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UNITED STATES DISTRICT COURT

FOR THE CENTRAL DISTRICT OF CALIFORNIA

SOUTHERN DIVISION

VALEANT PHARMACEUTICALS INTERNATIONAL,

Plaintiff,

v.

KATHLEEN SEBELIUS, *et al.*,

Defendants,

and

SPEAR PHARMACEUTICALS, INC.

Intervenor-Defendant.

No. SA CV 08-00449-AG

**FEDERAL DEFENDANTS' MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT**

DATE: July 20,2009
TIME: 10:00 a.m.
COURTROOM: 10D

Hon. Andrew J. Guilford

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## Glossary

| | |
|---|---|
| AK | Actinic keratoses |
| ANDA | Abbreviated New Drug Application |
| APA | Administrative Procedure Act |
| AR | Administrative Record |
| BE | Bioequivalence |
| CDER | Center for Drug Evaluation and Research |
| CP | Citizen Petition |
| DDDP | Division of Dermatologic and Dental Products |
| FDA | Food and Drug Administration |
| FDCA | Federal Food, Drug, and Cosmetic Act |
| 5-FU | 5-Fluorouracil, 5% |
| HHS | Department of Health and Human Services |
| ODE III | Office of Drug Evaluation III |
| OGD | Office of Generic Drugs |
| PI | Preliminary Injunction |
| sBCC | Superficial Basal Cell Carcinoma |
| TRO | Temporary Restraining Order |

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 innovator) version of 5-FU and markets it under the brand name Efudex®.

FDA approved Spear Pharmaceuticals, Inc.'s ("Spear") abbreviated new drug application ("ANDA") for a generic version of 5-FU on April 11, 2008, and reaffirmed that approval on May 30, 2008. Spear's product, like Valeant's product, contains 5% of the active ingredient, fluorouracil. There are some differences in inactive ingredients – which is common for generic drugs – but FDA has determined that those differences in formulation do not affect the bioavailability of the active ingredient, and thus the bioequivalence ("BE") of Spear's product to Valeant's product. After consideration of challenges raised by Valeant and other issues identified by the agency, senior FDA officials and scientists have concluded that Spear adequately demonstrated BE, and that its product has met all applicable statutory and regulatory requirements. Thus, by statute, Spear's product must be approved.

On June 18, 2008, this Court denied Valeant's motion for a preliminary injunction to enjoin FDA's approval of Spear's product. Nevertheless, Valeant persists in its attempt to undo FDA's approval. Perhaps recognizing that it will not succeed in directly challenging FDA's scientific conclusions, Valeant alleges that FDA's decision should be overturned under principles of administrative law because the agency assertedly failed to defer to the views of scientists within its dermatology division. In so arguing, however, Valeant completely disregards the appropriate process that FDA undertook to resolve internal agency disagreement between the Office of Generic Drugs and the dermatology division, which is

thoroughly documented in the administrative record, and ignores the agency's lengthy and logical rationale for concluding as a scientific matter that the dermatology division's views on appropriate BE testing were not correct. The Court thus properly rejected this argument the first time Valeant raised it, correctly pointing out that "the authorized decision maker in connection with Spear's original approval was the Office of Generic Drugs, not the dermatologists in the Office of New Drugs, and the authorized decision makers in connection with the reaffirmation of Spear's approval were Drs. Throckmorton, Woodcock, and von Eschenbach." Conclusions of Law (June 18, 2008) ¶ 34, at 28-29.

Valeant also alleges that FDA's decision is tainted because Dr. Jonathan Wilkin, who submitted an expert opinion on behalf of Spear's application, had previously signed off on memoranda involving Spear's application while he was the head of the dermatology division. This argument too has already been presented to and rejected by this Court. Indeed, FDA candidly disclosed this potential conflict of interest to the Court and parties, and promptly initiated measures to address it by undertaking the formal reconsideration of Spear's ANDA approval without reference to Dr. Wilkin's opinion. As this Court observed, FDA took the "responsible course of action" by seeking a stay of proceedings in order to "assess the effect" of the potential conflict and "determine whether any additional scientific data were needed in support of Spear's ANDA approval." *Id.* ¶ 40, at 30. The agency's actions were fully sufficient to ensure the integrity of its decision making. Contrary to Valeant's suggestion, FDA was under no legal obligation to involve "new" agency personnel in the reconsideration process, as this Court has already held." *Id.* ¶ 41, at 31.

Thus, as the Court made clear in denying Valeant's bid for preliminary injunctive relief, FDA's decision to approve Spear's ANDA falls squarely within the agency's scientific and technical expertise, and the agency has taken ample precautionary measures to ensure the integrity of its decision. Because there are

no material facts in dispute and the administrative record overwhelmingly demonstrates that the agency's decision was not arbitrary, capricious, or contrary to law, it should be upheld as a matter of law.

## BACKGROUND

### A. Statutory and Regulatory Background

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), pharmaceutical companies seeking to market "pioneer" 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 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.

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 5-FU), "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 BE, 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 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. Administrative Record ("AR") at 603.

