UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

GRACEWAY PHARMACEUTICALS, LLC, Plaintiff, v. KATHLEEN SEBELIUS, Secretary, Department of Health and Human Services, et al., Defendants, and NYCOMED US, INC., Defendant-Intervenor.	)	Civil Action No. 10-1154 (RBW)

MEMORANDUM OPINION

The plaintiff filed its Complaint in this case on July 8, 2010, alleging that certain actions taken by the United States Food and Drug Administration (the "FDA") violated both the Administrative Procedure Act ("APA"), 5 U.S.C. § 702 (2006), and the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(a) (2006). This case is now before the Court on the parties' cross-motions for summary judgment. See Plaintiff's Motion for Summary Judgment ("Pl.'s Mot."); Federal Defendants' Motion for Summary Judgment ("Defs.' Mot.").[1] Defendant-

[1] In resolving these motions, the Court also considered the following: the Complaint ("Compl."); the Memorandum of Points and Authorities in Support of Plaintiff's Motion for Summary Judgment ("Pl.'s Mem."); the Plaintiff's Statement of Administrative Record Citations Pursuant to Local Rule 7(H) ("Pl.'s Stmnt."); the Federal Defendants' Memorandum in Opposition to Plaintiff's Motion for Summary Judgment and in Support of Cross-Motion for Summary Judgment ("Defs.' Mem."); the Federal Defendants' Statement of Facts ("Defs.' Stmnt."); Nycomed US, Inc.'s Opposition to Plaintiff's Motion for Summary Judgment and in Support of the Federal Defendants' Cross-Motion for Summary Judgment ("Def.-Int.'s Mem."); the Plaintiff's Reply in Support of its Motion for Summary Judgment and Opposition to Defendants' Motion for Summary Judgment ("Pl.'s Reply"); the (Continued . . .)

Intervenor Nycomed US, Inc. ("Nycomed") opposes the plaintiff's motion for summary judgment and supports the federal defendants' motion for summary judgment.[2] See Def.-Int.'s Mem. at 1. For the reasons explained below, the plaintiff's motion for summary judgment is denied and the defendants' motion for summary judgment is granted.

I. BACKGROUND

A. Statutory and Regulatory Framework

The FDCA provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to . . . this section is effective with respect to such drug." 21 U.S.C. § 355(a). In other words, the FDCA "requires all new prescription drugs to obtain FDA approval under a new drug application ('NDA') before they can enter the marketplace." Pl.'s Mem. at 4. An NDA submitted by a drug manufacturer seeking FDA approval of a brand name drug, also known as a pioneer drug,[3] must include, among other information, "full reports of investigations which have been made to show whether . . . [the] drug is safe for use and whether [the] drug is effective in use." 21 U.S.C. § 355(b)(1)(A). A drug manufacturer seeking FDA approval of a generic drug may, however, obtain such approval with an abbreviated new drug application ("ANDA"). Id. § 355(j)(1). An ANDA "must show that the generic drug contains the same active ingredient as the pioneer, in

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Federal Defendants' Reply Memorandum in Support of Cross-Motion for Summary Judgment; and Nycomed US, Inc.'s Reply to Graceway's Opposition to the Defendants' Cross-Motion for Summary Judgment.

[2] The Court granted Nycomed's unopposed motion to intervene pursuant to Federal Rule of Civil Procedure 24(a)(2) on August 20, 2010. See Graceway v. Sebelius, et al., Civil Action No. 10-1154 (RBW) (D.D.C. August 20, 2010).

[3] A brand name or pioneer drug is also known as a "listed" drug. See 21 U.S.C. § 355(j)(2)(A)(i) (noting that a drug previously approved through an NDA will be referred to in that statutory subsection, which addresses abbreviated new drug applications, as the "listed" drug); Astellas Pharma US, Inc. v. FDA, 642 F. Supp. 2d 10, 13 (D.D.C. 2009) ("Once approved, the pioneer drug is referred to as a 'listed' drug.").

the same strength, dosage form, and route of administration; is labeled for the same uses and . . . is shown to be 'bioequivalent' to the pioneer." Pl.'s Mem. at 5 (citing 21 U.S.C. § 355(j)(2)(A)). Thus, rather than requiring a new showing of the generic's safety and effectiveness, the FDCA "requires a showing that the proposed generic operates in the same manner as the pioneer drug on which it is based." Astellas Pharmas, 642 F. Supp. 2d at 14. The FDA must approve the generic manufacturer's ANDA unless the ANDA fails to provide the statutorily required information. See id. (citing 21 U.S.C. § 355(j)(4)).

"A drug shall be considered to be bioequivalent to a listed drug 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). Additionally, for locally acting, topical drugs, "the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the [proposed generic] drug and the listed drug in safety and therapeutic effect." Id. § 355(j)(8)(C).

