UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ASTRAZENECA PHARMACEUTICALS LP, Plaintiff, v. FOOD AND DRUG ADMINISTRATION, *et al*., Defendants.	Civil Action No. 12-00472 (BAH) Judge Beryl A. Howell

AMENDED MEMORANDUM OPINION

Plaintiff AstraZeneca Pharmaceuticals LP ("AstraZeneca") has manufactured the drug quetiapine fumarate ("quetiapine") under the brand name Seroquel® ("Seroquel") since 1997 without generic competition. AstraZeneca brought this lawsuit, which presents a question of statutory interpretation, against the Food and Drug Administration, Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, and Kathleen Sebelius, Secretary of Health and Human Services (collectively, "the FDA"), to challenge the FDA's approval, on March 27, 2012, of generic versions of Seroquel. *See* Complaint, ECF No. 1 ("Compl."), ¶ 3.

AstraZeneca believes that, under the plain language of 21 U.S.C. § 355(j)(5)(F)(iv), codifying Section 505(j)(5)(F)(iv) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), it is entitled to total market exclusivity until December 2, 2012 for the safety information encapsulated in "Table 2," which was approved for all Seroquel labels on December 2, 2009 and must be included on the labels of all generic versions of quetiapine. Based upon this belief, AstraZeneca seeks a judgment that the FDA's recent approval of generic versions of quetiapine, while AstraZeneca retains exclusivity over Table 2, violated AstraZeneca's exclusivity rights and was arbitrary, capricious, and contrary to law.

Pending before the Court are Cross-Motions for Summary Judgment filed by AstraZeneca, ECF No. 21, and the FDA, ECF No. 26. For the reasons explained below, the Court denies AstraZeneca's Motion for Summary Judgment and grants the FDA's Motion for Summary Judgment.

I. BACKGROUND[1]

A. STATUTORY AND REGULATORY BACKGROUND

1. New Drug Applications

The pharmaceutical drug approval process for both new and generic drugs is governed by the FDCA, as amended by, *inter alia*, the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 ("Hatch-Waxman Amendments") (codified at 21 U.S.C. §§ 355, 360cc (2000), and 35 U.S.C. §§ 156, 271, and 282 (2000)).[2] The FDA is the agency charged with approving all new and generic drugs for market. *See* 21 U.S.C. § 355(a).

Under the FDCA, pharmaceutical drug manufacturers interested in marketing a new pharmaceutical drug (otherwise known as an "innovator" or "pioneer" drug), such as Seroquel, must file a new drug application ("NDA") with the FDA as required by 21 U.S.C. § 355(b)(1), and must demonstrate, *inter alia*, the safety and efficacy of the drug. *See id.*; Compl. ¶ 29. Pioneer drug companies must file with the FDA "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use," 21 U.S.C. § 355(b)(1)(A), and other information, including "a full statement of the composition of such drug," 21 U.S.C. § 355(b)(1)(C), and "specimens of the labeling proposed to be used for

[1] This Court provides a brief background below and also incorporates by reference the extensive statutory, regulatory and case-specific background set forth in *AstraZeneca Pharms. LP v. FDA*, No. 12-00388, 2012 U.S. Dist. LEXIS 39611, at *4-24 (D.D.C. Mar. 23, 2012).

[2] As noted, section 505 of the FDCA is codified in section 355 of Title 21 of the United States Code. For clarity, this Opinion refers to the provision by its U.S. Code section number, 355, but maintains 505 when quoting from parties' briefs.

such drug," 21 U.S.C. § 355(b)(1)(F). "Once the drug is approved, it is referred to as a 'listed drug.'" *Sanofi-Aventis U.S. LLC v. FDA*, No. 10-1255, 2012 WL 373214, at *1 (D.D.C. Feb. 7, 2012) (citing 21 C.F.R. § 314.3(b)).

The FDA publishes listed drugs in the "Orange Book," which includes information about applicable patents and periods of exclusivity. *See* Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, available at http://www.fda.gov/cder/ob/ ("Orange Book"). The Orange Book provides notice to generic drug applicants about when drug patents and periods of exclusivity expire, and when there will be openings to market generic versions of pioneer drugs. *See* Defs.' Mem. in Supp. of Mot. for Summ. J. ("Defs.' Mem.") at 4.

2. Abbreviated New Drug Applications

The Hatch-Waxman Amendments to the FDCA allowed manufacturers to seek approval from the FDA to market generic drugs by filing an abbreviated new drug application ("ANDA"). *See* 21 U.S.C. § 355(j). The significance of the Hatch-Waxman Amendments has been aptly noted by other Judges in this Circuit:

> Prior to 1984, all applicants seeking to market pioneer drugs or generic non-antibiotic drugs had to file [a new drug application ("NDA")] containing, *inter alia*, extensive scientific data demonstrating the safety and effectiveness of the drug. *See* 21 U.S.C. § 355(a)-(b); 21 C.F.R. § 314.50. As a result, few generic non-antibiotic drugs were approved by [the] FDA. *See* [*Glaxo, Inc. v. Heckler*, 623 F. Supp. 69, 72 (E.D.N.C. 1985)]. Hatch-Waxman created an abbreviated approval process for generic non-antibiotic drugs, while retaining incentives for pioneer drugs, such as marketing exclusivity and patent protections. *See* 21 U.S.C. § 355(j). The abbreviated new drug application ("ANDA") process shortens the time and effort needed for approval of a generic drug by allowing the applicant to merely demonstrate its product's bioequivalence to the NDA drug, without reproducing the entirety of the NDA's extensive scientific research. *See Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676, 110 S. Ct. 2683, 110 L. Ed. 2d 605 (1990) (describing the ANDA process).

ViroPharma, Inc. v. Hamburg, No. 12-0584, 2012 U.S. Dist. LEXIS 56128, at *6-7 (D.D.C. Apr. 23, 2012) (quoting *Allergan, Inc. v. Crawford*, 398 F. Supp. 2d 13, 16-17 (D.D.C. 2005)).

Unlike applicants for pioneer drugs, applicants for generic drugs are not required to submit clinical data to demonstrate the safety and efficacy of their product. Instead, according to the FDA, "if an ANDA applicant establishes that its proposed drug product has the same active ingredient, strength, dosage form, route of administration, labeling (with certain permissible differences), and conditions of use as a listed drug, and that it is bioequivalent to that drug, the applicant" may rely on the FDA's earlier findings of safety and efficacy for the drug when it was approved as an NDA. Defs.' Mem. at 5; *see also* 21 U.S.C. § 355(j); Compl. ¶ 34.

FDA-approved generic versions of a drug must utilize the "same" labeling as the labeling approved for the reference-listed drug, except for labeling differences "based on a suitability petition or because the generic drug and the reference drug are produced or distributed by different manufacturers." Compl. ¶ 35; 21 U.S.C. § 355(j)(2)(A)(v) (an ANDA must include "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) . . . ."). FDA regulations require that, when a manufacturer submits an ANDA, "[l]abeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug," with certain exceptions not applicable here. 21 C.F.R. § 314.94(a)(8)(iv); *see* AR 294, 305 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca, explaining that the "FDA concurs that these portions of the labeling are essential to safe use of a generic quetiapine product referencing Seroquel for any indication, and the agency would not approve a quetiapine ANDA referencing Seroquel that omitted them"); Defs.' Mem. at 3 (noting that "the safety information in Table 2 is necessary for safe use of the product and therefore cannot be carved out . . . ").

3. Exclusivity Periods

Since "Congress still wanted to provide incentives for new drug development, alongside the ANDA process that eased the marketing of generic drugs, Hatch-Waxman entitles an NDA applicant to a period of market exclusivity (3 or 5 years, depending on the degree of innovation reflected in the NDA) . . . ." *ViroPharma*, 2012 U.S. Dist. LEXIS 56128, at *7 (quoting *Allergan, Inc.*, 398 F. Supp. 2d at 17). During an exclusivity period, the FDA is barred from approving a generic ANDA for the NDA product. *See id.* (citing 21 U.S.C. §§ 355(c)(3)(D)(ii)-(iv), (j)(5)(D)(ii)-(iv)). In this case, for example, following Seroquel's approval on September 26, 1997, the FDA granted AstraZeneca a five-year period of "new chemical entity" exclusivity for Seroquel. Defs.' Mem. at 8.

Pioneer drugs may also be eligible under statutorily prescribed circumstances for additional periods of exclusivity on the basis of medical studies completed after the drug approval process. These additional exclusivity periods "provide incentives to pioneer companies to conduct new clinical investigations [for] previously approved NDAs, including through 'supplemental' NDAs ('sNDAs')." Compl. ¶ 32 (citation omitted).

The statutory provision at issue in this case, 21 U.S.C. § 355(j)(5)(F)(iv), describes one such circumstance, for new indications or uses of the already approved pioneer drug. This section provides:

> If a supplement to an application approved under subsection (b) is approved after the date of enactment of this subsection [enacted Sept. 24, 1984] and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an [ANDA] . . . for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

21 U.S.C. § 355(j)(5)(F)(iv).[3]

Three-year exclusivity under this statutory provision is sometimes referred to as "new indication exclusivity" or "new patient population exclusivity" because it often applies to applications for approval of the use of an already-approved drug for a new medical indication, such as to treat a different disorder, or a new population of patients, such as a new age group. *See* Defs.' Mem. at 6 (citation omitted); *ViroPharma*, 2012 U.S. Dist. LEXIS 56128, at *8-9. Under FDA regulations, the FDA will not approve an ANDA for three years following the grant of exclusivity to a pioneer drug if the ANDA "relies on . . . information supporting a change approved in the supplemental new drug application." 21 C.F.R. § 314.108(b)(5)(ii). In this case, for example, the FDA has granted AstraZeneca exclusivity over two pediatric indications for Seroquel until December 2, 2012. Therefore, any generic version of Seroquel approved before that date may not be marketed as a drug for the pediatric indications for which AstraZeneca retains exclusivity.[4]

Under section 355(j)(5)(F)(iv), approval for a new use of a drug must be predicated on new clinical investigations. The FDA defines "new clinical investigation" in its implementing regulation, 21 C.F.R. § 314.108(a), as "an investigation in humans the results of which have not been relied on by [the] FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 C.F.R. § 314.108(a). The FDA elaborates that "data from a clinical investigation previously

[3] The FDA notes that "[o]ther exclusivities apply to products that are new chemical entities, or for studies undertaken for original approval. *See* 21 U.S.C. § 355(j)(5)(F)." Defs.' Mem. at 5 n.4. The only exclusivity period at issue here, however, is the three-year period of exclusivity under 21 U.S.C. § 355(j)(F)(iv). *See id*.

[4] An additional six-month period of pediatric exclusivity, until June 2, 2013, applies to Seroquel but that period is not at issue here. *See* Defs.' Mem. at 1.

submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new." *Id*. In other words, data from a previously submitted clinical investigation may nonetheless be considered "new" if the previous submission was to support the safety of indications already approved in the NDA and the data is later presented in a supplemental NDA to show the effectiveness of the drug for new populations or new indications. Moreover, under section 355(j)(5)(F)(iv), the new clinical investigations must be "essential to the approval of the supplement." In its regulations, the FDA explains that "[e]ssential to approval means, with regard to an investigation, that there are no other data available that could support approval of the application." 21 C.F.R. § 314.108(a).

