and submit a specific type of efficacy test upheld as "within the agency's special expertise."); Sereno Labs.,158 F.3d at 1320 (Reviewing court upheld FDA's decision to rely on animal studies to demonstrate the safety and effectiveness of the drug at issue as "within its area of expertise."); Zeneca, Inc., 213 F.3d at 170 (FDA's decision to permit ANDA applicant to include substituted inactive ingredient in its formulation with the addition of a warning to the label directed to those at risk of injury was upheld by the reviewing court as "squarely within the ambit of the FDA's expertise.").

F. Supp. at 863 (reviewing the propriety of 21 C.F.R. § 320.22(b)). While examining the issue, the court held that, although the FDA is required by statute to determine bioequivalence of the generic product, "as part of its expertise or discretion in making that finding, [it] may elect to waive certain testing procedures where the make-up of pioneer and generic products are similar in all pertinent ways." Id. at 865. Using the deference required, and based on that reasoning, the court determined that "[t]he FDA's waiver provision [wa]s well within the scope of its broad discretion." Id. at 866.

In examining a bioequivalence determination in the context of another non-systemically effective drug, the reviewing court agreed with the FDA's argument that bioequivalence "can be measured by using one of several methodologies, including absorption . . . [and the] appropriate method used depends on the type of drug under consideration for approval." Schering Corp., 51 F.3d at 393. The Court recognized that "the [FDCA] mandate[s] a showing of bioequivalence for approval, [but that] there is 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. Using that touchstone, the Court held that the FDA's determination that ANDAs directed to non-systemically effective drugs can demonstrate bioequivalence by measuring when the drug becomes available at the site of action "f[e]ll squarely within the ambit of the FDA's expertise and merit[ed] deference . . . " Id.

In Bristol-Myers Squibb Co., 923 F. Supp. at 217, the court held that Congress, through enactment of the Hatch Waxman Amendments, "expressed [the] desire . . . that the FDA retain its historically wide discretion in defining showings of bioequivalence." Recognizing that "[t]he parties' dispute is fundamentally a scientific one over which the court lacks expertise and over which the FDA is the expert . . ." the court held that it could not conclude "that the agency's decision [permitting *in vitro* testing to serve as the sole evidence of bioequivalency] was arbitrary and capricious." Id. at 220.

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Similarly, in Somerset Pharms., 973 F. Supp. at 453, the court rejected a brand company's challenge which requested that the ANDA applicants be required to test for blood levels of both the drug and the drug's metabolite in order to prove bioequivalence. The court held "that the determination of which method is the most accurate, sensitive, and reproducible for measuring bioequivalence is a matter of scientific judgment, falling squarely within the FDA's discretion." Since the record showed extensive deliberations within "OGD, between [FDA] divisions, and with [the innovator] itself" regarding the scientific merit of the innovator's claims, the court determined that it "may not substitute its scientific judgment for that of the FDA," and concluded that "[c]onsidering the care with which this decision was apparently made, it does not seem likely that plaintiff will succeed on the merits." Id. at 453-54.

In Glaxo Group v. Leavitt, No. 06-469 (D. Md.),[5] Glaxo attempted to block generic approval and competition for its Flonase® product. Glaxo filed a citizen petition that was rejected by the FDA on grounds similar to those at issue here. Specifically, Glaxo requested, inter alia, that the FDA decline to approve a generic product based on the absence of clinical tests directed to what it characterized as the most difficult to treat indication for which Flonase® was approved. When the FDA rejected Glaxo's Citizen Petition, Glaxo filed a complaint requesting injunctive relief. The district court rejected Glaxo's arguments on the merits and denied the motion for a preliminary injunction.

Indeed, as recently as March 2007, Biovail attempted to block the FDA's approval of a generic version of its Wellbutrin XL product based on the FDA's alleged improper application of the bioequivalency and labeling standards of the Act. Biovail Corp., 519 F. Supp. 2d 39. Specifically, Biovail argued that, because the FDA had required it to demonstrate that the brand Wellbutrin XL product was bioequivalent to "two previously-approved versions of Wellbutrin – Wellbutrin IR (immediate

[5] In the Glaxo case, the Court did not issue a written decision. Bhatt Dec., Ex. 6 (excerpt of the transcript of the preliminary injunction hearing).