**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. Spear's ANDA**

In 1999, Spear submitted a proposed BE clinical study design to FDA's Office of Generic Drugs ("OGD"). AR 955-71. Spear's proposed product presented unique regulatory challenges because it was a topical product for use in two different indications, and the active ingredient or active moiety cannot adequately be measured in the blood (or other body fluids). AR 1093. Spear proposed to conduct a clinical BE study for AK, but not sBCC. OGD sought input from another component within the agency, the Division of Dermatologic

and Dental Products ("DDDP") on whether Spear should also be required to do a clinical study for sBCC. AR 947-49.

DDDP replied in a consult memorandum dated November 9, 1999. The DDDP stated, *inter alia*, that "[e]fficacy in the primary indication may be extrapolated if a secondary indication has similar pathology and is easier to treat. Although both [AK] and [sBCC] may arise in photodamaged skin, their pathologies are not similar. Moreover, it is unlikely that [sBCC] is any easier to treat than [AK]. It should be noted that although Efudex is available in three formulations (2% and 5% solutions and 5% cream), only the 5% formulations are approved for the treatment of [sBCC]." AR 949.

At that time, Dr. Jonathan Wilkin was the director of the DDDP, and his signed initials appear on the November 9, 1999 memorandum from DDDP. AR 949. Dr. Wilkin also signed his initials on another consult memorandum from DDDP regarding Spear's ANDA on January 27, 2000. That memorandum primarily concerned whether Spear should be required to do a placebo arm, and did not involve the issue of whether a clinical BE study should be performed for the sBCC indication. AR 977-82.

Spear submitted an ANDA for a generic version of 5-FU on December 22, 2004. AR 1084. In accordance with the BE protocol that it had worked out with OGD, which did not include a clinical trial for sBCC (AR 938-39, 950-51, 984-85, 992-95), Spear completed the clinical trial for the AK indication and submitted the results as part of its ANDA. Spear's BE study compared its product to Efudex Cream, 5%, to treat patients with AK in order to show that the Spear formulation did not result in a significant difference in the availability of the active ingredient (5-FU) at the site of action for treating both AK and sBCC. AR 1036-46.

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. AR 1-138. Valeant argued that

any sponsor for a generic version of 5-FU should be required to do a BE study for sBCC. FDA received multiple comments in support of and opposing this petition. AR 141-583.

After Valeant submitted its petition, FDA again considered whether Spear should be required to conduct a BE study for sBCC. AR 1093-1095. This discussion took place within the Center for Drug Evaluation and Research ("CDER"), and included OGD, the Office of Drug Evaluation III ("ODE III"), and DDDP. *Id.* The DDDP is a division within ODE III. *See* http://www.fda.gov/oc/orgcharts/orgchart.html. On October 27, 2005, DDDP sent OGD a consult memorandum, recommending "that both AK and sBCC should be studied to yield independent confirmation of bioequivalence for these indications which may be different with regard to kinetic profile needed to achieve efficacy and a determination in one may not be extrapolated to the other." AR 630.

In June 2006, OGD, ODE III, and DDDP met, and reached an apparent consensus that Spear should be required to conduct a BE clinical trial in sBCC, not AK. AR 631-32, 1094. This approach was later revisited, and, in September 2006, DDDP was of the view that clinical trials should be conducted in both AK and sBCC. AR 633-35.

On February 20, 2007, Dr. Dena Hixon of OGD wrote a consult response memorandum, addressing the issues raised in the citizen petition and the points made by DDDP. AR 636-56. Contrary to DDDP, OGD believed that a study in AK would be sufficient to establish BE for both AK and sBCC. *Id.* Dr. Hixon's memorandum for OGD refuted each point made by DDDP (AR 653-56), concluding that "there is reasonable scientific evidence that equivalent performance in a clinical endpoint study in AK will also predict equivalent delivery of the drug substance to the site of action for sBCC in the adjoining cell layer. Therefore, there is not a substantial risk that a generic 5-FU cream product showing equivalence in a study of AK would result in a clinical disadvantage

compared to the RLD [reference listed drug] when used in the treatment of sBCC when conventional methods of surgical excision are impractical." AR 653-54.

The DDDP responded on March 1, 2007, stating that "[a]ctinic keratoses are not the same disease as superficial basal cell carcinoma. The two diseases have different behaviors and different outcomes." AR 659. DDDP argued that: (1) OGD was taking a "reductionist approach to regulation of topical drug products"; (2) sBCC and AK "have histopathological differences which translate to different requirements in their treatment with regard to depth of penetration and site of drug action"; (3) sBCC is cancerous and AK is not; (4) sBCC "can evolve into a more invasive cancer and be pleomorphic [*i.e.*, having different forms], thus a demonstration of treatment effect in [AK] cannot be extrapolated to bioequivalence for [sBCC] treatment"; and (5) OGD should reconsider the "one study fits both" approach "when one of the indications in question is a cancer and the other is not." AR 661.