According to the FDA, the new indication exclusivity regulation, 21 C.F.R. § 314.108, when read in context with the definition of "new clinical investigation," "requires a relationship between the information from the new clinical investigation, the change to the product or to the use of the product approved in the supplement, and the scope of any resulting three-year exclusivity." Defs.' Mem. at 7. Thus, "[i]n accordance with the statute and regulation, the scope of three-year exclusivity depends on the nexus between the subject of the new clinical investigations and the changes to the product that the investigations support." *Id.*; *see also ViroPharma*, 2012 U.S. Dist. LEXIS 56128, at *9 ("The FDA has interpreted [§ 355(j)(5)(F)(iv)] as establishing a relationship between the information obtained from the clinical investigation, the change approved through the pioneer drug company's [sNDA], and the scope of the information relied upon by a generic competitor in a specific ANDA.") (quoting *AstraZeneca*, 2012 U.S. Dist. LEXIS 39611, at *3).

The FDA has issued additional regulations on the implementation of 21 U.S.C. § 355(j)(5)(F)(iv). While not defining all types of changes approved in a supplement warranting 3-

year exclusivity, the FDA discussed limits on the scope of this statutory provision. For example, during consideration of proposed implementing regulations, the FDA received comments requesting clarification "whether a clinical investigation establishing new risks could be eligible for exclusivity." Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,356 (Oct. 3, 1994). The FDA responded that "such studies would not qualify for exclusivity because 'protection of the public health demands that all products' labeling contain all relevant warnings.'" *Id*. (quoting preamble to proposed rule published in 54 Fed. Reg. 28,872, 28,899). The FDA explained that:

> Changes that would not warrant exclusivity are, as discussed in the preamble to the proposed rule, changes in labeling that involve warnings or other similar risk information that must be included in the labeling of generic competitors. Applicants obtaining approval for such changes in labeling would, in any event, have no valid interest in precluding such information from the labeling of other products.

59 Fed. Reg. 50,338, 50,357.

The FDA further noted that it "does not consider a study to be 'essential to approval' simply because the applicant conducted it and submitted the study for agency review . . . ." *Id*. Rather, citing the legislative history, the FDA stated that 3-year exclusivity is reserved for investigations "that are necessary for approval of important innovations," and require "a considerable investment of time and money." *Id*. at 50,358. According to the FDA, "an applicant is not entitled to 3-year exclusivity merely because it supplements an approved application based in part on a clinical investigation or because it certifies to FDA that the clinical investigation is essential to approval of the application or supplement." *Id*.[5] In short, the FDA

[5] The FDA has consistently indicated that only "significant changes in already approved drug products, such as a new use, which require new clinical studies" are covered by the 3-year exclusivity provisions. 54 Fed. Reg. 28,872, 28,896 (July 10, 1989). "Congress understood that the substantial economic rewards of exclusivity might well encourage drug companies to make minor and unimportant alterations in their marketed drug products or to conduct additional tests which they could claim provide important new information about a marketed drug product. To avoid rewarding such behavior, the 3-year provision includes the special criteria intended to restrict eligibility to

regulations make clear that 3-year exclusivity is not triggered merely by labeling changes related to the safety or risks posed by the drug for indications already approved; such changes, if known, would have been incorporated into the original labeling at the time of the approval of the original NDA. Nor is a 3-year period of exclusivity triggered by the simple submission of new clinical investigations or on the applicant's "say-so."

B. CASE-SPECIFIC BACKGROUND

AstraZeneca developed and now manufactures the drug Seroquel, which was first approved by the FDA as an NDA (NDA 20639) on September 26, 1997. *See* AR 70-81 (FDA Approval, dated Sept. 26, 1997, of Seroquel, NDA 20639); *see also* Defs.' Mem. at 8 (citing Orange Book). Seroquel is an atypical antipsychotic medication that is used to treat a variety of psychological disorders, including schizophrenia and bipolar disorder.[6] Although more than 50 generic atypical antipsychotics have FDA approval, Compl. ¶ 39, Seroquel has been marketed without generic competition for the past fourteen years. *See* AR 66-67 (Orange Book); *see also* Defs.' Mem. at 8.

Since Seroquel's approval in 1997, AstraZeneca has filed multiple supplemental applications ("sNDAs"). Based on the approval of those sNDAs, Seroquel has been approved for multiple new medical indications and new patient populations. Although originally used solely for the treatment of schizophrenia, through several sNDAs, Seroquel is now approved for use with the following medical indications and populations: "(1) in adults and adolescents (ages 13 to 17) to treat schizophrenia; (2) in adults, adolescents and children (ages 10 to 17) for the

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significant innovations. See Cong. Rec. H9114, 9124 (daily edition September 6, 1984) (statement of Representative Waxman); Cong. Rec. S10505 (daily edition August 10, 1984) (statement of Senator Hatch)." *Id*.

[6] "The term 'atypical antipsychotic' refers to a class of drugs that, in comparison to the prior generation of antipsychotic drugs, effectively treats mental disorders while presenting a reduced tendency to cause significant side effects known as extrapyramidal symptoms—involuntary movement disorders such as tics, tremors and writhing." Compl. ¶ 38.

acute treatment of manic episodes associated with bipolar I disorder, both as a monotherapy and as an adjunct to lithium or divalproex; (3) in adults as a monotherapy for the acute treatment of depressive episodes associated with bipolar disorder; and (4) in adults for the maintenance treatment of bipolar I disorder, as an adjunct to lithium or divalproex." Defs.' Mem. at 9; *see* AR 66-69 (Orange Book); *see also* Compl. ¶¶ 21, 42.

AstraZeneca's labeling has also changed multiple times since Seroquel's original approval. The labeling changes fall into two main categories. First, as the FDA has approved supplements to Seroquel's NDA, the newly-approved medical indications and patient populations ("with accompanying three-year exclusivity periods") have been added to Seroquel's labeling. Defs.' Mem. at 8-9 (citing AR 66-69 (Orange Book)). Second, changes involving new safety information have been made to the labeling. These additional labeling changes, according to the FDA, "have not resulted in exclusivity." *Id*.

Atypical antipsychotics, such as Seroquel, may have numerous side effects, including hyperglycemia. To minimize the risk of hyperglycemia in users of atypical antipsychotics, the FDA has investigated the metabolic changes caused by that class of medications. *See* Compl. ¶ 51. To this end, the FDA has required manufacturers of atypical antipsychotic drugs to provide data and has mandated labeling changes. *See id*. ¶¶ 50-54. In 2000, the FDA performed a "comprehensive review" of pre-clinical, clinical, and post-marketing data to see whether atypical antipsychotics disturb glucose regulation. *Id.* ¶ 51. After reviewing the entire class of atypical antipsychotics, in 2001, the FDA announced that "further study will be needed to elucidate the potential causality of [diabetes mellitus] by" atypical antipsychotics. *Id.* In September 2003, after years researching the issue, the FDA "mandated a class-wide diabetes/hyperglycemia label change for all atypical antipsychotics," including Seroquel. *Id.*

The FDA's concern about the effects of atypical antipsychotics on diabetes and hyperglycemia has prompted the agency to require AstraZeneca and other manufacturers continually to update the labels for their atypical antipsychotics with warning information and data that informs prescribers about possible metabolic effects, including glucose shift data.[7] *Id.* ¶ 52. The FDA intended to use the glucose shift data to "'create a universal format for presentation of metabolic information in the atypical package insert labels,'" thereby standardizing the hyperglycemia warning across the entire class of atypical antipsychotic medications. *Id.* ¶ 53 (quoting the FDA); *see also* AR 325-39 (FDA Letter, dated Jan. 8, 2008, to AstraZeneca, referencing original NDAs for Seroquel and Seroquel XR and requesting metabolic data analyses for the FDA to evaluate the "effects of atypical antipsychotic drugs on metabolic parameters (e.g., weight, lipids, glucose)"); AR 21 (FDA Email, dated July 22, 2011, to AstraZeneca, stating that "[t]he Division has been working with sponsors class-wide to create a universal format for presentation of metabolic information in the atypical package insert labels.").

As the FDA considered the metabolic data issue for the entire class of antipsychotic drugs, AstraZeneca continued to market Seroquel and invest in research and development to find new indications, patient populations, and forms of Seroquel. In 2007, the FDA approved a new drug application for Seroquel XR, an extended-release tablet version of Seroquel that only had to be taken once a day, unlike Seroquel, which had to be taken two to three times per day. Compl. ¶¶ 44-45.[8]

[7] Glucose shift data describes "the frequency with which patients shift, from beginning to end of treatment, from a state of normal or borderline glucose levels to a state of hyperglycemia." Compl. ¶ 52.

[8] The Complaint discusses at length Seroquel XR® extended-release tablets ("Seroquel XR") and seeks the same declaratory and injunctive relief it seeks with respect to Seroquel. Compl. at 25-26 (seeking, for example, "[a] permanent injunction prohibiting FDA from issuing final approval of any ANDA for which Seroquel or Seroquel XR is the reference-listed drug, and vacating and rescinding any final approvals that have issued, until after

The FDA continued to focus attention on hyperglycemia safety information related to both Seroquel and Seroquel XR and the class of atypical antipsychotics. Although Seroquel already had a label with a general risk statement about hyperglycemia and diabetes, *see* AR 883, the FDA was interested in displaying more specific hyperglycemia clinical data. In a letter, dated January 8, 2008, the FDA requested that AstraZeneca provide tables of data with summaries of clinical trials related to metabolic parameters for both Seroquel and Seroquel XR. The FDA requested that this information from various clinical trials "be submitted in stages . . . as they are completed." AR 326-38, 338 (FDA letter, dated Jan. 8, 2008, to AstraZeneca, requesting metabolic data analyses); *see also* AR 295 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca, noting that the "FDA requested glucose-related metabolic data for Seroquel by letter dated January 8, 2008"); Defs.' Mem. at 9-10.