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release) and Wellbutrin SR (sustained release)," that the generic ANDA applicant should be required to make the same showing. Id. at 42. Instead, the Court upheld the FDA's decision to approve the generic version of Wellbutrin XL based on bioequivalency testing directed solely to the reference listed drug, basing its decision "on the FDA's evaluation of scientific data within its area of expertise." Id. at 47 (quoting Serono Labs., 158 F.3d at 1320).

Thus, in previous cases, when the FDA has made a determination well within its discretionary powers, compliant with the statute and regulations over which it presides, and within its scientific expertise in the determination of bioequivalence, the reviewing court has deferred to that expertise and held that the innovator's challenge did not meet the likelihood of success necessary to permit the grant of the extraordinary relief of a temporary restraining order. This Court should do the same.

C. Virtually Every Court Asked To Enjoin FDA Approval Has Acknowledged The Deference Owed To Such Approvals And Denied The Motions.

Additionally, in nearly every case in which the NDA holder has requested that the FDA be enjoined from approving an ANDA, or that an ANDA approval already granted be revoked, the request has been denied. See, e.g., Biovail Corp., 519 F. Supp. 2d 39 (ANDA approval upheld based on the FDA's scientific assessment and interpretation of its own regulations); Apotex, Inc. v. FDA, 449 F.3d 1249 (D.C. Cir. 2006) (ANDA approval upheld based on the FDA's interpretation of its own regulations); Sigma-Tau Pharms. v. Schwetz, 288 F.3d 141, 146 (4th Cir. 2002) (ANDA approval upheld based on the FDA's interpretation of its own regulations); Zeneca, Inc., 213 F.3d 161 (ANDA approval upheld based on the FDA's scientific assessment and application of its express regulations); Warner-Lambert Co., 202 F.3d 326 (ANDA approval upheld based on FDA's determinations and regulations regarding the definition of a "dosage form"); Serono Labs., 158 F.3d 1313 (ANDA approval upheld based on FDA's determination that in vitro testing was sufficient to demonstrate bioequivalency); Schering Corp., 51 F.3d at 399 (ANDA approval upheld

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because, although bioequivalence is required by statute, Congress did not intend "to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of ANDA approval"); Torpharm, Inc. v. Thompson, 260 F. Supp. 2d 69 (D.D.C. 2003), aff'd sub nom., Purepac Pharm. Co. v. TorPharm, Inc., 354 F.3d 877 (D.C. Cir. 2004) (ANDA approval upheld based on the FDA's interpretation of its own regulations); Somerset Pharms., 973 F. Supp. at 453 (ANDA approval upheld based on the FDA's wide discretion in what types of testing are required to demonstrate bioequivalence); Upjohn Co., 938 F. Supp. at 444 (denying request for a preliminary injunction prohibiting the FDA from approving applicant's ANDA based on the FDA's safety analysis and determinations); Bristol-Myers Squibb Co., 923 F. Supp. at 220 (ANDA approval upheld based on the FDA's wide discretion regarding the type of testing required to demonstrate bioequivalence); Fisons Corp., 860 F. Supp. 859 (ANDA approval without submission of certain in vivo testing upheld).[6]

In all of these cases, the deciding court recognized either (1) deference owed to the FDA in the interpretation of the FDCA and its accompanying regulations, or, (2) deference owed to the FDA's determinations regarding scientific evidence submitted by the ANDA applicant. See, e.g., Apotex, Inc. v. FDA, No. 06-0627, 2006 U.S. Dist. LEXIS 20894, at *25 (D.D.C. Apr. 19, 2006) ("When the agency decision is based upon its interpretation of the statute that it is charged with administering, a court's deference to the agency is at its apex.") (emphasis added). "Deference [with respect

[6] Spear has located only two cases in which a court has ordered the revocation of an already granted ANDA approval. See Am. Bioscience, Inc. v. Thompson, 269 F.3d 1077 (D.C. Cir. 2001); Mova Pharm. Corp. v. Shalala, 955 F. Supp. 128 (D.D.C. 1997), aff'd, 140 F.3d 1060 (D.C. Cir. 1998). **Neither of these cases involved requests for review of the FDA's scientific determinations.** In Am. Bioscience, the court was required to analyze the FDA's interpretation of a court order. In such circumstances, the court is not required to give deference to that interpretation. Am. Bioscience, Inc., 269 F.3d at 1085 ("We, of course, owe no deference to an agency's reading of judicial orders or decisions."). In Mova, a case relied on by Valeant in its brief, the FDA had incorrectly interpreted a statutory provision in a case involving approval of the second filing generic's ANDA while the first filer was still involved in patent litigation with the NDA holder. Mova Pharm. Corp., 955 F. Supp. 128. The Court determined that the approval had been contrary to the plain language of the statute and, thus, granted Mova's request that the second filer's ANDA approval be withdrawn. Id. No scientific issue was involved.