A demonstration of bioequivalence can depend on the type of drugs involved. For example, for drugs that work systemically by circulating in the bloodstream after ingestion in the form of a pill or capsule, bioequivalence is typically measured "by comparing the rate and extent of absorption of the active ingredients in the blood." Compl. ¶ 21. More relevant to this case, for products that are administered topically and act locally, bioequivalence must be measured differently, using a more subjective approach. Id. ¶ 22. For such products, the FDA must often rely on comparative clinical studies to conclude that a proposed generic drug and a pioneer drug are bioequivalent. Id. (citing 21 C.F.R. § 210.24(b)(4)). In a comparative clinical trial, patients are given either the proposed generic drug, the listed drug, or a placebo, with the goal being the determination "whether there is a clinically significant difference in the performance of the two

drugs in treating a specific" condition.[4] Id. ¶ 23. A comparative clinical trial, therefore, does not directly measure "the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of action." Id.¶ 24 (quoting 21 C.F.R. § 320.1(e), the federal regulation defining bioequivalence); see Compl. ¶ 24 (citing 21 C.F.R. § 324(b) and observing that FDA regulations list methodologies for determining bioequivalence). Nonetheless, because a comparative clinical trial measures the effect of the pioneer drug and the proposed generic in treating a specific condition and compares the results, there can be a finding of bioequivalence even though there is no direct measurement of the rate and extent of drug absorption. Compl. ¶ 24. The bioequivalence analysis can be more complicated when a single, locally acting drug is approved for treating two or more conditions. Id. ¶ 25. Nevertheless, the FDA has allowed a comparative study of a locally acting drug approved to treat one condition to suffice as proof of bioequivalence in the treatment of another condition when the conditions are "related" and involve the "same site of action." Id. ¶ 26. According to the plaintiff, the "rationale behind this practice is that if two conditions are related and occur at the same site of action, [the] FDA can properly extrapolate bioequivalence from one condition to the other." Id.

B. Factual and Procedural History

The plaintiff manufactures Aldara, a topical, locally acting cream that was first approved as a pioneer drug by the FDA on February 27, 1997. Pl.'s Stmnt. ¶ 1. Aldara's active ingredient is imiquimod. Id. Aldara is currently approved by the FDA for the treatment of three conditions (also known as "indications"). Id. ¶ 2; see Defs.' Stmnt. ¶ 1. First, in 1997, the FDA approved

[4] A comparative clinical trial should not be confused with a standard clinical trial. In a standard clinical trial, patients are given only a test drug or a placebo. Compl. ¶ 23. The goal of the trial is therefore simply to ascertain whether the test drug has a clinical effect over and above that seen with the placebo in treating a specific condition, not the comparison of the effectiveness of two different drugs in treating one condition. Id.

Aldara for the treatment of external genital and perianal warts ("genital warts" or "EGW"), a form of sexually transmitted disease caused by infection with certain strains of the human papillomavirus. Pl.'s Stmnt. ¶ 2. Then in 2004, the FDA approved Aldara for the treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses ("actinic keratoses") on the face or scalp. Id. ¶ 3. Actinic keratoses are flat, scaly growths on the skin that usually form on parts of the body that are exposed to direct sunlight. Id. In order to obtain this approval for the use of Aldara in treating actinic keratoses, the FDA required the plaintiff to conduct clinical studies involving patients with actinic keratoses and did not allow the plaintiff to extrapolate the drug's effectiveness in treating actinic keratoses from studies conducted in connection with Aldara's approval in treating genital warts. Id. "Also in 2004, [the] FDA approved Aldara for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma" ("sBCC"), which "is among the most common forms of cancers in" Caucasians. Id. ¶ 4.

On June 23, 2004, defendant-intervenor Nycomed submitted to the FDA a draft protocol for conducting a clinical bioequivalence study involving patients with EGW as part of its effort to obtain FDA approval for a generic version of Aldara. Id. ¶ 8. On March 11, 2005, the FDA's Office of Generic Drugs, the division of the FDA charged with reviewing Nycomed's ANDA, provided written comments on Nycomed's proposed protocol in which it instructed the applicant to perform a single clinical bioequivalence study involving patients with actinic keratoses, rather than EGW. Id. ¶ 9; Pl.'s Mem. at 8. On that same date, the Office of Generic Drugs provided the same instructions regarding clinical bioequivalence studies involving patients with actinic keratoses to a number of other applicants seeking approval for generic versions of Aldara. Pl.'s Stmnt. ¶ 10. Four years later, in March of 2009, the Office of Generic Drugs prepared a draft guidance for imiquimod and sent it to the FDA Dermatology Division for review. Id. ¶¶ 12-13.