On June 26, 2008, in response to the FDA's letter requesting tables summarizing metabolic data, AstraZeneca submitted the data to the FDA from which Table 2 was eventually derived, expressly referencing the original NDAs for Seroquel and Seroquel XR. AR 431 (AstraZeneca Letter, dated June 26, 2008, to FDA); *see also* AR 295 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca); AR 883 (Internal FDA Consultative Review, dated Mar. 27, 2012, to

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December 2, 2012"). Yet, Seroquel XR is not at issue here. Contrary to the allegations in the Complaint that, on March 27, 2012, the FDA granted final approval to "one or more abbreviated new drug applications ('ANDAs') for generic versions of Seroquel and Seroquel XR," *id.* ¶ 3, the FDA expressly stated that its decision to grant approvals to ANDAs relates only to Seroquel. *See* AR 303 at n.20 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca, explaining that "[t]oday's decision relates only to Seroquel. For Seroquel XR, there continue to be multiple overlapping exclusivities, two of which expire on April 8, 2012, as well as patent protections. These protections could have implications for carve-out decisions made by a line-by-line review of product labeling which involves consideration of issues beyond Table 2."); *see also* Defs.' Mem. at 12 n.12 ("The agency did not issue any ANDA approvals or decision for Seroquel XR [on March 27, 2012]."). Indeed, the parties' briefs make clear that only exclusivity for Seroquel is at issue in this case and is the focus of AstraZeneca's motion for summary judgment. *See generally* Pl.'s Mem; Pl.'s Reply at 2 n.1 (noting that "because FDA has only granted final approvals for generic versions of Seroquel, AstraZeneca focuses here on the December 2, 2009 approval for Seroquel."). Moreover, AstraZeneca only asks the Court to "(a) vacate FDA's approvals of any ANDA for which Seroquel is the reference-listed drug; and (b) declare that FDA could not have lawfully granted approval of any ANDA for which Seroquel is the reference-listed drug prior to December 3, 2012." Pl.'s Mem. at 23; Pl.'s Reply at 23. Accordingly, this Court addresses AstraZeneca's claims with respect to the exclusivity of Table 2 only for Seroquel. Nevertheless, to the extent that AstraZeneca seeks in the Complaint to bar FDA approval for ANDAs for Seroquel XR on the basis of its marketing exclusivity for labeling containing Table 2, those claims are bound by the ruling here.

the FDA Office of Generic Drugs ("OGD"), analyzing information in Table 2). In its letter, AstraZeneca noted that the data "follows the criteria as specified in the January 2008 letter, and subsequent clarifications" from the FDA. AR 431. The FDA explains that this data, submitted to the FDA in a letter by AstraZeneca, was "coded by FDA as general correspondence, not as a prior approval supplement (PAS) or a Changes Being Effected ("CBE") supplement to the Seroquel NDA." AR 295 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca).

Although the data submitted by AstraZeneca in June 2008 are not part of the Administrative Record,[9] the parties do not dispute that this data consisted of fifteen clinical trials, three of which were conducted with Seroquel alone for the treatment of bipolar depression or disorder; two were conducted with both Seroquel and Seroquel XR for schizophrenia; and ten were conducted with Seroquel XR alone, including six trials for the treatment of bipolar disorder and major depressive disorder ("MDD"). AR 309. None of these clinical trials were conducted on pediatric patients or for purposes of generating data for Table 2. AR 301; Defs.' Mem. at 10. AstraZeneca describes only seven of the trials as "new" because they had not been previously submitted to the FDA. Pl.'s Mem. at 3 (Statement of Facts, ¶ 4).

Almost four months after submission of the data related to metabolic changes "in Patients Receiving Quetiapine," AR 431, which led to Table 2, on October 28, 2008, AstraZeneca sought two new pediatric indications for Seroquel by submitting formal supplemental applications, referred to as "S-045" and "S-046," respectively, for: (1) adolescents (ages 13 to 17) to treat schizophrenia, and (2) adolescents and children (ages 10 to 17) for the acute treatment of manic episodes associated with bipolar I disorder. AR 95. These sNDAs appear to have been the subject of multiple years of study. As early as 2001, AstraZeneca proposed a pediatric study

[9] The table of contents for the Supplemental Administrative Record notes, in connection with AstraZeneca's June 26, 2008 letter, that the "06/13/2008 data submission of 1152 pages [is] omitted." ECF No. 14-1 at 3.

request to the FDA and, in 2003, the agency requested that the results "from trials in pediatric patients with (1) schizophrenia, and with (2) acute mania, as part of bipolar disorder" be submitted within 5 years. *See* AR 311-24, 312 (FDA Letter, dated Feb. 11, 2003, to AstraZeneca, requesting pediatric clinical trial information and making "[r]eference . . . to [AstraZeneca's] Proposed Pediatric Study Request submitted on March 2, 2001, to [AstraZeneca's] New Drug Application for Seroquel (quetiapine fumarate) tablets.").

When AstraZeneca submitted its formal applications for FDA approval to market Seroquel for two new pediatric indications, AstraZeneca expressly requested 3-year exclusivity for those pediatric indications. *See* AR 433-34 (AstraZeneca's claim (undated) for three-year exclusivity for supplemental new drug application for pediatric indications, stating: "The new clinical investigation(s) provide safety and efficacy data regarding the use of Seroquel . . . Tablets for the treatment of bipolar mania in pediatric patients ages 10-17 and schizophrenia in pediatric patients ages 13-17 that could not be gleaned from published information. Accordingly, these new clinical investigations are essential to the approval of this supplemental new drug application."). By contrast, the Administrative Record contains no explicit request from AstraZeneca for 3-year exclusivity for the addition of Table 2 to Seroquel labeling.

The FDA considered AstraZeneca's formal supplemental applications for pediatric indications of Seroquel while simultaneously continuing to refine the labeling of antipsychotic drugs, including Seroquel, with respect to metabolic effects for all approved indications. Until the end of 2008, the FDA and AstraZeneca addressed the sNDAs for the approval of pediatric indications and the class-wide metabolic data separately in their communications. AstraZeneca's applications for the pediatric indications, as noted, had been submitted as formal supplements to the Seroquel NDA (an "sNDA") on October 28, 2008 and AstraZeneca made eleven subsequent

submissions particularly regarding the pediatric supplements. *See* AR 95 (FDA Letter, dated Dec. 2, 2009, to AstraZeneca approving sNDAs 045 and 046 and summarizing submissions relevant to approval). Moreover, in its earlier request for exclusivity for the pediatric indications, AstraZeneca discussed clinical trials it believed were essential to approval, but did not mention Table 2. AR 433-34.

While AstraZeneca and the FDA addressed in the same correspondence multiple pending issues related to Seroquel and Seroquel XR, the agency viewed the labeling changes prompted by metabolic data and the new pediatric indications as distinct and separate issues, which were being considered independently. Nothing in the Administrative Record suggests that the exclusivity periods for which AstraZeneca had applied for the pediatric indications would be extended to include other changes being negotiated between the agency and the pharmaceutical company.

For example, shortly after submission of the sNDAs for the new pediatric indications, the FDA sent a letter, dated December 18, 2008, to AstraZeneca directing the company to include additional data regarding glucose levels in the labeling for Seroquel and Seroquel XR and to "elevat[e]" the data for "glucose changes . . . from the clinical trials [from the Adverse Reactions section] to the Warnings/Precautions section of labeling." AR 11; Pl.'s Mem. at 16. The FDA further directed AstraZeneca to use the label of another antipsychotic drug, Zyprexa, as a model for the correct formatting of the label. AR 11. The FDA commented that it was "currently reviewing [AstraZeneca's] metabolic data submission and the pediatric efficacy supplements submitted under this NDA (S-045 and S-046)," evidently treating them as separate submissions, and noting that the agency would "be providing further labeling comments . . . ." AR 12; *see also, e.g.*, AR 706-09 (FDA Pediatric Exclusivity Determination Checklist, dated Jan. 21, 2009,

referring only to the pediatric indications, supplements #045 and #046, and not discussing Table 2); AR 710 (AstraZeneca Letter, dated Feb. 12, 2009, to FDA, updating tables with changes in metabolic parameters in response to the FDA's February 2009 request); AR 711-844, 718 (FDA Clinical Review on Metabolic Parameters (Hyperglycemia, Hyperlipidemia, and Weight Gain), dated Mar. 26, 2009, relating to adult data and noting that the pediatric data is being reviewed separately); AR 845-52, 849 (NDA Regulatory Filing Review, dated Apr. 22, 2009, noting as background in a "Memo of Filing Meeting," with no mention of Table 2, that "[t]hese supplements (S045 / S046) include data to support the use of Seroquel (molecular entity was approved in 1997) for the following pediatric indications, schizophrenia (13-17 years of age) and bipolar mania (10-17 years of age). The supplements are in response to a written request issued on 2/11/2003."); AR 853-65, 860 (FDA Memorandum, dated Aug. 13, 2009, recommending approval of NDA supplements for pediatric indications and noting as a "Comment" in the text that "[t]he Division also requested that the sponsor conduct an analysis of all clinical trials to study [metabolic effects] . . . . The sponsor has recently submitted these data for both pediatric and adult population. Further modifications to product labeling will be made based on our review of these submitted data (refer to separate metabolic reviews)."). Thus, the communication between the agency and AstraZeneca in no way suggested that AstraZeneca was eligible for exclusivity for its response to the agency's requests for metabolic data.

On October 16, 2009, the FDA requested that AstraZeneca "[p]lease include a table summarizing the shift changes from normal to high fasting glucose and from borderline to high fasting glucose for the short-term, placebo-controlled clinical trials in adults." AR 15-19, 18 (FDA Email, dated Oct. 16, 2009, to AstraZeneca, forwarding attachment with labeling changes). The agency also instructed AstraZeneca to "[p]lease refer to current Zyprexa labeling

for examples of these tables." *Id*. AstraZeneca responded, in a letter on November 18, 2009, stating that it was "providing a response to the proposed label and Medication Guide," and forwarding an "Amendment to a Pending Application." AR 1969. As part of this submission, AstraZeneca included draft labeling for Seroquel that included not only metabolic data in Table 2 but also referred to many other labeling changes. Tellingly, in track changes, the FDA referred to labeling changes in connection with multiple pending applications, not just sNDAs 045 and 046, the supplemental applications for the pediatric indications. *See* AR 1973 (Apparent FDA note in draft labeling referring to "your labeling changes submitted under S-042, 044, 045, 046 and 048. In this version, we have made additional modifications in several sections. We have included bracketed comments to note these changes or request additional revisions where needed."). Thus, it appears that the FDA was communicating with AstraZeneca about numerous proposed changes all at once, with no suggestion that exclusivity was at stake for all of the many changes proposed in track changes in the draft label.

As noted, one of the many proposed changes in the draft label was Table 2. *See* AR 1991. Next to Table 2, AstraZeneca noted that it "[a]dded table summarizing the shift changes from normal to high fasting glucose and from borderline to high fasting glucose as requested by FDA in the 10/16/09 FDA communication." *Id*. The "Source" of Table 2 is listed as "NDA 20-639, Metabolic Response, submitted 26 June 2008, Table #339." *Id*. Thus, the November 2009 draft labeling proposal from AstraZeneca demonstrates that the addition of Table 2 was derived from its submission to the FDA on June 26, 2008, almost four months before it submitted separately its two formal supplemental applications for the pediatric indications.

Less than a month after AstraZeneca transmitted to the FDA track changes in the proposed labeling, the FDA approved, on December 2, 2009, the pediatric supplemental

applications for Seroquel as well as AstraZeneca's proposed labeling changes, including the addition of Table 2. AR 95-99 (FDA Letter, dated Dec. 2, 2009, to AstraZeneca, approving supplemental new drug applications for pediatric indications) ("Approval Letter"). The FDA's decision to approve Table 2 for inclusion in the labeling and its decision to approve the pediatric indications for Seroquel were two separate actions. *See id*. The FDA, however, communicated its decisions to approve both the display of class-wide safety information, including Table 2, and the approval of the pediatric sNDAs in the same letter. *Id*.

The Approval Letter primarily focused on the approval of the two pediatric sNDAs, for which AstraZeneca earned 3 years of exclusivity, stating that:

> These supplemental new drug applications provide for the use of Seroquel (quetiapine fumarate) tablets for the treatment of schizophrenia in adolescents 13 to 17 years of age and the treatment of bipolar mania in children and adolescents 10 to 17 years of age. We have completed our review of these applications. They are approved….

AR 95.