On March 14, 2007, Spear submitted an opinion letter from Dr. Jonathan Wilkin, M.D., who had retired from his position as director of the DDDP. AR 1047-49. Dr. Wilkin stated that "[i]t is well known and accepted that the greatest barrier to penetration through the skin is the stratum corneum." He also noted that sBCC "have little or no barrier to percutaneous penetration, with the disrupted or absent stratum corneum in most presentations." He concluded that "the substantially greater barrier with AKs provides for an assay with greater sensitivity to detect a subtle, even clinically unimportant, difference between the test and reference products." AR 1048.

Because DDDP disagreed with OGD's position, Dr. Julie Beitz (as Director of ODE III, of which DDDP is a component) was asked to review the matter. AR 1095. After her own independent review of the issues and her own literature search, Dr. Beitz agreed with OGD that a study in AK would be sufficient to establish BE for both AK and sBCC. AR 727-38. She memorialized her decision

on December 3, 2007.

Dr. Beitz cited numerous reasons for her conclusion, including: (1) Efudex itself had been previously shown to be safe and effective for the treatment of both AK and sBCC; (2) the literature indicates that the sites of action for AK and sBCC are the same (epidermis and upper dermis); (3) "[t]he stratum corneum is the predominant barrier to topical drug delivery for both the epidermis and upper dermis;" (4) "[e]rosion or compromise of the skin in sBCC can result in greater drug exposure than in AK, which typically involves a thickened stratum corneum"; (5) because Efudex cream and solution are both approved for treating sBCC, this "argues against some critical formulation issue that could meaningfully affect the ability of these topical 5-fluorouracil products to deliver drug to the site of action"; (6) Spear's cream produced complete clearing of AK lesions comparable to Efudex; (7) Spear's product contains the same active ingredient and Spear's study had shown that the differences in inactive ingredients do not change the performance; and (8) because Efudex has an 88% clearance rate, a lesser penetration by Spear's product would have been seen as a lower complete clearance rate for the Spear formulation. AR 736-37.

Dr. Beitz reviewed and described the AK and sBCC disease states in detail. She noted DDDP's statement on September 5, 2006, that, for sBCC, "drug delivery to the various nests of tumor cells will vary depending on the thickness of the tumor, availability of cellular transport mechanisms (such as multi-drug resistance proteins). AKs are less likely to have drug resistance." AR 735. She also noted DDDP's subsequent clarification that, "in many cases, sBCCs are characterized by 'erosions which lead to circumvention of the need for cross skin diffusion to the uppermost layers of tumor,'" and that drug resistance for sBCC was "rare." AR 735-36. Dr. Beitz concluded that neither AK or sBCC was particularly "difficult to treat," and rejected Valeant's argument in its citizen petition that a BE study needed to be done in sBCC as the more "difficult to treat"

condition. AR 737-38.

FDA approved Spear's ANDA on April 11, 2008, and denied Valeant's citizen petition that same day. The citizen petition response was drawn largely from the rationale independently researched and articulated by Dr. Beitz. AR 599-609.

**3. Post-Litigation Developments**

Valeant sued FDA on April 25, 2008, seeking a TRO to enjoin FDA's approval of Spear's ANDA. On April 30, 2008, FDA sought a stay in the TRO proceedings to address a potential conflict of interest that agency staff identified while compiling the administrative record. Agency staff realized that Dr. Wilkin, while Director of DDDP from 1994 to 2005, had been involved as a reviewer of a consult regarding Spear's ANDA. Although Dr. Beitz knew that Dr. Wilkin's expert opinion, prepared after he left FDA, had been submitted by Spear to support its ANDA, Dr. Beitz was not aware until after FDA approved Spear's ANDA that Dr. Wilkin had been involved with Spear's application while at the agency. AR 730 n.6. This Court granted the requested stay on May 1, 2008. During the pendency of the stay, Spear agreed to stop marketing its product.

Subsequently, FDA identified two additional issues that prompted the agency to issue a formal administrative stay of Spear's ANDA, so that it could fully reconsider the approvability of Spear's ANDA. Those issues were whether Spear should have been required to submit (1) pharmacokinetic data ("PK data") concerning the level of active ingredient that may be absorbed into the blood; and (2) additional clinical efficacy data.

Dr. Douglas Throckmorton, M.D., the Deputy Director of CDER, wrote the agency's reconsideration memorandum. Dr. Throckmorton oversees the offices within CDER, including ODE III and OGD. As Deputy Director of CDER, Dr. Throckmorton is the second-highest-ranking official within CDER responsible for reviewing and acting upon applications for the approval of drugs for human use.

With respect to the two scientific issues, Dr. Throckmorton concluded that no additional data was needed for approval of Spear's application, based largely on the studies that Spear had already conducted and the nature of the active ingredient, 5-FU. AR 1099-1101.