In its June 15, 2009 response, the Dermatology Division rejected the Office of Generic Drugs' view that a single study concerning actinic keratoses was appropriate. Id. ¶ 14. Rather, the Dermatology Division recommended that if the FDA were going to allow generic applicants for Aldara to conduct a single clinical trial for purposes of demonstrating bioequivalence, that the study should involve patients with sBCC, not actinic keratoses. Id. The Dermatology Division later went a step further and recommended that applicants for generic versions of Aldara conduct clinical studies involving patients with EGW as well. Id. ¶ 15.

On July 30, 2009, the plaintiff filed a Citizen Petition in which it asked the "FDA to require any ANDA for a generic imiquimod cream product relying on Aldara as the [pioneer drug, or] referenced product[,] to include [among other things,] comparative clinical data showing bioequivalence in patients with genital warts."[5] Id. ¶ 19. The Petition set forth the plaintiff's view that genital warts are completely unrelated to actinic keratoses and sBCC, both in terms of the cause and the nature of the conditions. Id. ¶ 21. The Petition further explained the plaintiff's position that genital warts have a different site of action than actinic keratoses and sBCC because they occur in "very different skin at very different locations on the body." Id. In other words, the plaintiff's Citizen Petition made both "relatedness" and "site of action" arguments. July 30, 2009 Citizen Petition of Graceway Pharmaceuticals ("Citizen Petition") at 7 (FDA 000007).[6]

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[5] FDA regulations permit the filing of a citizen petition by those with rights to or scientific knowledge of a brand name drug. A citizen petition requests that the FDA either take or refrain from taking certain administrative action. See 21 CFR §§ 10.25(a) (identifying a citizen petition as one means by which an administrative proceeding may be initiated) and 10.30(e) (setting forth the Commissioner's duties in ruling upon citizen petitions).

[6] Where the Court determines that a citation to documents in the administrative record is appropriate, the Court will identify the name of that document, its internal page number, and where that page may be found in the administrative record.

As part of the FDA's review and analysis of the plaintiff's Citizen Petition, the FDA's Center for Drug Evaluation and Research ("CDER"), Office of Regulatory Policy, prepared a set of questions and formally presented them to both the FDA's Office of Generic Drugs and the Dermatology Division. Defs.' Stmnt. ¶ 33. The Office of Generic Drugs responded to the Office of Regulatory Policy's questions with a 42-page memorandum, in which it set forth its reasons for concluding that a "well-designed imiquimod bioequivalence study that did not include an EGW study would be sufficiently sensitive to detect formulation differences." Id. ¶ 34. By contrast, the Dermatology Division responded to the questions with a five-page memorandum, in which it noted its agreement with the plaintiff that EGW is unrelated to and occurs at different anatomical locations than actinic keratoses and sBCC. Id. ¶ 35. The Dermatology Division also recommended that trials involving patients with EGW should be required to establish bioequivalence between Aldara and generic imiquimod creams. Id. Due to the conflicting recommendations from the Office of Generic Drugs and the Division of Dermatology, "the matter was elevated" within the FDA and Dr. Julie Beitz, the Director of the Office of Drug Evaluation III, of which the Division of Dermatology is a component, was asked to review and resolve the disputed issues. Id. ¶ 36. Dr. Beitz, an oncologist, an internist, and the supervisor of the FDA dermatologists, id., conducted an independent review of the issues and the relevant scientific literature before ultimately concluding that a clinical trial using patients with actinic keratoses would be "sufficient to establish bioequivalence for generic imiquimod." Id. ¶ 37. Dr. Beitz's decision thus overruled the Division of Dermatology, supported the Office of Generic Drug's conclusion, and resolved the conflict that had arisen between the two divisions of the FDA. Id.

On January 26, 2010, the FDA issued a Citizen Petition Response (the "Response") in which it concluded that a single comparative clinical study involving patients with actinic keratoses is sufficient to demonstrate bioequivalence in all three conditions for which Aldara has FDA approval—genital warts, actinic keratoses, and sBCC.[7] Pl.'s Stmnt. ¶ 22; see January 26, 2010 letter from Dr. Janet Woodcock at 1 (FDA000366). The Response drew largely from Dr. Beitz's research and conclusions. Defs.' Stmnt. ¶ 41. In its Response, the FDA rejected the plaintiff's argument that indications must be related for a clinical trial in one indication to establish bioequivalence for a multi-indication drug. Id. ¶ 9. Despite its rejection of the plaintiff's argument that indications must be related in order for the extrapolation of data from a study of one indication to be appropriate, the FDA Response nevertheless concluded that genital warts, actinic keratoses, and sBCC "were in fact related because each [condition] responds to topical treatments that enhance local and cell-mediated immunity in immunocompetent individuals." Id. ¶ 15. The FDA's Response also gave two reasons why the FDA rejected the plaintiff's site of action argument. Id. ¶ 16. First, the FDA concluded that it would be appropriate to use an actinic keratoses trial to establish bioequivalence between Aldara and a generic imiquimod cream even if the sites of action for genital warts and imiquimod were different. See id. ¶ 17 ("The [FDA] explained that 'even for drugs with multiple sites of action, one study would be sufficient to show bioequivalence if the [FDA] reasonably concluded that a showing of equivalent drug delivery . . . in an indication with a certain site of action was sufficiently predictive of equivalent drug delivery at the other site or sites of action."). Second,