The Approval Letter also noted, however, that the supplemental drug applications "are approved, effective on the date of this letter, *for use as recommended in the enclosed, agreed-upon labeling text*." *Id*. (emphasis added). The letter directed that the content of the labeling shall be formatted in structured product labeling (SPL) format and "[f]or administrative purposes . . . designate[d] [as] 'SPL for approved NDA 020639/S-045/S-046.'" AR 95-96.

In a separate section of the Approval Letter, captioned "Risk Evaluation and Mitigation Strategy Requirements, the FDA explained that "[s]ince Seroquel (quetiapine fumarate) was approved on September 26, 1997, [the FDA has] become aware of additional clinical trial data and postmarketing safety data that show a risk of hyperglycemia, hyperlipidemia and weight gain associated with all forms of Seroquel (quetiapine fumarate) in all patient populations. [The FDA

considers] this information [in Table 2] to be 'new safety information' as defined in section 505-1(b) of FDCA." AR 96 (Approval Letter). Immediately following that statement, the letter states that AstraZeneca's proposed REMS (Risk Evaluation and Mitigation Strategy), "submitted on October 22, 2009 . . . is approved." *Id*. Attached to the Approval Letter is the approved labeling showing Table 2 in the "*Adults*" rather than the "*Children and Adolescents*" section of the document. AR 112-13.

Although the FDA expressed approval for both the new pediatric uses and the Table 2 labeling change in a single letter, each change was approved on its own merit. The FDA notes that it "consolidated a number of . . . actions" referred to in the approval letters sent to AstraZeneca for the two new pediatric indications (S-45, S-46). *See* AR 295 n.9 (FDA Letter, dated March 27, 2012, to AstraZeneca). Support for this assertion is found, *inter alia*, in an internal FDA Memorandum, noting that "the addition of Table 2 was not related to approval of these new indications. It is not unusual for DPP [the Division of Psychiatry Products] to bundle actions together . . . . [M]odifications to product labeling usually occur in concert with other actions being taken." AR 883 (Internal FDA Consultative Review, dated Mar. 27, 2012, to OGD regarding, *inter alia*, quetiapine ANDAs and information included in Table 2); s*ee also* AR 866-68 (FDA Internal Memorandum, dated Dec. 2, 2009, recommending approval of the pediatric sNDAs based on pediatric clinical trial results and the opinion of the Psychopharmacologic Drugs Advisory Committee that the efficacy and safety of Seroquel had been established, and discussing labeling changes but with no mention of Table 2); *see also* AR 869-76, 873 (FDA Exclusivity Summary, dated Dec. 11, 2009, for Seroquel Tablets, noting the three "clinical investigations submitted in the [pediatric] application that are essential to approval," none of which are Table 2 or contributed to the creation of Table 2).

The FDA's communications following the December 2, 2009 approval of the pediatric indications and proposed labeling only reinforce that the addition of Table 2 was a decision distinct from the decision to grant the sNDAs for pediatric indications and related exclusivity, and was part of the agency's broader efforts with respect to the provision of safety information related to the metabolic effects of atypical antipsychotics. In an email from the FDA to AstraZeneca, on July 22, 2011, for example, the FDA explained that the agency "has been working with sponsors class-wide to create a universal format for presentation of metabolic information in the atypical package insert labels." AR 21 (Email from FDA, dated July 22, 2011, to AstraZeneca). The FDA referenced AstraZeneca's pending supplements (NDA 20639, S-053, NDA 22047, S-026) and requested that AstraZeneca "please submit revised labeling to these supplements that incorporates this new format - Hyperglycemia and Diabetes Mellitus/Dyslipidemia/Weight Gain as separate headings under one warnings and precaution section, with the same introductory paragraph preceding the headings, as in the Latuda/Invega labels." *Id.* Thus, the FDA's efforts to improve metabolic data in the labeling of atypical antipsychotics continued, apart from the indications for which AstraZeneca was granted exclusivity on December 2, 2009.

The crux of the instant dispute is that AstraZeneca believes that it is entitled to a 3-year period of exclusivity for use of Table 2 in Seroquel labeling because Table 2 was a change based on clinical trials approved as part of a supplemental application. AstraZeneca contends that the FDA's approval of ANDAs for generic versions of Seroquel violates its right to exclusive use of the labeling, and was arbitrary, capricious, and contrary to law. The FDA does not dispute that Table 2 is essential information for all quetiapine labels, but believes that Table 2 is not entitled to exclusivity in part because it was not "essential" to approval of the pediatric supplement under

21 U.S.C. § 355(j)(5)(F)(iv). *See* AR 294 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca, noting that the addition of Table 2 is "essential to safe use of a generic quetiapine product referencing Seroquel for any indication, and the agency would not approve a quetiapine ANDA referencing Seroquel that omitted them"); *see also* AR 882-85 (Internal FDA Consultative Review, dated Mar. 27, 2012, noting that the "effects of Seroquel on glucose are not specific to a particular indication and that the data in Table 2 are relevant to any population receiving quetiapine").

C. PROCEDURAL BACKGROUND

Under 21 C.F.R. § 10.25(a), "[a]n interested person" may petition the FDA "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action." *See* AR 277-92 (Guidance for Industry: Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act, dated June 2011). In September of 2011, AstraZeneca filed two "Citizen Petitions" with the FDA requesting that the agency not grant final approval to any ANDA based on Seroquel or Seroquel XR unless the labeling of the ANDA includes the labeling that the FDA has required of AstraZeneca, including Table 2. *See* AR 1-21 (AstraZeneca Citizen Petition regarding Seroquel, dated Sept. 2, 2011) ("Seroquel Citizen Petition"); AR 28-59 (AstraZeneca Citizen Petition regarding Seroquel XR, dated Sept. 2, 2011) ("Seroquel XR Citizen Petition"); *see also* Compl. ¶ 6.[10] More to the point, AstraZeneca argued in its Citizen Petitions that Table 2 was entitled to exclusivity based on clinical trials that AstraZeneca performed for Seroquel XR that were essential to the approval of the addition of Table 2 to labeling for both Seroquel and Seroquel

[10] AstraZeneca also asked the FDA not to approve generic quetiapine fumarate tablets if the labeling omitted two other warnings regarding increased suicidality in children, adolescents, and young adults and the clinical worsening of depression and the risk of suicide. Neither of these warnings are at issue here.

XR. *See* AR 2, 4-6 (Seroquel Citizen Petition) ("Because these new clinical investigations with Seroquel XR for the treatment of bipolar disorder and MDD [major depressive disorder] were essential to the approval of the labeling supplement for Seroquel, the labeling is entitled to three years of exclusivity in accordance with Section 505(j)(5)(F)(iv) of the FDCA."); *see also* Defs.' Mem. at 3.[11]

The FDA denied AstraZeneca's Citizen Petitions "without comment" on March 7, 2012, the last day of the 180-day period in which the FDA was statutorily required to respond. AR 23-27 (FDA Letter, dated March 7, 2012, to Covington and Burling LLP, noting that "[w]e have carefully considered the information submitted in the Petitions. For the reasons stated below, the Petitions are denied without comment on whether we will take the actions that you request.") ("Citizen Petition Denial"); *see also* 21 U.S.C. § 355(q); Defs.' Mem. at 11. Although the FDA acknowledged AstraZeneca's assertion of exclusivity periods over the labeling, the agency ducked this issue, merely stating that "[t]he periods of exclusivity described above for Seroquel and Seroquel XR may or may not apply or be relevant to the Agency's final decisions with respect to any individual application and its labeling depending on the particulars of an ANDA and the timing of its approval." AR 26 (Citizen Petition Denial); Compl. ¶¶ 7-8 (citation omitted). Since the FDA had not yet approved any generic versions of Seroquel, the FDA noted that it would not "be appropriate" to address the merits of AstraZeneca's claims. AR 26.

[11] As the FDA points out, the "theory for exclusivity that AstraZeneca raised in its citizen petition, which was that Table 2 was entitled to three-year exclusivity based on clinical trials that AstraZeneca had performed for a different drug product [i.e. Seroquel XR]," differs from the position it asserts now. Defs.' Mem. at 3; *see also* AR 6 (Seroquel Citizen Petition, arguing that "the data and information in Table 2 cannot be included in the labeling of a generic version of Seroquel until the exclusivity periods for the Seroquel XR bipolar disorder and MDD indications have expired"). Rather than rely on Seroquel XR's sNDA for new indications of MDD and bipolar disorder, AstraZeneca is now hitching its proverbial wagon to the Seroquel sNDAs for new pediatric indications, as well as the approval of Table 2 itself, as the bases for exclusive use for 3 years of Table 2.

The FDA conveniently conflated the legal issues raised by the Citizen Petitions: namely, (1) whether the agency would approve ANDAs for generic versions of Seroquel without the identical labeling required to be used by AstraZeneca, and (2) whether the agency concurred in AstraZeneca's legal judgment that Table 2 was derived from "protected data" that was subject to exclusivity periods, which did not expire until December 2, 2012. While the former issue was dependent upon the specific ANDA application pending before the FDA, the second issue could have been addressed even if no ANDA were ever approved.

Less than one week later, following the FDA's denial of AstraZeneca's Citizen Petitions, AstraZeneca filed a Complaint together with a Motion for a Preliminary Injunction in the District Court for the District of Columbia. AstraZeneca sought to prevent the FDA from granting final approval to ANDAs to manufacture generic forms of Seroquel. *See AstraZeneca Pharms. LP v. FDA*, No. 12-388, 2012 U.S. Dist. LEXIS 39611 (D.D.C. Mar. 23, 2012). The case was assigned to another Judge on this court and, on March 12, 2012, that Judge denied the Motion for Preliminary Injunction and dismissed the case as unripe because the FDA had not yet decided to grant approval to any ANDA for a generic version of Seroquel. *See id.* at *55-56.

Only four days after AstraZeneca's case was dismissed, on March 27, 2012, the FDA granted final approval to eleven ANDAs for generic versions of Seroquel. Pl.'s Mem. at 3 ¶ 6; Compl. ¶ 11; Defs.' Mem. at 12.[12] On the same day, the FDA also issued a letter to AstraZeneca explaining its reasoning for granting approval to the ANDAs, stating in relevant part:

[12] The approval letters for the eleven ANDAs, all approved on March 27, 2012, may be found in the Administrative Record. *See* AR 978-81 (Accord Healthcare Inc.); AR 1010-13 (Apotex Corp.); AR 1085-88 (Aurobindo Pharma USA, Inc.); AR 1121-24 (Caraco Pharmaceutical Labs, Ltd.); AR 1171-74 (Dr. Reddy's Laboratories, Inc.); AR 1241-44 (Mylan Pharmaceuticals Inc.); AR 1253-56 (Lupin Pharmaceuticals Inc.); AR 1321-24 (Roxane Laboratories, Inc.); AR 1358-61 (Roxane Laboratories, Inc.); AR 1377-80 (Torrent Pharma, Inc.); AR 1429-32 (Teva Pharmaceuticals USA). Certain of these ANDAs had been pending before the FDA with tentative approvals granted several years before the final approval. *See, e.g.*, AR 1429 (FDA Letter, dated Mar. 27, 2012, to Teva Pharmaceuticals USA, approving ANDA for quetiapine fumarate tablets and referring to "the tentative approval letter issued by this office on December 22, 2008" and "your amendments dated August 2, and December 23,

> In sum, FDA concurs that these portions of the labeling [including Table 2] are essential to safe use of a generic quetiapine product referencing Seroquel for any indication, and the agency would not approve a quetiapine ANDA referencing Seroquel that omitted them. FDA does not concur, however, that an ANDA referencing Seroquel is precluded from including Table 2 or the suicidality warnings by virtue of AstraZeneca's 3-year exclusivity on certain indications for Seroquel XR.