As part of the agency's reconsideration of Spear's application, FDA addressed Dr. Wilkin's potential conflict of interest by, among other things, asking Dr. Beitz to "evaluate whether [she] would have reached the same conclusion as stated in [her] December 3, 2007 decision, even if Dr. Wilkin had not made his March 14, 2007 submission in support of Spear's ANDA." AR 1107. In her analysis, dated May 29, 2008, Dr. Beitz determined that the scientific information presented by Dr. Wilkin was independently supported by references in the record, including references that had previously been submitted to FDA and that she had independently found. AR 1107-08 (citing references at AR 60-86; 412-422; 801-806; 807-814; 815-823; 870-875). Dr. Beitz "unequivocally state[d] that [she] would have reached the same conclusion regarding the approvability of Spear's ANDA even if [she] had not considered Dr. Wilkin's submission." AR 1108.

Dr. Throckmorton reviewed the memorandum from Dr. Beitz, and agreed with her conclusion that "the statements made by Dr. Wilkin were based on information that is generally available and could reasonably have been derived from other submitted materials. As a result, omitting Dr. Wilkin's statement from the record does not change the conclusion regarding the approvability of the Spear ANDA." AR 1096.

Consistent with the full scope of the agency's administrative reconsideration process, Dr. Throckmorton also evaluated the agency's rationale for not requiring a clinical BE study for the sBCC indication. AR 1096-98. He grouped his conclusions into two different areas related to (1) the use of the single study in AK and (2) the rigor of the BE design used by OGD. AR 1096. As to the first issue, he concluded that "if a study demonstrated efficacy for a topical 5-FU formulation

in AK, this would provide assurance that the formulation would also penetrate the skin to be effective in the treatment of sBCC." AR 1098. Dr. Throckmorton also rejected the argument that an sBCC clinical trial was necessary because sBCC is a cancer and harder to treat, noting that neither condition was especially difficult to treat and that the clearance rate for sBCC is even higher than that for AK. AR 1097. In addition, he made several important findings related to arguments made by Valeant and its experts: that the AK clinical trial was designed to lessen the impact of the variability of the disease state; that there was no evidence that sBCC must be treated with a higher concentration of 5-FU; and that "the available data, from the approved label for the Valeant product, suggests that 5% 5-FU is very effective in treating sBCC, even when formulations vary widely in their composition." AR 1097-98.

With respect to the rigor of the BE study, Dr. Throckmorton noted that "[t]he purpose of a bioequivalence test is to detect significant differences in formulations that are intended to have the same effects, rather than to show similar effects for different formulations." AR 1098. He concluded "that AK was the appropriate disease state to study in a clinical bioequivalence study comparing 5% 5-FU creams, as it is the model that is more sensitive at detecting differences in product performance between two formulations of 5-FU cream." *Id.* He further observed that "[a] bioequivalence study in the treatment of sBCC was not considered to be adequately sensitive to detect product differences, in part because of the longer treatment duration and wider range of treatment durations recommended for this indication." AR 1099.

Dr. Throckmorton also made several findings specific to the test that Spear conducted for AK, noting that the study conducted by Spear was "robust and carefully planned," and that "FDA (OGD) conducted a thorough analysis of the data from the Spear AK trial, including standardized, rigorous statistical methods to assess bioequivalence, which clearly demonstrated the bioequivalence of the

Spear and Valeant products." AR 1099.

Dr. Janet Woodcock., M.D., reviewed Dr. Throckmorton's memorandum. As Director of CDER, and the immediate supervisor of Dr. Throckmorton, Dr. Woodcock is the highest-ranking official within CDER responsible for reviewing and acting upon applications for the approval of drugs for human use. She concurred with Dr. Throckmorton's conclusions and recommended that Spear's approval be reaffirmed. AR 1089-90. Dr. Andrew C. von Eschenbach, M.D., reaffirmed the approval of Spear's ANDA, based on Dr. Woodcock's recommendation and Dr. Throckmorton's memorandum. AR 1088. At that time, Dr. von Eschenbach was the FDA Commissioner and oversaw the entire agency.

On May 31, 2008, one day after FDA issued its reconsideration decision, this Court granted Valeant's application for a TRO. The Court subsequently extinguished the TRO (and denied a preliminary injunction) on June 18, 2008, after submission of the administrative record, full briefing, and a hearing. Valeant filed an amended complaint on September 17, 2008, seeking a declaratory judgment that FDA's approval of Spear's ANDA is unlawful and invalid, and that any review of the ANDA can lawfully be conducted only by agency officials who were not "tainted" by the initial approval or reconsideration of the ANDA, who review the administrative record without regard for Dr. Wilkin's statement, and who afford "proper deference" to DDDP. For the reasons set forth below, Valeant's claims are meritless, and FDA's determination approving Spear's ANDA and denying Valeant's citizen petition should be upheld as a matter of law.

**ARGUMENT**

This Court may grant a motion for summary judgment if "the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). "Only disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of

summary judgment. Factual disputes that are irrelevant or unnecessary will not be counted." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). "The mere existence of a scintilla of evidence in support of the non-moving party's position is not sufficient." *Triton Energy Corp. v. Square D Co.*, 68 F.3d 1216, 1221 (9th Cir. 1995). When cross-motions for summary judgment are at issue, the court "evaluate[s] each motion separately, giving the nonmoving party in each instance the benefit of all reasonable inferences." *ACLU v. City of Las Vegas*, 333 F.3d 1092, 1097 (9th Cir. 2003).