[7] After the filing of its first Citizen Petition on July 30, 2009, on August 28, 2009, the plaintiff filed a second Citizen Petition in which it raised additional reasons why generic imiquimod creams should not be approved without studies more extensive than those required by the FDA. Defs.' Stmnt. ¶ 6. This second Petition was apparently also denied by the FDA, but the plaintiff has not challenged this denial. Id. Accordingly, the only Citizen Petition denial at issue in this case is the denial of the July 30, 2009 Petition.

the FDA concluded that even if separate clinical trials were required where the site of action is different, the outcome with regard to Aldara and generic imiquimod creams would be unchanged because the sites of action for genital warts and sBCC are the same. Id. ¶ 18. The FDA explained that because "the therapeutic action of topical imiquimod occurs within the epidermis itself, that is the site of action for each of the drug's three approved indications." Id. The Response was signed by Dr. Janet Woodcock, the Director of the CDER, and the person specifically delegated the authority to decide Citizen Petitions pertaining to human drugs. Id. ¶ 41; see id. ("The Office of Generic Drugs, [the Office of Drug Evaluation III] (including [the Division of Dermatology]), and every other FDA office responsible for the review and approval of human drugs ultimately report to Dr. Woodcock.").

On February 25, 2010, the FDA approved Nycomed's ANDA for an imiquimod topical cream. Pl.'s Stmnt. ¶ 24. The demonstration of bioequivalence in Nycomed's ANDA was supported by clinical trials conducted by Nycomed involving patients with actinic keratoses. Id. ¶ 26.

II. STANDARD OF REVIEW

A. Summary Judgment

Courts will grant a motion for summary judgment under Rule 56(a) of the Federal Rules of Civil Procedure only if the moving party has shown "that there is no genuine dispute as to any material fact and [it] is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). Moreover, "in ruling on cross-motions for summary judgment, the Court shall grant summary judgment only if one of the moving parties is entitled to judgment as a matter of law upon material facts that are not genuinely disputed." Muwekama Ohlone Tribe v. Kempthorne, 452 F. Supp. 2d 105, 113 (D.D.C. 2006) (Walton, J.) (citation omitted). Summary judgment "is an

appropriate procedure when a court reviews an agency's administrative record," Shays v. FEC, 424 F. Supp. 2d 100, 109-10 (D.D.C. 2006), and, because this case "involves a challenge to a final administrative action, the Court's review is limited to the administrative record." Fund for Animals v. Babbitt, 903 F. Supp. 96, 105 (D.D.C. 1995) (citing Camp v. Pitts, 411 U.S. 138, 142 (1973)).

B. Judicial Review of Agency Actions

The APA entitles a person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action to judicial review. 5 U.S.C. § 702; Hill Dermaceuticals, Inc. v. FDA, 524 F. Supp. 2d 5, 9 (D.D.C. 2007). The APA requires the reviewing court to set aside an agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). In conducting this review, considerable deference must be accorded to the agency. See Citizens to Pres. Overton Park, Inc. v. Volpe, 401 U.S. 402, 416 (1971). Specifically, in the context of this case, the FDA's evaluations of scientific data within its area of expertise are entitled to a high level of deference. See Serono Labs., Inc., v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998). Accordingly, "[t]here is a presumption in favor of the validity of the administrative action." Bristol-Myers Squibb Co. v. Shalala, 923 F.Supp. 212, 216 (D.D.C. 1996).

Despite the presumption of validity and the deference that must be afforded to an agency's actions, a reviewing court "must consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." Marsh v. Or. Natural Res. Council, 490 U.S. 360, 378 (1989) (internal quotation marks omitted). At a minimum, the agency must have considered relevant data and articulated an explanation establishing a "rational connection between the facts found and the choice made." Bowen v. Am.