AR 305-06 (FDA letter, dated Mar. 27, 2012, to AstraZeneca). The FDA provided several explanations for finding that Table 2 was not protected by a period of exclusivity, including, *inter alia*, (1) that the data was not specific to any indication and generally changes in labeling that involve the addition of warnings are not entitled to 3-year exclusivity; (2) Table 2 does not include data from indications for which Seroquel has 3-year exclusivity and does not include any pediatric data; and (3) the "coincidental" timing of the addition of Table 2 being approved at the same time as the pediatric supplements does not mean that the labeling change merits a period of exclusivity. *See* AR 301-03.

Following the FDA's approval of the eleven ANDAs, on March 28, 2012, AstraZeneca again filed a Complaint in the District Court for the District of Columbia, as well as a Motion for a Temporary Restraining Order, seeking to (1) vacate the FDA's final approval of ANDAs for which Seroquel and Seroquel XR are the reference-listed drugs and (2) enjoin the FDA from granting any other such final approvals pending the Court's resolution of AstraZeneca's Motion for a Preliminary Injunction. Pl.'s Mot. for Temp. Restraining Order (TRO) ("Pl.'s Mot. for TRO"), ECF No. 3, at 1; Compl. ¶ 85. AstraZeneca argues that "[a]bsent immediate relief from

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2011"); AR 1171 (Letter, dated Mar. 27, 2012, from FDA to Dr. Reddy's Laboratories, referring to "the tentative approval for your Quetiapine Fumarate Tablets . . . issued by this office on June 17, 2009 . . . .").

the Court, FDA's final approval of these generics before they are lawfully subject to final approval could cost AstraZeneca in the range of $2 billion in lost revenues." Compl. ¶ 18.

This Court denied Plaintiff's motion for a Temporary Restraining Order on March 28, 2012, finding that AstraZeneca had not shown a likelihood of success on the merits. *See Astrazeneca Pharms. LP v. FDA*, No. 12-472, 2012 U.S. Dist. LEXIS 54863, at *7-10 (D.D.C. Mar. 28, 2012).[13]

Following this Court's denial of AstraZeneca's Motion for a Temporary Restraining Order, the parties supplemented the Administrative Record and briefed the pending Cross-Motions for Summary Judgment.[14] The parties' Cross-Motions for Summary Judgment are now before this Court.

II. STANDARD OF REVIEW

A. SUMMARY JUDGMENT

Pursuant to Rule 56 of the Federal Rules of Civil Procedure, summary judgment shall be granted "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." FED. R. CIV. P. 56(a); *Anderson v. Liberty*

[13] The Court also observed that it appeared from the record that the FDA had made "'tactical decision[s]' to prevent the plaintiff 'from seeking judicial review of FDA's legal position,'" including denying AstraZeneca's Citizen Petition without comment on the merits on the last day of the comment period and advocating for denial of AstraZenca's Motion for a Preliminary Injunction on ripeness grounds when the FDA, only four days following the court's denial of the Motion for Preliminary Injunction, gave final approval to the ANDAs for generic versions of Seroquel. *See Astrazeneca Pharms. LP, 2012 U.S. Dist. LEXIS 54863*, at *10-12 (quoting Pl.'s Mot. for TRO). The FDA had the opportunity both at the time of responding to AztraZeneca's Citizen Petitions and the Motion for Preliminary Injunction to reveal the agency's legal position that Table 2, as incorporated in the labeling for Seroquel, did not warrant a 3-year exclusivity period. *Accord CollaGenex Pharms., Inc. v. Thompson*, No. 03-1405, 2003 U.S. Dist. LEXIS 12523, at *16-17 (D.D.C. July 22, 2003) (rejecting FDA argument that company's effort to prevent approval of ANDA, which was "not quite final," was unripe because company's challenge was to agency's determination that drug at issue was an antibiotic and not entitled to protections from generic drugs available under the Hatch-Waxman Amendments rather than an attack on the possible ANDA itself) (emphasis omitted).

[14] The Administrative Record in this case consists of 101 documents totaling 2,070 pages. When AstraZeneca filed its motion for a Temporary Restraining Order before this Court, it filed the identical Administrative Record, consisting of 38 documents totaling 292 pages, that had been filed before Judge Kollar-Kotelly when she decided AstraZeneca's earlier Motion for a Preliminary Injunction. Pl.'s Mot. for TRO, ECF No. 3, Ex. A, at 8-11 (Index of Administrative Record); *AstraZeneca Pharms. LP v. FDA*, No. 12-388, 2012 U.S. Dist. LEXIS 39611 (D.D.C. Mar. 23, 2012).

Lobby, Inc., 477 U.S. 242, 247 (1986); *Estate of Parsons v. Palestinian Auth.*, 651 F.3d 118, 123 (D.C. Cir. 2011); *Tao v. Freeh*, 27 F.3d 635, 638 (D.C. Cir. 1994). Summary judgment is properly granted against a party who "after adequate time for discovery and upon motion . . . fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986). The burden is on the moving party to demonstrate that there is an "absence of a genuine issue of material fact" in dispute. *Id.* at 323.

In ruling on a motion for summary judgment, the Court must draw all justifiable inferences in favor of the nonmoving party, and shall accept the nonmoving party's evidence as true. *Anderson*, 477 U.S. at 255; *Estate of Parsons*, 651 F.3d at 123; *Tao*, 27 F.3d at 638. The Court is only required to consider the materials explicitly cited by the parties, but may on its own accord consider "other materials in the record." FED. R. CIV. P. 56(c)(3). For a factual dispute to be "genuine," *Estate of Parsons*, 651 F.3d at 123, the nonmoving party must establish more than "the mere existence of a scintilla of evidence" in support of its position, *Anderson*, 477 U.S. at 252, and cannot simply rely on allegations or conclusory statements, *Greene v. Dalton*, 164 F.3d 671, 675 (D.C. Cir. 1999). Rather, the nonmoving party must present specific facts that would enable a reasonable jury to find in its favor. *See Anderson*, 477 U.S. at 250. If the evidence "is merely colorable, or is not significantly probative, summary judgment may be granted." *Id.* at 249-50 (citations omitted). An agency is "entitled to summary judgment if the path of its reasoning is sufficiently discernible in light of the record." *Settles v. U.S. Parole Comm'n*, 429 F.3d 1098, 1108 (D.C. Cir. 2005).

B. ADMINISTRATIVE PROCEDURE ACT

Under the Administrative Procedure Act ("APA"), the reviewing Court must set aside those agency actions that are in excess of an agency's statutory jurisdiction, authority, or limitations. 5 U.S.C. § 706(2)(C). In order to determine whether an agency has acted in excess of its statutory authority, this Court must engage in a two-step inquiry set out in *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984); *see also Fox v. Clinton*, No. 11-5010, 2012 U.S. App. LEXIS 11852, at *22 (D.C. Cir. June 12, 2012) ("As a general matter, an agency's interpretation of the statute which that agency administers is entitled to *Chevron* deference.").

In *Chevron* Step One, the Court first asks whether "Congress has directly spoken to the precise question at issue." *Bhd. of R.R. Signalmen v. Surface Transp. Bd.*, 638 F.3d 807, 811 (D.C. Cir. 2011) (quoting *Chevron*, 467 U.S. at 842). If so, the Court "'must give effect to the unambiguously expressed intent of Congress.'" *Id.* (quoting *Chevron*, 467 U.S. at 843). In deciding whether a statute is ambiguous, the Court has "a duty to conduct an 'independent examination' of the statute in question." *Martini v. Fed. Nat'l Mortg. Ass'n*, 178 F.3d 1336, 1345 (D.C. Cir. 1999) (citation omitted).

"If Congress has not directly addressed the precise question at issue, the reviewing court proceeds to *Chevron* Step Two." *Ass'n of Private Sector Colls. & Univs. v. Duncan*, Nos. 11-5174, 11-5230, 2012 U.S. App. LEXIS 11269, at *23 (D.C. Cir. Jun. 5, 2012) (quoting HARRY T. EDWARDS & LINDA A. ELLIOTT, FEDERAL STANDARDS OF REVIEW — REVIEW OF DISTRICT COURT DECISIONS AND AGENCY ACTIONS 141 (2007)). In *Chevron* Step Two, "the question for the court is whether the agency's answer is based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843; *see also Ne. Hosp. Corp. v. Sebelius*, 657 F.3d 1, 4-5 (D.C. Cir. 2011).

"The whole point of *Chevron* is to leave the discretion provided by the ambiguities of a statute with the implementing agency." *Ass'n of Private Sector Colls. & Univs.*, 2012 U.S. App. LEXIS 11269, at *24 (citations omitted). In conducting its *Chevron* Step Two analysis, the Court will "defer to the agency's permissible interpretation, but only if the agency has offered a reasoned explanation for why it chose that interpretation." *Vill. of Barrington, Ill. v. Surface Transp. Bd.*, 636 F.3d 650, 660 (D.C. Cir. 2011).

III. DISCUSSION

AstraZeneca contends that the FDA's final approval of generic versions of Seroquel was in contravention of 21 U.S.C. § 355(j)(5)(F)(iv), violating AstraZeneca's exclusivity rights over Table 2 as established by that section, and was arbitrary, capricious, and contrary to law. Pl.'s Mem. in Supp. of Mot. for Summ. J. ("Pl.'s Mem."), ECF No. 21, at 1. Specifically, AstraZeneca argues that Table 2 is subject to exclusivity under the plain language of 21 U.S.C. § 355(j)(5)(F)(iv) because this table was derived from new clinical investigations and was "essential" to the changes approved by the FDA as part of the sNDAs approved on December 2, 2009. AstraZeneca asks that the Court enter summary judgment in its favor, vacate the approvals of generic drugs, and permanently enjoin the FDA from granting any other final approvals of generic versions of Seroquel before December 3, 2012. Pl.'s Mot. for Summ. J. ("Pl.'s Mot."), ECF No. 21, at 1. Since there is no dispute of material fact, and the dispute centers around a purely legal question of statutory interpretation, it is appropriate to resolve the case on summary judgment.[15]

[15] AstraZeneca has requested oral argument on the pending motions for summary judgment. *See* Pl.'s Mot. at 1. Having carefully considered the briefs and administrative record, as well as having heard argument by the parties on the Motion for a Temporary Restraining Order, the Court exercises its discretion to decide the motions on the papers. LCvR 7(e).