## I. FDA PROPERLY APPROVED SPEAR'S ANDA

### 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). 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. *Id.* "The court is not empowered to substitute its judgment for that of the agency." *Id.*

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). Moreover, 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 Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996) (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.").[1]

**B. FDA's Scientific Judgment Should Be Upheld as a Matter of Law**

FDA's conclusion that a controlled clinical endpoint BE study for AK established BE between Spear's and Valeant's 5-FU products is consistent with the statute and regulations, and is not arbitrary and capricious. AR 608, 1096-99.

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[1] Indeed, courts have uniformly 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. *See, e.g., Glaxo Group v. Leavitt*, AMD 06-469 (D. Md., Mar. 6, 2006) (Davis, J.) (unpublished opinion) (transcript attached to defendants' initial TRO brief)*; Schering*, 51 F.3d 390; *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*, 923 F. Supp. 212; *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994). *See also, e.g.*, *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1324 (D.C. Cir. 1998); *Warner Lambert Co. v. Shalala*, 202 F.3d 326, 328 (D.C. Cir. 2000); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499-1500 (D.C. Cir. 1996).

Although the FDCA does not require clinical studies, it has been FDA's policy to require a BE study with a clinical endpoint to demonstrate BE for certain topical drugs such as 5-FU cream for which the amount of active ingredient of the drug cannot reliably be measured in the blood or urine, and there is no other reliable, objective measure of the drug's action. AR 603. For such drugs, the FDCA allows FDA to "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).[2]

Spear's clinical BE study demonstrated not just that there was no significant difference between the Spear product and the Valeant product in treating AK, but also 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 bioequivalent to Valeant's product for both indications). AR 1098. FDA's regulation at 21 C.F.R. § 320.24(b)(4) provides that such clinical BE studies are particularly appropriate for demonstrating BE for topical products intended to deliver the active moiety locally, such as 5-FU. This method fully meets the statutory BE requirements at 21 U.S.C. § 355(j)(8)(B)(i) and 21 U.S.C. § 355(j)(8)(C).

FDA's decision to approve Spear's ANDA is also consistent with agency precedent approving generic versions of other topical drugs with more than one indication based on studies that are not specific for each indication. *See, e.g.*, AR 602 (noting FDA approval of generic topical corticosteroid drug products for

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[2] Bioequivalence is defined 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).

multiple indications based on pharmacodynamic studies that "provide evidence for the amount of drug entering the skin and thus serve as the basis for comparing drug delivery").

FDA fully documented the scientific bases for its decision throughout the administrative record, including in Dr. Hixon's February 20, 2007 memorandum, Dr. Beitz's December 3, 2007 memorandum, the agency's April 11, 2008 citizen petition response, and Dr. Throckmorton's May 30, 2008 memorandum upon reconsideration. AR 636-56; 727-38; 599-609; 1091-1125. In particular, Dr. Throckmorton concluded that FDA's "earlier decision that a single study in AK is adequate to establish bioequivalence for these products is scientifically and procedurally sound." AR 1096. He described the robustness of the BE study that Spear had performed for the AK indication, and concluded "that AK was the appropriate disease state to study in a clinical bioequivalence study comparing 5% 5-FU creams, as it is the model that is more sensitive at detecting differences in product performance between two formulations of 5-FU cream." *Id.* at 1098-99. His decision cited several reasons for concluding "that Spear has demonstrated that the availability of 5-FU at the site of action for both AK and sBCC from its formulation does not differ significantly from that of the Efudex 5% cream." AR 1098.

Once FDA determined that Spear's product was bioequivalent and had satisfied all other requirements for approval, FDA was required by statute to approve Spear's ANDA. 21 U.S.C. § 355(j)(4) ("the Secretary *shall* approve an application for a drug unless the Secretary finds . . .") (emphasis added). Thus, Valeant cannot demonstrate that FDA's thoroughly reasoned, science-based decision to approve Spear's ANDA and deny Valeant's citizen petition was arbitrary and capricious, an abuse of discretion, or otherwise contrary to law. Indeed, at the preliminary injunction stage of this litigation, the Court rejected Valeant's request that FDA be compelled to suspend its approval of Spear's

ANDA "and to evaluate, using its scientific expertise, certain scientific and medical issues," because the FDA had already "done just that." Conclusions of Law (June 18, 2008) ¶ 28, at 26. Nothing that has occurred in the subsequent year can or should alter the Court's conclusion.[3] Because FDA has already thoroughly addressed the scientific and other challenges raised by Valeant, this Court should again decline to "disturb [FDA's] scientific judgment," *id.*, and enter judgment for the federal defendants as a matter of law.