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to the FDA's evaluation of scientific data] is the norm." Allergan, Inc., 398 F. Supp. 2d at 26.

D. The FDA's Approval Of Spear's ANDA Was Correct.

The FDA approved Spear's ANDA based on the bioequivalency testing comparing the Spear ANDA product to Efudex in the treatment of AK. Such approval took place only after an extensive review of the test results submitted to the FDA, the preliminary study proposal submitted by Spear prior to the ANDA submission, primary and secondary statistical reviews, and, the scrutiny by both the Office of Generic Drugs ("OGD") and the New Drug Division of the arguments submitted by Valeant. This detailed and careful review deserves this Court's deference and should not be disturbed lightly. Somerset Pharms., 973 F. Supp. at 453 (extensive scientific deliberations regarding the merit of the innovator's challenge lend to the conclusion that the court may not substitute its own judgment for that of the agency with applicable expertise).

Each of Valeant's substantive arguments is without merit. **First**, Valeant asserts that the FDA violated the "plain language" of the FDCA and failed to follow its own regulations because it accepted the AK clinical study as proof of bioequivalence in both AK and sBCC. Valeant Br., at pp. 3-6.[7] However, the argument Valeant makes is based on a selective reading of the FDA's denial of Valeant's Citizen Petition. Valeant admits that the FDCA permits the FDA to determine the suitability of a method for determining bioequivalence as long as that method is "expected to detect a significant difference between the [generic] drug and the [approved] drug in safety and therapeutic effect." Valeant Br., at p. 4. Then Valeant describes the FDA's evaluation of scientific data demonstrating that a 0.5% fluorouracil cream was as effective as a 5.0% fluorouracil cream. Id. From these two facts, Valeant argues that given the study data cited by the FDA, a clinical test in AK

[7] Interestingly, Valeant's application never once mentions that 98% of the prescriptions for Efudex are dispensed to patients with AK, not sBCC. Spear Dec. ¶ 11.

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is "**incapable** of detecting. . . . 'a significant difference' between Spear's product and Efudex cream." Id. (emphasis in original). Valeant's mistake is taking the FDA's evaluation of that data out of context. Specifically, the FDA used that information to come to the conclusion that, because the stratum corneum is often thickened in those with AK, the barrier to the drug's entry to the skin is higher. Spear Dec., Ex. 4 at p. 8. Since in sBCC patients, the skin is characterized by a compromised outer layer, a successful AK treatment would mean that the drug would also be successful in treating sBCC. Spear Dec., Ex. 4 at p. 8. As reasoned and explained by the FDA in its decision, a clinical study of the drug in AK would be expected to be more predictive of its effectiveness as compared to a clinical study in sBCC patients. Id.

Second, Valeant argues that the FDA relied on "false and contradictory" assertions regarding interpretation of scientific data and conclusions to arrive at its decision. Valeant Br. at pp. 6-7. As explained above, the FDA used the fact that there was no significant difference between the lower dose and higher dose treatment of AK in the literature to conclude that a study in sBCC was not necessary simply because, given the relative permeability of the skin in each of the conditions, a successful AK trial would also indicate that treatment would be likewise effective in sBCC. Spear Dec., Ex. 4 at p. 8. The FDA's analysis is reasonable and internally consistent.

Third, Valeant contends that the FDA did not consider or address relevant scientific evidence which was presented during the course of the Citizen Petition process. Valeant Br. at pp. 7-8. This argument is contradicted by the facts.