AstraZeneca argues in support of its Motion for Summary Judgment that the FDA's approval of the ANDAs was unlawful, for two distinct reasons based on the plain and unambiguous language of 21 U.S.C. § 355(j)(5)(F)(iv). First, AstraZeneca argues that "the sNDAs approved in December 2009 were supported by new clinical investigations on pediatric use essential to approval of the sNDAs, and Table 2 was a 'a change approved in th[os]e supplement[s].'" Pl.'s Reply at 1. Second, AstraZeneca argues that "separately, considered by itself, Table 2 contains reports of new clinical investigations essential to approval of the *labeling change* supplement required by FDA and approved in December 2009—the addition of a table of glucose shift data." *Id*. (emphasis in original). Since AstraZeneca's overarching claim, and the two distinct arguments in support of that claim, focus on statutory interpretation, the Court "must begin with the first step of the two-part framework announced in *Chevron* . . . and ask whether Congress has directly addressed the precise question at issue." *Nat'l Auto. Dealers Ass'n v. FTC*, No. 11-1711, 2012 U.S. Dist. LEXIS 70831, at *12 (D.D.C. May 22, 2012) (citations and quotation marks omitted). "When determining whether Congress has spoken to the precise question at issue, courts must first exhaust the traditional tools of statutory construction." *Mylan Pharms., Inc. v. Sebelius*, No. 12-524, 2012 U.S. Dist. LEXIS 56178, at *27 (D.D.C. Apr. 23, 2012) (citations and internal quotation marks omitted). "If, however, the statute is silent or ambiguous on the specific issue, 'the question for the court is whether the agency's answer is based on a permissible construction of the statute.'" *Univ. Med. Ctr., Inc. v. Sebelius*, No. 11-260, 2012 U.S. Dist. LEXIS 53395, at *27 (D.D.C. Apr. 17, 2012) (quoting *Chevron*, 467 U.S. at 843). "When the agency's construction of a statute is challenged, its interpretation need not be the best or most natural one by grammatical or other standards . . . . Rather [it] need be only reasonable to warrant deference." *Id*. (citations and internal quotation marks omitted).

As explained above, the threshold question is whether the statute is ambiguous, or instead, by its plain terms, compels the result urged by AstraZeneca. If the statute is ambiguous, then the Court must defer to the FDA's determination, which was well within the agency's expertise, so long as its decision was not arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. *See, e.g.*, *ViroPharma, Inc.*, 2012 U.S. Dist. LEXIS 56128, at *37 ("It bears emphasis that [i]n an area as complex as the regulatory system for pharmaceuticals, the agency Congress vests with administrative responsibility must be able to exercise its authority to meet changing conditions and new problems.") (citations and internal quotation marks omitted and alteration in original). Upon review of the administrative record, and for the reasons explained below, the Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute, and therefore its final approval of the ANDAs was not arbitrary, capricious, or an abuse of discretion.

A. *CHEVRON* STEP ONE

Under *Chevron* Step One, "[f]irst, always, is the question whether Congress has directly spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at 842-43; *see also NRDC v. EPA*, 643 F.3d 311, 322 (D.C. Cir. 2011) ("We begin with the statute."). As noted, the relevant provision of the FDCA subject to this Court's statutory interpretation and *Chevron* analysis, and at the heart of the dispute, is 21 U.S.C. § 355(j)(5)(F)(iv).

AstraZeneca's position is that the Court's analysis should end at *Chevron* Step One because the plain language of 21 U.S.C. § 355(j)(5)(F)(iv) sets forth a condition that, if met, leads to a specific result. AstraZeneca interprets the statute to mean that "*if* (1) there is an

approved sNDA containing reports of new clinical investigations sponsored or conducted by the applicant that were essential to the approval of the sNDA, *then* (2) the sNDA applicant has three years of exclusivity over a 'change approved in the supplement.'" Pl.'s Mem. at 1. Since the sNDAs for Seroquel approved on December 2, 2009 included reports of clinical investigations that were essential to approval of the sNDAs, then, AstraZeneca argues, the labeling change (i.e., the inclusion of Table 2) approved in the supplement, is entitled to exclusivity by the plain words of the statute. As noted, AstraZeneca bases its exclusivity rights on "two separate types of new clinical investigations": (1) "the new clinical investigations conducted to establish the efficacy of Seroquel to treat schizophrenia and bipolar disorder in adolescents," and (2) "the new clinical investigations that provided glucose shift data for Table 2." Pl.'s Reply at 2; *see also id*. at 3 (Table illustrating alleged bases for AstraZeneca's statutory exclusivity rights). The question, then, AstraZeneca argues, is "whether Section 505(j)(5)(F)(iv) 'means what it says.'" Pl.'s Mem. at 7 (quoting *Landstar Express Am., Inc. v. Fed. Maritime Comm'n*, 569 F.3d 493, 498 (D.C. Cir. 2009)). If it does mean what it says, AstraZeneca argues, then AstraZeneca has exclusivity over Table 2 through December 2, 2012. *See* Pl.'s Mem. at 7.

The FDA, on the other hand, has interpreted the statutory provision at issue as requiring a relationship between the subject of the "new clinical investigations," the change to the product or use of the product, and the scope of the three-year exclusivity, explaining as follows:

> The statute sets up a relationship between the "new clinical investigations" that are "essential to the approval of the supplement," and the scope of the exclusivity. That is, if an applicant submits a supplement and gets 3-year exclusivity for a change in the use of the drug product supported by new clinical investigations, the FDA may not approve an ANDA referencing that drug product for the "change approved in the supplement" during that 3-year exclusivity period. Because the change in the drug product or use of the drug product that was approved in the supplement was based at least in part on the new clinical investigations, it naturally follows that the scope of any exclusivity also will relate to the scope of those new clinical investigations.

AR 299 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca).

Although the FDA, in its briefs, framed its argument as a "reasonable interpretation" of the statute, the Court believes that the FDA's interpretation is closest to the plain meaning of the statute. Indeed, the Court agrees with the FDA that the statute sets up a "logical relationship between the change in the product for which the new clinical investigations were essential to approval of the supplement, and the scope of any resulting three-year exclusivity." Defs.' Reply at 3-4. Interpreting the plain meaning of the statute in this way means that only changes to labeling derived from clinical studies related to the changes approved in the supplement may be entitled to exclusivity. *See id.* at 3-4. Thus, AstraZeneca is not automatically entitled to exclusivity for Table 2 by virtue of unrelated clinical studies supporting the pediatric indications approved on December 2, 2009.

AstraZeneca also argues, however, that Table 2 deserves exclusivity on its own merit, independent of the pediatric supplements. *See* Pl.'s Mem. at 17. Section 355 (j)(5)(F)(iv), however, requires that a "supplement to an application" contain reports of "new clinical investigations" and be "essential to the approval of the supplement." Here, the administrative record demonstrates, and AstraZeneca admits, that Table 2 was an "amendment" to the pediatric supplemental new drug applications, not a supplement itself. *See* Pl.'s Reply at 14. Nor was Table 2 a part of AstraZeneca's three supplements that were "superseded" by the December 2009 approval letter. Defs.' Reply at 7, n.1.[16] Moreover, as noted, the data from which Table 2 was derived was submitted by AstraZeneca in 2008 pursuant to general correspondence between the

[16] The December 2, 2009 Approval Letter stated that previous labeling supplements "have been superseded by this approval action." AR 95. The supplements referred to are dated July 19, 2007, September 11, 2008, and December 4, 2008. According to the FDA, "[n]one of those supplements have submission dates that relate to Table 2; nor does AstraZeneca assert that those supplements are for Table 2." Defs.' Reply at 7 n.1.

parties. *See* AR 883, 295; Defs.' Mem. at 9. It does not appear "plain" to the Court that data submitted in correspondence is a "supplement" or that the data submitted for Table 2 constitutes a "new clinical investigation" for purposes of the statute.

Although the statute's plain meaning favors the FDA, since plausible plain meaning arguments cut both ways, the Court believes the better reading of the statute is that section 355(j)(5)(F)(iv) is ambiguous. *See ViroPharma*, 2012 U.S. Dist. LEXIS 56128, at *46 ("[T]he fact '[t]hat a statute is susceptible of one construction does not render its meaning plain if it is also susceptible of another, plausible construction[.]'") (citation omitted) (finding ambiguous 21 U.S.C. § 355(v)(3)(B), which exempts certain drugs from the exclusivity provided for under 21 U.S.C. § 355(j)(5)(F)(iv), and deferring to agency's interpretation of the statute).

Section 355(j)(5)(F)(iv) is ambiguous because key phrases in the statutory provision are undefined and their meaning disputed. The parties dispute, for example, whether or not Table 2 is even a "supplement" within the meaning of the section. *Compare* Pl.'s Reply at 4 ("The new clinical data in Table 2 . . . is an approved supplement to the Seroquel NDA."), *with* Defs.' Mem. at 9 ("The data from which Table 2 was derived were [not] submitted . . . as a supplement."). This dispute over whether Table 2 is a "supplement" is due to the ambiguities in the terms used to define the scope of which supplements trigger the 3-year marketing exclusivity under section 355(j)(5)(F)(iv). The statutory provision at issue does not define "new clinical investigation," or what makes a particular investigation "essential to approval," or what it means when a change is approved at the same time as a supplement is approved when that change is not part of the original supplemental application. While a lack of definitions does not automatically mean that a statute is ambiguous, *see Goldstein v. SEC*, 451 F.3d 873, 878 (D.C. Cir. 2006), without these key definitions, "nothing about 'the specific context in which [the phrase] is used' or 'the

broader context of the statute as a whole' is likely to compel the conclusion that the phrase has a definite meaning." *ViroPharma*, 2012 U.S. Dist. LEXIS 56128, at *43 (quoting *Blackman v. District of Columbia*, 456 F.3d 167, 176 (D.C. Cir. 2006)). Each of these key phrases is examined in more detail below.

First, the Court turns to the phrase "new clinical investigation." It is an established principle of statutory construction that a provision's context should be used to assist in determining whether a statute commands a certain interpretation or has a plain meaning. *See, e.g.*, *Samantar v. Yosuf*, 130 S. Ct. 2278, 2289 (2010) ("[W]e do not … construe statutory phrases in isolation; we read statutes as a whole.") (quoting *United States v. Morton*, 467 U.S. 822, 828 (1984)); *see also Dolan v. U.S. Postal Serv.*, 546 U.S. 481, 486 (2006) ("Interpretation of a word or phrase depends upon reading the whole statutory text, considering the purpose and context of the statute[.]"). In the context of this provision, the meaning of "new clinical investigation" is not "plain." It is not immediately apparent that AstraZeneca's clinical studies underlying Table 2 are "new clinical investigations" for purposes of the statute. In 2008, AstraZeneca submitted to the FDA the clinical studies that are the basis for Table 2 in AstraZeneca's unrelated effort to have new indications of Seroquel XR approved. *See* Defs.' Mem. at 9; Defs.' Reply at 15. AstraZeneca was later asked to reanalyze this data to produce Table 2. Defs.' Mem. at 10. Since the same clinical investigations were used to support unrelated applications, it is not clear that these studies are "new" with respect to Table 2. Furthermore, if these investigations are deemed "new" to support exclusivity for Table 2, are they then ineligible to count again as "new" to support exclusivity for any of the unrelated applications for which AstraZeneca originally submitted them? In other words, the statute does

not describe the circumstances when clinical investigations are considered "new." Thus, the Court is not persuaded that "new clinical investigations" is unambiguous.