**C. FDA Properly Resolved the Debate Between OGD and DDDP**

Valeant raises two primary challenges to FDA's decision in its amended complaint, neither of which has any merit. First, Valeant alleges that FDA's decision is arbitrary and capricious because FDA did not defer to the opinions of the dermatologists in the DDDP. Am. Compl. ¶ 46. As a matter of administrative law, Valeant asserts that agencies "cannot depart from relying on their own experts . . . and still benefit from deference by the courts." *Id.* ¶ 44. That proposition is simply incorrect, and utterly disregards this Court's conclusion of law, citing the *Serono* decision, 158 F.3d at 1321, that courts "owe[] deference to the view of the agency's authorized decision maker," and that, "[i]n this case, the authorized decision maker in connection with Spear's original approval was the Office of Generic Drugs . . . and the authorized decision makers in connection with the reaffirmation of Spear's approval were Drs. Throckmorton, Woodcock, and von Eschenbach." Conclusions of Law (June 18, 2008) ¶ 34, at 28-29.

As *Serono* recognizes, agencies can and must be able to resolve internal

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[3] Although the administrative record is unchanged from a year ago, Valeant has sought leave to take limited discovery and supplement the record with additional documents. FDA and Spear have opposed Valeant's motion, which is currently pending before Magistrate Judge Alicia Rosenberg. Even if Valeant were to obtain any of the relief it seeks, however, it would provide no basis for overturning FDA's scientific decision – which is based upon unassailable factors and fully supported by the already-voluminous record.

disagreement and the final decision of the authorized decision maker is entitled to deference, notwithstanding internal dissent, including dissent expressed by other scientific experts within the agency. In *Serono*, the court of appeals reversed the district court's grant of a preliminary injunction, noting that "disagreement among FDA chemists" on the scientific issue does not diminish the deference owed to the authorized decision maker. *Serono*, 158 F.3d at 1321. So too, here, the fact that agency scientists disagreed among themselves concerning the appropriateness of a single AK trial for determining BE does not render the agency's conclusion arbitrary and capricious or contrary to law. *Serono*, 158 F.3d at 1320-21; *Pub. Citizen Health Research Group v. FDA*, 740 F.2d 21, 29-30 (D.C. Cir. 1984) (court would not bind Secretary to the advice and recommendations of his subordinates and advisory committees); *Homemakers N. Shore, Inc. v. Bowen*, 832 F.2d 408, 413 (7th Cir. 1987) ("'The Secretary's position' is the position of the Department as an entity, and the fact that people in the chain of command have expressed divergent views does not diminish the effect of the agency's resolution of those disputes.").

Valeant does not and cannot reasonably argue that dermatologists in the DDDP were the authorized decision makers.[4] Authority for approval of generic

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[4] Nor were all of the DDDP personnel involved with the consult on Spear's ANDA actually dermatologists. In fact, the physician who drafted the response first articulating DDDP's view that a clinical trial should be required for the sBCC indication is a certified immunologist, but not a dermatologist. *See* AR 947-49 (consult memorandum from Dr. Hon Sum Ko). In any event, Valeant's request that FDA be directed to "properly consider the conclusions of, and afford proper deference to" DDDP would usurp the agency's Congressionally-directed role as the scientific decision maker for the approval of generic drugs. While a remand to consider DDDP's views might have been warranted had FDA failed to initially consider those views, the remand that Valeant seeks goes much further, and would "propel the court into the domain which Congress has set aside exclusively for the administrative agency." *SEC v. Chenery Corp.*, 332 U.S. 194, 196 (1947). "The Court, it is true, has power 'to affirm, modify, or set aside' the order of the Commission 'in whole or in

drugs is vested in the Office of Generic Drugs (OGD), which has expertise in interpreting and applying the BE requirements imposed by statute and regulation. *See* http://www.fda.gov/smg/vol2/1410/1410_104.html; http://www.fda.gov/smg/vol2/1410/1410_10.html (delegations of agency authority). OGD appropriately sought input from DDDP in resolving whether a single AK study would be sufficient. OGD disagreed with DDDP's views, and, as this Court has already found, "there was a spirited scientific debate" that was resolved by Dr. Beitz, "an oncologist and internist in the Office of New Drugs and the supervisor of the dermatologists." Conclusions of Law ¶ 33, at 28.[5] OGD was not bound to accept DDDP's views on BE, particularly when those views were rejected by the supervisory component over DDDP.

In Dr. Beitz's December 3, 2007 memorandum, she reviewed and described the AK and sBCC disease states in detail, and cited numerous reasons for her conclusion that a single AK study would suffice to demonstrate BE between Spear's and Valeant's products. *See* AR 736-37 & text *supra* at 8 (summarizing reasons). Her memorandum thus dispels any claim by Valeant that FDA failed adequately to consider the views of its scientists in the DDDP.

FDA's decision makers fully addressed the points raised by DDDP and explained the agency's ultimate disagreement with those views as a scientific matter. The agency's decision – subsequently reaffirmed by Drs. Throckmorton, Woodcock, and then-Commissioner von Eschenbach and articulated at great

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part.'… But that authority is not power to exercise an essentially administrative function." *Fed. Power Comm'n v. Idaho Power Co.*, 344 U.S. 17, 21 (1952).