The denial of the citizen petition addresses each of the arguments which were raised by Valeant's three experts, and, in fact, even quotes one of those arguments. The denial sets forth Valeant's arguments regarding the site of action of AK vs. sBCC (addressed by Dr. Khanh P. Tran) and the reasons why it did not accept those arguments – "the epidermis is only 0.06 to 0.8 millimeters thick, and, as explained below, there is no reason to conclude that if the formulation provides the active ingredient to the stratum spinosum, it would not also provide the active ingredient to

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the stratum basale." Spear Dec., Ex. 4 at p. 7. That conclusion is then expressly supported by further analysis and by citation to several scientific studies on the issue. Id. at pp. 7-8. The denial sets forth Valeant's arguments regarding whether or not topical delivery of the generic cream in AK patients could predict its bioequivalence and/or effectiveness in treating sBCC (addressed by Drs. Howard Maibach and Dennis M. Fisher), and the reasoned analysis of why an AK study is sufficient in both respects. Id., at pp. 7-10. In this discussion, contrary to Valeant's assertions, the FDA **specifically quotes** Dr. Maibach's declaration and goes on to explain why his conclusions are incorrect based on other available information. Spear Dec., Ex. 4 at pp. 7-8. Thus, contrary to Valeant's claims, the FDA's decisional document takes pains to explain and support each of its conclusions – conclusions which were reached after more than three years of deliberation, including express consideration of Valeant's experts' opinions.[8]

Valeant wholly fails to address the extensive case law discussed above addressing the deference due to the FDA's scientific decisions and the appropriateness of the FDA's actions in making determinations of bioequivalence. Instead, it relies almost entirely on a 1995 U.S. district court decision that, when carefully reviewed does not support its argument. In A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484 (D.C. Cir. 1995), A.L. had argued that a study submitted by the other pharmaceutical company did not establish bioequivalence because (1) the testing was directed to only the drug's ability to fight disease and not to the drug's ability to promote growth and feed efficiency in chickens; and, (2) the drugs were tested at a single dosage, which did not allow for an evaluation of a dose-response curve of blood levels in the chickens. Id. at 1490. A.L. had submitted affidavits and information from sixteen

[8] Moreover, even if Valeant were correct and the FDA's decisional document did not specifically address each argument advanced by Valeant, the determination of whether evidence was considered or not is made by analysis of "the agency's decisionmaking process" and not "de novo review of the action itself." Ranchers Cattlemen Action Legal Fund United Stockgrowers of Am. v. USDA, 499 F.3d 1108, 1117 (9th Cir. 2007).

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veterinary researchers supporting one or the other of these two assertions. Id. Based on a review of the whole of the administrative record, the court held that the FDA had satisfactorily explained its reasoning regarding the first point, but had not done so with respect to the second. Id. at 1491-92. That is, as to the second point, because the FDA did not have any regulations in place regarding what testing was required to establish bioequivalence in veterinary products, it was not clear whether the FDA had held the bioequivalence test to the same standards as those performed in human subjects. It therefore remanded the case to the FDA (**leaving the approval in place**) to permit the FDA to either reconsider its conclusion or explain the reasoning behind its action. Id. Moreover, in the portion of the A.L. Pharma case that is most applicable here, the court determined that the FDA had provided a reasoned analysis on the issue of why the study directed to the treatment of the disease was sufficient to demonstrate equivalency in the growth and feed indications for the drug. A.L. Pharma, Inc., 62 F.3d at 1491.

III. VALEANT WILL NOT SUFFER IRREPARABLE INJURY IF THE TRO IS NOT GRANTED

In the absence of a temporary restraining order, Valeant will not suffer the type of irreparable harm required in this circuit to support emergency injunctive relief for at least the following reasons. **First**, Valeant's sales of the Efudex product are less that 10% of its worldwide sales.[9] **Second**, in late 2006 Valeant authorized the launch of an "authorized" generic product by its Oceanside subsidiary. This fact strongly militates against a finding that it will be irreparably harmed by Spear's entry to the market. **Third**, Valeant's claims that its reputation will be tarnished based on Spear's introduction of a generic product are unsupported and conclusory.

[9] For purposes of this portion of its Opposition, Spear has constructed its argument based only on publicly available information concerning Valeant's sales figures. Such action was necessitated because Valeant has refused to provide unredacted versions of its filings to Spear despite both repeated requests and representations that the redacted information would be treated as Outside Counsel Only information. See Bhatt Dec., ¶¶ 2-6, Exs. 1-2.