Hosp. Ass'n, 476 U.S. 610, 626 (1986) (citation omitted). An agency action usually is arbitrary or capricious if

> the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Motor Veh. Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983); see also County of L.A. v. Shalala, 192 F.3d 1005, 1021 (D.C. Cir.1999) ("Where the agency has failed to provide a reasoned explanation, or where the record belies the agency's conclusion, [the court] must undo its action."). As noted, the "requirement that agency action not be arbitrary or capricious includes a requirement that the agency adequately explain its result." Pub. Citizen, Inc. v. FAA, 988 F.2d 186, 197 (D.C. Cir.1993). This requirement is not particularly demanding, however. Id. Nothing more than a "brief statement" is necessary, so long as the agency explains "why it chose to do what it did." Tourus Records, Inc. v. DEA, 259 F.3d 731, 737 (D.C. Cir. 2001). If the court can "reasonably . . . discern[ ]" the agency's path, it will uphold the agency's decision. Pub. Citizen, 988 F.2d at 197 (citing Bowman Transp., Inc. v. Arkansas-Best Freight Sys., Inc., 419 U.S. 281, 286 (1974)).

III. ANALYSIS

The Court's analysis begins with the District of Columbia Circuit's pronouncement that the FDA's "evaluations of scientific data within its area of expertise . . . [are] entitled to a high level of deference." Serono, 158 F.3d at 1320 (internal quotation marks and citation omitted). This Circuit has also stated that the FDA's "judgment[] as to what is required to ascertain the safety and efficiency of drugs falls squarely within the ambit of the FDA's expertise and merit[s] deference" from the courts. A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1490 (D.C. Cir. 1995)

(citation omitted). Moreover, this "high degree of deference has been applied to the FDA's determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic." Astellas Pharma, 642 F. Supp. 2d at 19 (citing Serono, 158 F.3d 1325; Bristol-Myers Squibb, 923 F. Supp. at 217-18; Somerset Pharm., Inc. v. Shalala, 923 F. Supp 443 at 453 (D.Del. 1997)); see Schering Corp. v. FDA, 51 F.3d 390, 399 (3d. Cir. 1995) (holding that the FDA's approval of an ANDA was valid because, although a finding of 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").

As noted above, the plaintiff makes two principal arguments why the FDA's actions in denying its Citizen Petition were arbitrary, capricious, and contrary to law. First, the plaintiff challenges the FDA's conclusion in its Response that external genital warts, actinic keratoses, and sBCC all share the same site of action. See Pl.'s Mem. at 15. Second, the plaintiff maintains that the FDA's conclusion in its Response that external genital warts are related to actinic keratoses and sBCC was based on an illogical conclusion and was contrary to the evidence before it. See id. at 23. The FDA, on the other hand, maintains that both of these conclusions were based upon reasoned scientific analysis, and were therefore not arbitrary, capricious, or otherwise contrary to law. See Defs.' Mem. at 14-16. For the reasons that follow, the Court must side with the defendants.

A. The plaintiff's site of action argument

The plaintiff contends that the FDA's conclusion that there is not a "sufficiently material difference in absorption properties between skin located in the genital area and skin located on the face and scalp" was a departure from its past agency positions and not supported by sufficient explanation. Pl.'s Mem. at 16. The plaintiff further maintains that the "FDA tries to sidestep this

issue by asserting that the site of action for imiquimod is not where on the body the drug acts but rather in what layer of skin." Id. (internal emphases omitted). The plaintiff also strenuously asserts that the impropriety of the FDA's position is evidenced by the fact that the "FDA's own experts in the Dermatology Division" agreed with the plaintiff that "EGW occur at different anatomical locations with different types of skin." Id. at 15. Finally, the plaintiff argues that the FDA has improperly transferred the burden of proof concerning bioequivalency, or specifically the lack thereof, to the plaintiff rather than requiring the generic manufacturer seeking ANDA approval to show bioequivalence. Id. at 22. For these reasons, the plaintiff posits that it was a violation of the APA for the FDA to permit manufacturers seeking approval of generic imiquimod creams to submit bioequivalence studies based solely on actinic keratoses. See Pl.'s Mem. at 18 (discussing the site of action argument in connection to the labeling requirements imposed on Aldara).

The FDA responds that the pertinent question regarding the plaintiff's site of action argument "is not whether the two sites are the same in all respects, but whether they would respond to treatment with the generic product to the same extent that they would to Aldara, and that [this] is a question that requires scientific expertise to answer." Defs.' Mem. at 19. The FDA further contends that "[the plaintiff's] argument that the 'sites of action' are different, boils down to an assertion that the properties of [actinic keratoses] and EGW-affected skin must be different, and a belief that this must matter somehow." Id. (internal footnote omitted). The FDA maintains that its Response "considered and rejected all of these assertions and explained that it found 'no direct support in the literature for [the plaintiff's] contention that the absorptive properties of EGW-affected skin are significantly different from [actinic keratoses] or sBCC-affected skin.'" Id. (quoting the Response at 10). The FDA thus asserts that the Response's

rejection of the plaintiff's site of action argument was based on reasonable and well-founded scientific research. See id. at 14 (the "FDA issued a thorough and well-considered response to [the plaintiff's] Citizen Petition"), 27 (the FDA's Response "reflects and details its final position on the bioequivalence issues after the resolution of the intra-agency disagreements").