[5] Dr. Throckmorton, who subsequently reviewed Dr. Beitz' conclusions, is likewise a board-certified internist as well as a nephrologist. Indeed, all of the FDA senior scientists who considered these issues and reaffirmed the approval of Spear's ANDA during the reconsideration process (including Dr. Woodcock and Dr. von Eschenbach) are distinguished and eminently qualified physicians.

length in the administrative record (AR 599-626, 727-739, 1091-1225) – was in no sense arbitrary or capricious, and merits this Court's continued deference.

**D. FDA Properly Mitigated Dr. Wilkin's Potential Conflict**

Secondly, Valeant alleges that FDA's decision to approve Spear's ANDA is tainted because FDA originally relied on an assertedly improper submission from Dr. Wilkin, and then failed to adequately mitigate the effect of that submission during the reconsideration process. Am. Compl. ¶¶ 47-61. In an analogous context, when plaintiffs alleged that an agency's decision should be voided by an improper ex parte communication, the Ninth Circuit considered whether the "agency's decisionmaking process was irrevocably tainted so as to make the ultimate judgment of the agency unfair, either to an innocent party or to the public interest that the agency is obliged to protect." *Sw. Sunsites, Inc. v. FTC*, 785 F.2d 1431, 1436 (9th Cir. 1986) (quoting *PATCO v. FLRA*, 685 F.2d 547, 564 (D.C. Cir. 1982)). Relevant considerations include the gravity of the communication, whether the communication may have influenced the decision, whether the party making the communication benefitted from the decision, whether opposing parties knew of the communication and had an opportunity to respond, and whether vacating or remanding the decision would serve a useful purpose. *Id.* The primary concern, however, is "the integrity of the process and the fairness of the result rather than adherence to mechanistic rules." *Id.*

Consistent with these principles, FDA took proper measures to maintain the "integrity of the process" and mitigate the potential conflict of interest that arose from Dr. Wilkin's submission. As noted, Dr. Julie Beitz, Director of CDER's Office of Drug Evaluation III ("ODE III"), which oversees the DDDP,[6] wrote the agency's decisional memorandum that served as the basis of the agency's approval

[6] ODE III (within the Office of New Drugs) oversees three separate divisions, including DDDP. *See* http://www.fda.gov/cder/cderorg/cder-all.pdf.

of Spear's ANDA and its April 11, 2008 citizen petition response. AR 1095. In her memorandum, she notes that Spear submitted the expert opinion of Dr. Jonathan Wilkin, M.D., to support approval of its ANDA. AR 730 n.6. Dr. Beitz acknowledged that Dr. Wilkin had been the Director of DDDP from 1994 to 2005, but stated her understanding that "Dr. Wilkin does not appear to have been involved in this matter during his tenure at FDA." *Id.* Subsequently, when compiling the administrative record for this case, FDA staff discovered that, in 1999 and 2000, Dr. Wilkin *had* reviewed a written response that DDDP had provided in consultation on Spear's application. AR 1107 (referring to consult documents at AR 947-949; 977-982).

Although Dr. Wilkin's action did not implicate the integrity of any agency decision maker, FDA took immediate steps to mitigate the potential conflict of interest concerning his submission out of an abundance of caution and to avoid any appearance of impropriety.[7] Accordingly, Dr. Beitz considered whether she would have reached the same conclusion if she discounted the information provided by Dr. Wilkin. In a memorandum dated May 29, 2008, Dr. Beitz concluded that she could "unequivocally state that I would have reached the same conclusion regarding the approvability of Spear's ANDA even if I had not considered Dr. Wilkin's submission." AR 1108. She found two of his comments of particular relevance. *Id.* at 1107.

First, Dr. Wilkin stated that "it is well known and accepted that the greatest

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[7] Apart from its actions with respect to Spear's application, FDA referred the Wilkin matter to its ethics office to determine whether to pursue criminal action against Dr. Wilkin for the potential conflict of interest, which is the only remedy available to the agency for actions taken by former FDA employees. At this Court's invitation, FDA submitted declarations from FDA and HHS officials describing their determination that no further investigation into the matter was warranted.

barrier to penetration through the skin is the stratum corneum." *Id.* After reviewing the literature, Dr. Beitz agreed that this observation was widely-held, and that the agency had considered that information prior to Dr. Wilkin's submission. *Id.* (citing references at AR 60-86; 412–22). Second, Dr. Wilkin stated that the stratum corneum is disrupted or absent in sBCC, but may have an abundance of adherent stratum corneum-related material in AK that prevents absorption. Again, Dr. Beitz determined that Dr. Wilkin's assertion was well supported in the published literature, including in a reference submitted by Valeant in support of its citizen petition well before Spear's submission of Dr. Wilkin's opinion to FDA. *Id.* at 1107-08 (citing references at AR 60-86; 412-422; 801-806; 807-814; 815-823; 870-875).