Second, the phrase "essential to approval" is ambiguous. Congress provides no guidance or criteria under which reports of new clinical investigations may be judged "essential" versus merely persuasive or noteworthy. *See Upjohn Co. v. Kessler*, 938 F. Supp. 439, 444 (W.D. Mich. 1996) (noting that a determination of what data is "essential to approval" is "squarely within the ambit of the FDA's expertise and merit[s] deference . . . ") (citations and internal quotation marks removed). Furthermore, AstraZeneca seems to interpret the FDA's judgment that Table 2 contains essential safety data as automatically making Table 2 "essential to approval" of the supplement containing unrelated pediatric data for new pediatric indications. *See* Pl.'s Mem. at 2. The words of the statute cannot bear this overbroad interpretation.

Third, AstraZeneca argues that the plain meaning of the phrase "a change approved in the supplement" means that any change approved in the supplement is entitled to exclusivity. *See* Pl.'s Mem. at 8. The clear implication of this reading is that any change approved in the supplement, whether or not it is related to the "new clinical investigation," or to the new uses approved in the supplement, is entitled to exclusivity. *See id*. AstraZeneca argues that this reading is compelled by Congress's use of the phrase "a change" rather than "the change." *See id*. This reading is unpersuasive for two reasons. First, it is not unusual for supplements to contain more than one change. *See* Defs.' Mem. at 23-24. By its use of "a" rather than "the," Congress provided the flexibility for the FDA to approve multiple changes within one supplement, rather than requiring a separate supplement for each change. Second, AstraZeneca's interpretation ignores the implication of the phrase "in the supplement." As noted, the most plausible meaning is that there must be a connection between the change and the supplement

beyond mere coincidence of appearing in the same approval letter. *See id.* at 24. Congress could not have intended that the FDA's decision to report on completely unrelated regulatory actions in the same letter for the sake of efficiency would confer on drug manufacturers additional periods of exclusivity when that exclusivity was not otherwise merited. Thus, even if this phrase has a plain meaning, it favors the FDA rather than AstraZeneca. At the very least, however, this phrase is ambiguous.[17]

Finally, the subsection read as a whole is ambiguous. AstraZeneca proposes one interpretation that goes thusly: (1) Any change to a pioneer drug application counts as a supplement under this statute; (2) This makes Table 2 a supplement; (3) The data to generate Table 2 is essential to the approval of Table 2; (4) Therefore, Table 2 is entitled to exclusivity. The FDA properly rejects this circular reading of the statute as omitting the proper emphasis on the nexus between the new clinical investigations and new uses required to trigger the additional period of exclusivity. *See* Defs.' Reply at 3-4.

While AstraZeneca is correct that "an agency's own regulations cannot create or give rise to ambiguity when the statutory language is unambiguous[,]" Pl.'s Reply at 6 (citing *Chevron*, 467 U.S. at 843 n.9 ("The judiciary is the final authority on issues of statutory construction and must reject administrative constructions which are contrary to clear congressional intent.")), in this case the parties' different interpretations of the statutory provision highlight the statute's ambiguity.

Accordingly, the Court proceeds to *Chevron* Step Two.

[17] The FDA could in the future minimize misunderstanding about which approved change warrants an exclusivity period, prompted by the ambiguity in the statute, by more carefully and precisely delineating at the time of the approval -- in separate communications if necessary -- those changes in an sNDA that warrant an exclusivity period and those changes that do not.

B. *CHEVRON* STEP TWO

As this Court found in denying AstraZeneca a Temporary Restraining Order, the FDA has reasonably interpreted 21 U.S.C. § 355(j)(5)(F)(iv) in denying exclusivity for Table 2. The FDA's determination that the approval of Table 2 for Seroquel labeling at the same time as the approval of the sNDA for pediatric indications "was only coincidental" is, itself, a determination "well within the agency's expertise . . . ." *AstraZeneca Pharms. LP v. FDA*, No. 12-472, 2012 U.S. Dist. LEXIS 54863, at *9 (D.D.C. Mar. 28, 2012). Therefore, the Court will defer to the FDA's conclusion here unless it was unreasonable. Following a review of the administrative record, the Court concludes that the agency's interpretation of the statute — that a substantive relationship between new clinical studies and changes in the supplement, not the format of a submission, dictates what changes receive exclusivity — is reasonable for several reasons. First, the administrative record shows that the pediatric supplements were approved on their own merits based upon clinical investigations unrelated to the Table 2 labeling change, which standing alone does not entitle AstraZeneca to exclusivity. Second, the FDA's interpretation of the statute is largely consistent with past practice, and therefore not arbitrary and capricious. Third, the FDA's interpretation is consistent with the legislative history.

1. The Administrative Record Shows that the Pediatric Supplements Were Approved on Their Own Merit, and Table 2 Standing Alone Does Not Entitle AstraZeneca to Exclusivity.

AstraZeneca posits two bases for exclusivity for Table 2 arising from two separate sets of clinical investigations: the clinical investigations supporting pediatric indications and the clinical investigations that yielded the data for Table 2. According to AstraZeneca, "each separately and independently establishes AstraZeneca's exclusivity rights under the plain, unambiguous language of the statute." Pl.'s Reply at 3. Since the Court finds the statute to be ambiguous,

however, analysis of these two arguments turns on whether the FDA's interpretation of the statute was reasonable, as explained below. *See Chevron*, 467 U.S. at 843.

a. Clinical Investigations Supporting Pediatric Indications Do Not Support Exclusivity For Table 2.

The administrative record shows that the pediatric supplements approved on December 2, 2009 were approved on their own merit, and the addition of Table 2 was not a factor in the evaluation of the safety and efficacy of Seroquel for pediatric indications. *See* AR 866-68 (FDA Internal Memorandum, dated Dec. 2, 2009, referring to pediatric indication issues only, not Table 2).

While AstraZeneca states repeatedly that "the addition of Table 2 to the label was part of the supplements approved on December 2, 2009," *see, e.g.*, Pl.'s Reply at 20-21, AstraZeneca has not established that the approval of Table 2 was *essential* to the approval of the pediatric sNDAs, which were supported by entirely different clinical trials. None of AstraZeneca's citations to the Administrative Record show that the FDA mandated changes to Table 2 "as a condition of approval of the sNDAs." Pl.'s Reply at 1; *see also* Pl.'s Mem. at 16. An example of evidence that conceivably supports AstraZeneca's position in the Administrative Record is an internal FDA Memorandum, dated August 13, 2009. *See* AR 853-64. In the memorandum, an FDA official stated that, "[w]e should be negotiating labeling changes with the sponsor prior to approval of these NDA supplements" and "I recommend the Division should consider approval of this set of NDA supplements provided that an agreement is reached between the sponsor [AstraZeneca] and the Agency regarding the language in the labeling." *Id*. at 863-64. Since Table 2 was not related to the pediatric supplements, however, which were approved on their own merit, this internal recommendation, without more, does not render Table 2 "essential to approval" of the pediatric supplements.

Moreover, the fact that the FDA said it would not approve generics without Table 2 does not mean that it would not have approved the pediatric indications for Seroquel without Table 2. Indeed, it appears to the Court that the addition of Table 2 merely coincided with, but was not essential to, the sNDA approvals on December 2, 2009. *See* AR 303 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca, stating that "[t]his data does not qualify for any protection solely by virtue of the timing of FDA's approval of the supplement, including Table 2. Rather, the scope of exclusivity must relate to the new clinical investigations that were conducted."); AR 883 (Internal FDA Consultative Review, dated Mar. 27, 2012, noting that "the addition of Table 2 was not related to approval of these new [pediatric] indications. It is not unusual for [the Division of Psychiatry Products] to bundle actions together - modifications to product labeling usually occur in concert with other actions being taken.").

As the FDA notes, AstraZeneca's reliance on approval of the pediatric indications to support a period of exclusivity for the unrelated addition of Table 2 seems to be an attempt "to bootstrap AstraZeneca's exclusivity for the pediatric indications into exclusivity for Table 2 because those separate changes were approved at the same time." Defs.' Mem. at 21. The FDA, however, has reasonably construed the phrase "a change approved in the supplement" to mean "a change relating to 'new clinical investigations.'" *Id.* at 24; *see also Univ. Med. Ctr., Inc.*, 2012 U.S. Dist. LEXIS 53395, at *27 (finding that the agency's "construction of a statute . . . need not be the best or most natural one . . . . Rather [it] need be only reasonable to warrant deference.") (citations and internal quotation marks omitted). "[T]he FDA was within its discretion to apply a limiting principle so that Hatch-Waxman's exclusivity provisions do not apply to *all* approved changes that are 'new' . . . . [T]he general exclusivity period provided in § 355(j)(5)(F)(iv) . . . is

itself limited to that which is 'new' about the given drug." *ViroPharma*, 2012 U.S. Dist. LEXIS 56128, at *50.

As noted, the FDA has also interpreted the statute to require a "nexus between the subject of the new clinical investigations and the changes to the product that the investigations support." Defs.' Mem. at 7. Here, AstraZeneca has not shown any nexus between the approval of the supplements for pediatric indications and the labeling change consisting of the addition of Table 2. First, it is undisputed that Table 2 contains no data from the new clinical investigations related to the pediatric indications. *See* AR 301; Defs.' Mem. at 10; Pl.'s Reply at 4, 11-12. Second, the data from which Table 2 was derived was submitted months before the data for the pediatric indications, and was submitted as correspondence from AstraZeneca to the FDA rather than as a formal supplemental application. *See* AR 431 (AstraZeneca Letter, dated June 26, 2008, to the FDA). Third, Table 2 was approved for addition to the "Adults" section of labeling and is thus explicitly unrelated to data from the pediatric clinical investigations. *See* AR 112 (Seroquel Current Labeling, dated Nov. 2011). AstraZeneca has therefore not shown that the clinical investigations supporting its sNDAs regarding pediatric indications provide a basis for exclusivity for labeling changes in the form of the addition of Table 2 to Seroquel labeling.

b. Clinical Investigations From Which Table 2 Is Derived Are Not A Basis For Exclusivity.

AstraZeneca also argues that it is entitled to exclusivity for Table 2 because the FDA had not previously relied on seven of the fifteen clinical investigations from which Table 2 was derived. *See* Pl.'s Reply at 18-19. This argument is unpersuasive for two reasons. First, it seems to depend on the assumption that Table 2 was approved as a formal "supplement." The FDA has made clear, however, that the approval of Table 2 was merely coincidental to the

approval of the pediatric indication supplements approved in December 2009, and that "Table 2 was not submitted pursuant to a supplement." Defs.' Mem. at 31.

Second, examining Table 2 separately from its coincidental inclusion with the pediatric supplement, the FDA's interpretation that Table 2 is not entitled to independent exclusivity is reasonable. The FDA's interpretation of the statute as only granting exclusivity for significant innovations is reasonable given the statute's careful balance between providing exclusivity rights to promote innovation and making generic alternatives available to patients. *See* Defs.' Mem. at 33-34; Defs.' Reply at 15; *see also Upjohn Co.*, 938 F. Supp. at 441 (citing *Abbott Labs. v. Young*, 920 F.2d 984, 985 (D.C. Cir. 1990)) ("At the same time that it expedited approval of generic drugs, Congress recognized the need to protect the interests of the original drug manufacturers and to provide incentives for the invention of new products."). The FDA's reading of the statutory provision is also reasonable given that the provision itself tethers the "change" approved in the supplement to subsection (b), and thereby imparts to the meaning of a formal supplement that it mark a sufficiently significant change that would have warranted an additional use or indication of the drug if it had been submitted with the original NDA under subsection (b). *See* 21 U.S.C. § 355(b); 21 U.S.C. § 355(j)(5)(F)(iv).