The plaintiff makes much of the Dermatology Division's assessment of the issues in question, namely, its opinion that a clinical trial based solely on patients with actinic keratoses would be insufficient to demonstrate bioequivalence between Aldara and generic imiquimod given the different sites of action. See Pl.'s Mem. at 15 ("But more telling still, in the matter at hand, [the] FDA's own experts in the Dermatology Division told the decisionmakers: 'We further agree that EGW occur at different anatomical locations with different types of skin. Of the three indications, EGW is the only one that could potentially involve mucosal skin. If there is some difference in behavior of a generic product on mucosal skin as compared to Aldara, such a condition could only be identified in the study of EGW.'") (quoting November 18, 2009 letter from Dr. Brenda Carr to Dr. Beitz)); Pl.'s Reply at 2 ("[A]s the FDA dermatologists aptly pointed out, [the] FDA simply can make no predictive statements about how the generic product will work in patients with EGW without running clinical tests in patients with that disease."). The fact remains, however, that within the FDA hierarchy, the Dermatology Division does not, and in this case did not, have the final word in responding to the plaintiff's Citizen Petition. Rather, that authority belongs to Dr. Janet Woodcock as the director of the CDER. Defs.' Stmnt. ¶ 41. As the District of Columbia Circuit observed in Serono,

> deference is owed to the decisionmaker authorized to speak on behalf of the agency, not to each individual agency employee. . . . Indeed, were we to hold otherwise, we would effectively empower any individual employee not just to veto the views of the agency head, but to preclude any deference to the agency at all, since we would have no basis for deciding to whose view we should defer.

> Dr. Woodcock was the authorized decisionmaker for the agency on this matter . . . and hers is the view to which the courts owe deference.

158 F.3d at 1321 (internal citations omitted). Accordingly, the Court must examine the extent to which the Response, signed by Dr. Woodcock and issued pursuant to her authority as director of the CDER, contained well-reasoned explanations.

The internal disagreement between the different divisions of the FDA is certainly not irrelevant, but neither is it the dispositive proof of arbitrary and capricious action that the plaintiff seems to believe it is. Had the FDA entirely ignored the opinion offered by the Dermatology Division regarding the need for tests run in patients with EGW, then there would be some evidence that the FDA's actions were perhaps arbitrary or capricious. Here, however, after the internal disagreement arose, the FDA elevated the matter to Dr. Beitz, the "supervisor of the dermatologists," Defs.' Stmnt. ¶ 36, who conducted a new round of research and offered her own, independent findings, id. ¶ 37. Examining the exact argument raised by the Dermatology Division, Dr. Beitz concluded that

> the "site of topical imiquimod is the epidermis where imiquimod induces the production of cytokines, including interferon alpha, that stimulate both a localized immune response and a cellular immune response" . . . [and that] "for all three indications, topical imiquimod will be effective only if the product can induce the requisite immune response in the immunocompetent host. If such response is induced, then the lesion will respond, regardless of the underlying pathophysiology of the lesion, its anatomic location, or the skin type involved."

Id. ¶¶ 38, 39 (quoting January 26, 2010 Memorandum from Dr. Beitz).[8] This language was then incorporated in the Response. Id. ¶ 39. In assessing whether the FDA actions in a similar

[8] Dr. Beitz discussed in her memorandum both how imiquimod works and where it works. The plaintiff asserts that the FDA's discussion of how imiquimod works in treating EGW, actinic keratoses, and/or sBCC is itself arbitrary and capricious because "for years, [the] FDA has consistently taken the position that the mechanism of action of imiquimod in treating [actinic keratoses] is not known." Pl.'s Mem. at 17 (internal emphasis omitted). This argument refers to decisions made in 2004 in connection to FDA requirements regarding the language that would be contained in Aldara's label. The FDA responds that it was actually the proposal of Graceway's predecessor, 3M, that was not supported and that the FDA did not pursue the mechanism of action because "in the context of labeling,

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context were arbitrary and capricious, the court in Actavis Elizabeth LLC v. FDA concluded that it could "quickly dispose of" the plaintiff's challenge because it made "too much of the draft manual provision and [the] FDA's alleged flip-flopping." 689 F. Supp. 2d 174, 180 (D.D.C. 2010). The Court noted that "[t]he official policy of the agency is expressed in the formal regulations, not in any draft manual provision that precedes the promulgation of the regulations." Id. Somewhat similarly, here, the Dermatology Division's opinion was not the opinion adopted by the FDA when all was said and done; and, so long as the FDA provided its reasons for disagreeing with its own Dermatology Division when rendering its final conclusion, which the Response did, then the Court must give deference to the FDA's official position.[9] See Sanofi-Aventis v. FDA, 733 F. Supp. 2d 162, 172 (D.D.C. 2010) (examining the parties' arguments, and finding "[n]or is this a case in which the FDA simply glossed over its earlier decisions. To the contrary, the FDA provided legitimate reasons for [its decisions]") (internal quotations and citations omitted)).