Notably, Dr. Beitz's conclusions are entirely consistent with the memorandum written by Dr. Dena Hixon of OGD on February 20, 2007, before Dr. Wilkin submitted his expert opinion. *See* Findings of Fact (June 18, 2008) ¶ 50, at 12. The OGD memorandum noted both that the stratum corneum is considered to be the predominant barrier to topical drug delivery, and that it is thickened for AK. AR 645-46. Dr. Hixon also thoroughly addressed the objections raised by DDDP. *Id.* at 653-66. Thus, Dr. Wilkin's submission added little new information to the wealth of information already before Dr. Beitz. Moreover, Dr. Wilkin did not support his assertions with references to the literature. Dr. Beitz independently identified and confirmed the scientific bases for her decision, as evidenced by her lengthy memorandum and supporting documentation in the administrative record. AR 727-909; *see also* CP Response, AR 606 ("The Agency's review of the relevant scientific studies suggests that the thickened stratum corneum in AK could provide a greater barrier to cutaneous penetration of topical 5-FU than the compromised stratum corneum in sBCC."). Valeant does not even challenge these scientific conclusions, suggesting instead that Dr. Beitz was somehow improperly swayed by Dr. Wilkin, a former FDA

employee who had once been *under* her authority. Valeant's speculation has no support in the record, nor has it raised any genuine issue of material fact that Dr. Beitz's decision was based on anything other than her own scientific conclusions.

In addition, Dr. Throckmorton considered Dr. Beitz's May 29, 2008, memorandum, and agreed with Dr. Beitz "that the statements made by Dr. Wilkin were based on information that is generally available and could reasonably have been derived from other submitted materials. As a result, omitting Dr. Wilkin's letter from the record does not change the conclusion regarding the approvability of the Spear ANDA." *Id.* at 1096. Dr. Woodcock independently reviewed the matter and concurred with Dr. Throckmorton. *Id.* at 1090. She conveyed her recommendation to the Commissioner, who reaffirmed the approval of Spear's ANDA. *Id.* at 1088.

Contrary to Valeant's assertion, FDA did not need to begin the process all over again with officials "who were not tainted by the approval or reaffirmation" of Spear's ANDA. Am. Compl. at 18. As this Court has already found, "FDA took the responsible course of action and requested a stay of proceedings in order to assess the effect, if any, of a potential conflict of interest and to determine whether any additional scientific data were needed in support of Spear's ANDA approval." Conclusions of Law ¶ 40, at 30. "Furthermore, there is no legal requirement that 'new' agency personnel must be involved in the reconsideration process." *Id.* ¶ 41, at 31. Here, given Dr. Beitz's determination that Dr. Wilkin's comments merely reiterated publicly available information, the thoroughness with which she had independently researched and documented her original decision, and her certainty that she would have reached the same conclusion without his submission, FDA determined that it was not necessary to start the review process from scratch. While Valeant may have desired a different method for addressing that issue, the particular procedure employed by FDA is reasonable, particularly given FDA's limited resources. Requiring FDA to find new personnel to review

Spear's ANDA without reference to Dr. Wilkin's submission – a submission containing statements that Valeant has not and cannot challenge from a scientific perspective – would simply divert valuable agency resources from other matters that are more pressing to public health.

Moreover, to the extent that Valeant challenges FDA' s decisionmaking process in addressing the Dr. Wilkin issue, that challenge must fail. "Courts have limited authority to impose procedural requirements upon a federal agency which seeks to exercise the responsibilities committed to it by Congress. A history of statutory and decisional law cautions 'reviewing courts against engrafting their own notions of proper procedures upon agencies entrusted with substantive functions by Congress.'" *Wilderness Soc'y v. Tyrrel*, 918 F.2d 813, 816 (9th Cir. 1990) (quoting *Vt. Yankee Nuclear Power Corp. v. Natural Res. Def. Council Inc.,* 435 U.S. 519, 525 (1978)); *accord Adkins v. Trans-Alaska Pipeline Liab. Fund*, 101 F.3d 86, 89 (9th Cir. 1996) ("absent constitutional constraints or extremely compelling circumstances, we defer to an administrative agency's fashioning of procedures"). Similarly, in *Lands Council v. McNair*, 537 F.3d 981, 993 (9th Cir. 2008), the *en banc* Ninth Circuit reasoned that such deference to an agency's procedures "acknowledges that "[w]e are not free to impose on the agency [our] own notion of which procedures are best or most likely to further some vague, undefined public good." *Id.* (internal quotation marks omitted) (alterations in original).

By removing consideration of Dr. Wilkin's submission and ensuring that its conclusion was scientifically sound notwithstanding that submission, FDA took reasonable action to mitigate the potential conflict of interest issue and ensure the integrity of its decisionmaking process, as the record clearly demonstrates. Valeant's attempt to dictate the agency's procedures for addressing this unique situation has no merit.

## CONCLUSION

For the foregoing reasons, summary judgment should be entered for the federal defendants.

Dated: June 8, 2009

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