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"It is well established . . . [that] monetary injury is not normally considered irreparable." Los Angeles Memorial Coliseum Comm'n. v. NFL, 634 F.2d 1197, 1202 (9th Cir. 1980). In its brief, Valeant sets forth nothing more than speculation about the sales it will lose as a result of the Spear generic product's launch. Moreover, given that Valeant is an international company with more than 300 products and nearly $786 million in sales in 2007, it is hard to fathom how the loss of less than 10% of its sales qualifies as irreparable on anyone's scale. Bhatt Dec. Ex. 3m p. 8. "To successfully shoehorn potential economic loss into the irreparable harm requirement, a plaintiff must establish that the economic harm is so severe as to cause extreme hardship to the business or threaten its very existence." Apotex, Inc. v. FDA, No. 06-0627, 2006 U.S. Dist. LEXIS 20894, at *54-56 (D.D.C. Apr. 19, 2006) (internal quotations and citation omitted).

Lastly, in an attempt to rescue its allegations of irreparable harm, Valeant turns to an unsupported allegation of reputational harm that it alleges it will suffer at the hands of Spear's ANDA product. Specifically, Valeant offers speculative and conclusory information that "if" the Spear product fails to successfully treat sBCC, somehow physicians and patients will believe that the source of the product is Valeant, which will result in reputational damage. Valeant Br., at pp. 13-14. This is a very curious argument – any patient using the Spear product would have the tube, clearly labeled as originating from Spear, not Valeant. "[S]peculative injury does not constitute irreparable injury." Goldie's Bookstore, Inc. v. Superior Court, 739 F.2d 466, 472 (9th Cir. 1984) (citation omitted). See also CKE Rest. v. Jack in the Box, Inc., 494 F. Supp. 2d 1139, 1148 (C.D. Cal. 2007) (Guilford, J.).

IV. A TRO WILL CAUSE SUBSTANTIAL HARM TO SPEAR

By contrast, Spear is a small company with only two products. Spear Dec. ¶¶ 5, 18. It expects that the fluorouracil product will constitute 80% of Spear's sales in 2008. Spear Dec. ¶ 18.

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Spear has already supplied pharmacies across the United States with its product – all would be affected by an interruption in supply. Spear Dec. ¶ 19. Suspension of its approval and inability to continue selling the product would also damage its reputation with both its clients and the purchasing public. Moreover, given that it is such a small company, its reputation would be difficult to rebuild.

V. THE PUBLIC INTEREST FAVORS DENIAL OF THE TRO

In passing the Hatch-Waxman Act, Congress determined that, the public interest is grounded in "expedit[ing] and increas[ing] the availability of generic substitutes." Apotex, Inc., 2006 U.S. Dist. LEXIS 20894, at *61. The Mova case, relied upon by Valeant (Valeant Br. at 16) is not to the contrary. In Mova, the issue was not whether a generic product would be made available to the public but rather whether under the Hatch-Waxman Act, one generic company was entitled to the exclusive statutory right to its products (vis-à-vis other generic companies) for 180 days. The court simply stated that in the face of plain statutory language, "our policy would be very different indeed if the courts could decline to enforce clear laws merely because they thought them contrary to the public interest." Mova Pharm. Corp. v. Shalala, 140 F.3d at 1060, 1066-1067, n.6 (D.C. Cir. 1998). That is, plainly, not the issue here.

Because "the public also has a well-recognized interest in receiving generic competition to brand-name drugs as soon as is possible," the public interest factor weighs in favor of denying the extraordinary relief Valeant requests. Biovail Corp., 2007 U.S. Dist. LEXIS 20238, at *29-30.

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CONCLUSION

For the foregoing reasons, Spear respectfully requests that the Valeant's application for a temporary restraining order be **denied**.

Dated: April 28, 2008 Respectfully submitted,

WINSTON & STRAWN LLP

By: _____

Gail J. Standish (State Bar No. 166334)
E-mail: gstandish@winston.com
Peter E. Perkowski (State Bar No. 199491)
E-mail: pperkowski@winston.com
WINSTON & STRAWN LLP
333 South Grand Avenue, 38th Floor
Los Angeles, California 90071-1543
Telephone: 213-615-1700
Facsimile: 213-615-1750

Steven Lieberman (admission pro hac vice pending)
Minaksi Bhatt (SBN 151312 – reactivation pending)
Lisa N. Phillips (admission pro hac vice pending)
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K Street, N.W.
Washington, D.C. 20005
Telephone: 202-783-6040
Facsimile: 202-783-6031

Attorneys for Defendant-Intervenor
Spear Pharmaceuticals, Inc.