Thus, upon the Court's review of the administrative record it is clear that the "FDA produced a comprehensive response to the plaintiff's Citizen Petition, in which it specifically

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(. . . continued)
once a determination has been made that a drug is safe and effective for its intended use, no decision needs to be made concerning the drug's mechanism of action. . . . In any event, 3M's decision in 2004 to not submit additional material in support of its proposed label language has no bearing on the Agency's scientific conclusions regarding the site of action six years later." Defs.' Mem. at 23. The Court agrees with the FDA. Simply because the mechanism of action was, for whatever reason, unknown when Aldara was approved for the treatment of actinic keratoses in 2004 does not mean that the mechanism of action will, for the purposes of this Court's review, remain forever unknown or that the FDA could not rely on the mechanism of action in its Response. Insofar as imiquimod's mechanism of action is discussed in the Response, the Court is satisfied that the mechanism of action is well-explained and supported by the FDA's interpretation of the relevant scientific evidence.

9 By the Court's count, by the time the Response was drafted, the issues raised in the plaintiff's Citizen Petition had been reviewed by three different groups or individuals within the FDA: the Office of Generic Drugs, the Dermatology Division, and Dr. Beitz. Presumably, the issues were reviewed prior to this by the CDER when it drafted the questions that it then circulated to the Office of Generic Drugs and the Dermatology division and subsequent to this by Dr. Woodcock in the preparation of the Response, which would bring the number of reviewing groups and individuals to five. In any event, these issues were considered by a number of people, in a number of divisions, within the FDA.

addressed the plaintiff's arguments and provided a detailed justification for its conclusion that additional bioequivalency testing was not needed." Astellas Pharma, 642 F. Supp. 2d at 20. In the portion of the FDA's Response in which it stated its disagreement with the plaintiff regarding the absorptive properties of EGW-affected skin and those of actinic keratoses-affected skin, the FDA wrote "[b]ut we do not think any such differences, if they exist, are significant enough to suggest that an [actinic keratoses] study would be insufficient to demonstrate bioequivalence, and you have not provided evidence that they are." Pl.'s Mem. at 22 (internal emphasis omitted) (quoting the Response at 11). Nonetheless, the plaintiff asserts that this "is not the way the regulatory approval process works. The burden is not on Graceway to prove lack of bioequivalence; rather, the burden is on the generic manufacturers to prove bioequivalence as a condition of ANDA approval." Pl.'s Mem. at 22.

The plaintiff is both correct in one respect and incorrect in another respect. The plaintiff is correct that the FDCA imposes upon the generic manufacturer the burden of demonstrating bioequivalence, and upon the FDA the burden of finding that the pioneer and the generic are bioequivalent before it approves the generic manufacturer's ANDA. The plaintiff is incorrect, however, in its understanding of how these burdens structure the regulatory process. For example, here, the generic manufacturer, Nycomed, submitted its ANDA, and, satisfied that the ANDA demonstrated bioequivalence, the FDA approved it. The FDA explained at length in its Response the reasons why it believed the studies conducted involving only patients with actinic keratoses were sufficient to demonstrate bioequivalence, and, in connection with this explanation, challenged the plaintiff to provide evidence disproving its conclusions. In other words, the FDA is not asking the plaintiff to prove lack of bioequivalence; rather, the FDA, after concluding that its proposed course of action would satisfy the duties imposed upon it by the

FDCA and the FDA regulations, merely explained that one reason it denied the plaintiff's Citizen Petition was because it found no scientific evidence, nor did the plaintiff submit scientific findings, contrary to or disproving its conclusion. The FDA was satisfied with the studies' ability to demonstrate bioequivalence; it was the plaintiff who was not. See Astellas Pharma, 642 F. Supp. 2d. at 20 (concluding that the plaintiff "has identified no studies or other evidence demonstrating that the FDA's conclusion was irrational, implausible[,] or contrary to existing scientific consensus"). Accordingly, as did the Court in Astellas Pharma, this Court concludes that "although the plaintiff provides ample support for the uncontroversial position that supplemental testing could reveal additional information pertinent to bioequivalency, it has made no showing that the testing guidelines established by the FDA were insufficient to meet its statutory obligation to ensure the safety and efficiency of new drugs." Id.

B. The plaintiff's relatedness argument

The plaintiff next argues that the "FDA's [denial of its Citizen Petition] also is predicated upon the unsubstantiated assertion that genital warts are 'related' to [actinic keratoses] and sBCC." Pl.'s Mem. at 23 (quoting the Response at 9 (FDA000374)). Again, the plaintiff seizes on the opinion of the Dermatology Division as support for its argument: "the [C]ourt need look no further than what [the] FDA's own experts said: 'the Dermatology Division agrees that the pathophysiology of EGW is wholly unrelated to [actinic keratoses] and sBCC.'" Pl.'s Mem. at 24 (quoting November 18, 2009 Letter from Dr. Brenda Carr (FDA 000429)); see Pl.'s Reply at 14 ("Deference is particularly unwarranted here, where [the] FDA's own dermatology experts agreed with Graceway and disagreed with the ultimate decision of the agency."). The plaintiff argues that the FDA's Response inadequately explained its rejection of the Dermatology Division's opinion, Pl.'s Mem at 24, and, in doing so, violated its enabling statute, which allows

the FDA to establish alternative methods of showing bioequivalence only when they are "scientifically valid" and "'may be expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect,'" id. at 26 (quoting 21 U.S.C. § 355(j)(8)(B)(i)).

The FDA responds that the plaintiff's argument is based on the "false premise[] that [the] FDA found the three indications to be related because they are treated by the same drug." Defs.' Mem. at 25 n.22 (internal emphasis omitted). The FDA contends that its Response adequately explained its conclusions that: (1) a presumption can be made that it is not necessary for one of the indications in a multi-indication drug to be related to the others to conclude that a comparative clinical study based on one indication is sufficient to show bioequivalence; (2) even without that presumption, a single study could suffice if the FDA could reasonably conclude that the rate and extent of absorption of the generic does not show a significant different from the pioneer; and (3) genital warts, actinic keratoses, and sBCC were, in fact, related in light of their response to topical treatments that enhance local and cell-mediated immunity in immunocompetent individuals. Id. at 25-26. Thus, much like its arguments in response to the plaintiff's site of action argument, the FDA maintains that its denial of the Citizen Petition was well-reasoned, thoroughly explained, and based on scientific evidence.

The Court once again notes that it is not the Dermatology Division's opinion that is afforded deference under the precedent of this Circuit. The Court's task in evaluating the plaintiff's relatedness argument is therefore similar to that undertaken above in reference to the site of action argument: was the FDA's denial of the plaintiff's Citizen Petition well-reasoned, sufficiently explained, and in line with the scientific evidence before it? After a thorough review

of the FDA's Response, and the entire administrative record, the Court concludes the answer to this question is yes.

In the portion of the Response addressing the relatedness of the three indications for which Aldara has FDA approval, the FDA explained that

> [w]hile we agree that EGW, arising from infection by human papillomavirus, differs pathophysiologically from [actinic keratoses] and sBCC, both of which arise from overexposure to ultraviolet light, this difference is not material for purposes of determining an appropriate bioequivalence study design. . . . If a topically applied imiquimod product can induce the local and cell-mediated immunological response . . . , EGW, [actinic keratoses], or sBCC lesions will respond to treatment regardless of the underlying pathophysiology or exact anatomic location of the lesion.

Response at 8 (FDA 000373) (internal footnote omitted). The FDA, therefore, did not conclude that genital warts, actinic keratoses, and sBCC are related for all purposes or simply on the basis that they could all be treated by imiquimod. Rather, the FDA concluded that all three are related in the manner in which they respond to imiquimod, which is the pertinent question when evaluating bioequivalence. See 21 U.S.C. § 355(j)(8)(B)(i). The Response continues for another thirteen pages, setting forth each of the arguments raised in the plaintiff's Citizen Petition and explaining why the FDA rejected those arguments. The Court's review of the Response satisfies it that the FDA has "examined the relevant data and 'articulated a satisfactory explanation for its action, including a rational connection between the facts found and the choice made.'" Bristol-Myers, 923 F. Supp at 219-20 (quoting Motor Veh. Mfrs. Ass'n, 463 U.S. at 43) (internal quotation marks and alteration omitted)). In short, the FDA's Response systemically addressed the plaintiff's concerns and rejected them in compliance with the APA. Therefore, because the Court can "reasonably . . . discern[ ]" the agency's path, it must uphold the agency's decision. Pub. Citizen, 988 F.2d at 197.

IV. CONCLUSION

As explained above, because the FDA addressed each argument raised in the plaintiff's Citizen Petition, explained its conclusion with respect to each argument, and cited the scientific literature on which it relied, the FDA's Response denying the plaintiff's Citizen Petition was not arbitrary, capricious, or otherwise contrary to law, and therefore does not violate the APA. The plaintiff's motion for summary judgment is therefore **DENIED**, and the defendant's cross-motion for summary judgment is **GRANTED**.[10]

SO ORDERED this 10th day of May, 2011.

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REGGIE B. WALTON
United States District Judge

[10] The Court will issue an Order consistent with this Memorandum Opinion.