AstraZeneca's interpretation, by contrast, "would effectively provide for whole-product exclusivity whenever FDA determined that data from a clinical trial would have relevance to the safety of the product for all indications, even if the data were insufficient to support approval (and exclusivity) for a new indication." Defs.' Mem. at 35. Accordingly, it is reasonable for the FDA not to grant exclusivity here because there would be no valid interest in withholding this safety data from consumers. Furthermore, the Court is not persuaded by AstraZeneca's argument that the existence of a "carve out" exception, whereby generics may receive approval

so long as they "carve out" minor labeling changes that have received exclusivity, *see* Pl.'s Reply at 16-17, renders the FDA's interpretation of the statute unreasonable. As previously discussed, the FDA's interpretation need only be reasonable to be accorded deference, and it is reasonable.

2. The FDA Did Not Act Arbitrarily or Capriciously.

The FDA's interpretation of the statute is consistent with its past practice.[18] The FDA has emphasized that generally applicable safety information in labeling should not be subject to exclusivity. *See* Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,357 (Oct. 3, 1994) (Supplementary Information Accompanying Final Rule, dated Oct. 3, 1994, noting that innovators have "no valid interest in precluding such information from the labeling of other products"). While the FDA declined in its final implementing regulations to define the nature of supplemental applications, which, "if supported by clinical investigations, would warrant 3-year exclusivity," the FDA noted that "[c]hanges that would *not* warrant exclusivity are . . . changes in labeling that involve warnings or other similar risk information that must be included in the labeling of generic competitors." *Id*. (emphasis added).

[18] The Court does not find convincing AstraZeneca's argument that the FDA should be "judicially estopped" due to the agency's "litigation tactics" from arguing that it has a longstanding practice of rejecting exclusivity rights in situations such as this one. Pl.'s Mem. at 11; Pl.'s Reply at 9-10. As noted, *supra* at note 13, the FDA should have been more forthcoming about its determination regarding AstraZeneca's lack of exclusivity rights to Table 2 in response to the company's Citizen Petitions and when this matter was before Judge Kollar-Kotelly. By waiting until March 27, 2012 to explain its reasoning for not recognizing exclusivity for Seroquel labeling, the FDA needlessly delayed consideration of the merits of the agency's determination, which could have been considered when AstraZeneca filed its first complaint for injunctive relief and caused the plaintiff and this Court to participate in a fire drill to resolve these significant legal issues in the context of a Temporary Restraining Order on March 28, 2012. While the Court faults the FDA for contributing to a needless waste of resources for the parties and the Court on this matter by not making its views plain earlier, AstraZeneca has shown no reason why the Court should prevent the FDA from relying on its past precedent in responding to a challenge to its final decision to approve generic drugs referencing Seroquel. Furthermore, AstraZeneca has raised new arguments in its Motion for Summary Judgment, and the FDA may respond in turn by including citations to its relevant past decisions.

Notably, the FDA has also denied exclusivity for similar labeling changes to other drugs in Seroquel's class of antipsychotics. *See* AR 303 n.21 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca, stating that "[t]he agency's conclusion that Table 2 is not protected and its implications for generic quetiapine products is consistent with the agency's treatment of other second-generation antipsychotics for which data regarding metabolic changes, including Table-2 like data, have been made."). According to the FDA, in fact, "[s]even drugs [in the same antipsychotic class as Seroquel] (Invega, Invega Sustenna, Abilify, Risperdal, Risperdal Consta, Fanapt, and Latuda) have included class-wide labeling changes for metabolic data, and none of them has received exclusivity for those changes." Defs.' Mem. at 36 n.22.

AstraZeneca cites the FDA's handling of four drugs (Meridia, Travatan, Rapamune, and Colcrys) as examples to support the proposition that the "FDA has an established practice of granting exclusivity to labeling information, even when such information is relevant to all indications of use for a drug, and even when such information appears in the 'warnings' section of a drug's label." Pl.'s Mem. at 20. These examples are readily distinguishable. For each of these four drugs, the FDA granted exclusivity to the labeling because the FDA found the labeling changes "substantively related to the new clinical investigations that were essential to the approval of a clinical efficacy supplement." Defs.' Reply at 16; *see also* Defs.' Mem. at 39 (labeling changes were "directly related to a clinical efficacy supplement for the protected indication.").

In the case of Meridia, according to the FDA, the labeling change for which exclusivity was granted was "substantively related to the new clinical investigations that were essential to the approval of a clinical efficacy supplement." Defs.' Reply at 16; *see also* Defs.' Mem. at 37-38. Similarly, in the case of Travatan, the FDA granted exclusivity to a labeling change on the

basis of clinical data that "expanded the patient population" by replacing a statement that Travatan had not been studied in patients with renal or hepatic impairment with clinical findings showing that "no clinically relevant changes were observed" when those patients took the drug. Defs.' Mem. at 38.

In the cases of Rapamune and Colcrys, information that was originally used to support new efficacy supplements was also considered necessary safety labeling information. With respect to Rapamune, the FDA determined that Rapamune was entitled to exclusivity for "a clinical efficacy supplement for cyclosporine withdrawal procedures in patients at low to moderate risk for rejection." Defs.' Mem. at 39 (citation omitted). The FDA concluded, however, that the labeling information exclusivity should be extended to the population at *high risk* of rejection because that "labeling information might help raise physicians' awareness of the risks of cyclosporine." Declaration of Benjamin C. Block ("Block Decl."), ECF No. 21, Ex. 2 (quoted in Defs.' Mem. at 39). Likewise, for Colcrys, 3-year exclusivity was originally granted to dosing information essential to treating acute gout flares. AR 957 (FDA Letter, dated May 25, 2011, to Sidley Austin LLP regarding the approval of Colcrys). When the FDA concluded that the same dosing information was necessary for the related indication of prophylaxis of gout flares, exclusivity was granted to the prophylaxis indication, even though it was previously not protected. *See id.* at 977; Defs.' Mem. at 39.

The critical difference in circumstances between the protected labeling information for the drugs Rapamune and Colcrys and unprotected Table 2 for Seroquel is that, in the cases of the former drugs, the labeling changes were tied to the approval of efficacy supplements, whereas the approval of Table 2 was never essential to the approval of any efficacy supplement for Seroquel. *See, e.g.*, AR 11-12 (FDA Letter, dated Dec. 18, 2008, to AstraZeneca, making clear

that metabolic data submissions, which led to creation of Table 2, are separate from the pediatric efficacy supplements under consideration). Table 2 did not contribute to the approval of the pediatric or any other efficacy supplement, and has not yet led to any other changes in efficacy, such as a new dosage or prescribing regimen or a new indication or use in a new patient population. In other words, if the safety data reflected in Table 2 had been known at the time of the FDA's approval of the Seroquel NDA for its original indications, it would have been included in the original labeling. Thus, although the FDA considers Table 2 "essential" safety information, the FDA's decision not to grant Table 2 exclusivity is consistent with its past decisions and distinguishable from the instances where the FDA has granted exclusivity for changed safety information in labeling.

Furthermore, the FDA provided a reasoned explanation for its decision to approve ANDAs for generic versions of Seroquel. On March 27, 2012, the FDA issued a seventeen-page letter to AstraZeneca explaining the agency's rationale for finding that Table 2 in Seroquel was not protected by a three-year exclusivity period. *See* AR 293-310; *see also* Defs.' Mem. at 12-13. Since this letter explains, *inter alia*, that generally-applicable safety information of the type in Table 2 is not subject to protection, the agency's decision to deny Table 2 exclusivity is not arbitrary and capricious. *See Motor Vehicles Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983) (quoting *Burlington Truck Lines v. United States*, 371 U.S. 156, 168 (1962), for the proposition that "the agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'").

Therefore, because the FDA provided a reasoned explanation for its decision, the FDA's decision to deny AstraZeneca exclusivity for Table 2 was not arbitrary and capricious.

The potential implications of AstraZeneca's broad reading of the statute also lend support to the FDA's interpretation. As noted, the FDA has undertaken an effort to implement updated safety labeling for drugs in the same class as Seroquel with metabolic data similar to what is displayed in Table 2. Defs.' Reply at 11. AstraZeneca's interpretation of this statutory provision would seriously impede the FDA's initiative to improve the safety data available for this class of drugs, which includes Invega, Invega Sustenna, Abilify, Risperdal, Risperdal Consta, Fanapt, and Latuda.[19] *Id*. Though all of the safety data added to the labels of these drugs is derived from clinical investigations, the FDA claims that none of these investigations provided the basis for three-year exclusivity. *Id.*; *see also* AR 303-04 n.21 (FDA Letter, dated Mar. 27, 2012, to AstraZeneca). A reading of the statutory provision at issue that could prevent the FDA from requesting from drug manufacturers any class-wide safety labeling changes involving clinical trials without triggering exclusivity periods is untenable and, as detailed below, plainly inconsistent with the legislative history.

3. The FDA's Interpretation of the Statute is Consistent with Legislative History.

The Court finds the FDA's interpretation of the statute consistent with the statute's legislative history. As noted, a central purpose of the Hatch-Waxman Amendments, as reflected in its title "The Drug Price Competition and Patent Term Restoration Act," was to promote competition by providing a mechanism through which generic drugs were more easily approved. *See* 21 U.S.C. § 355(j); *see also ViroPharma*, 2012 U.S. Dist. LEXIS 56128, at *7 ("The abbreviated new drug application ('ANDA') process shortens the time and effort needed for

[19] Since certain safety information, such as Table 2, "is necessary for safe use of the product," it would not be subject to the "carve out" exception for ANDAs, *see* Defs.' Mem. at 3, whereby ANDA applicants may receive FDA approval so long as they "carve out" protected portions of labeling. *See, e.g.*, *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996). By contrast, for example, the FDA determined that certain protected pediatric use information for Seroquel "may be safely carved out of generic quetiapine fumerate [sic] tablets labeling and replaced with appropriate legal disclaimers." AR 880 (FDA Memorandum to File, dated May 23, 2011).

approval of a generic drug by allowing the applicant to merely demonstrate its product's bioequivalence to the NDA drug, without reproducing the entirety of the NDA's extensive scientific research.") (citations omitted).

Congress had dual purposes, however, and enacted the abbreviated approval process for generic drugs while simultaneously retaining incentives, such as marketing exclusivity, to encourage innovation and development from pioneer drugmakers. *See* 21 U.S.C. § 355(j); *see also ViroPharma*, 2012 U.S. Dist. LEXIS 56128, at *7 ("Because Congress still wanted to provide incentives for new drug development, alongside the ANDA process that eased the marketing of generic drugs, Hatch-Waxman entitles an NDA applicant to a period of market exclusivity . . . which bars FDA approval of a generic ANDA for the NDA product . . . . Thus, pursuant to Hatch-Waxman's provisions, pioneer drug companies are entitled to certain periods of marketing exclusivity during which they are protected from generic competition.") (quotation marks and citations omitted). As the FDA notes, the Act struck a "careful balance between exclusivity and generic entry" into the market. Defs.' Reply at 11; *see also Abbott Labs.*, 920 F.2d at 985 ("Congress struck a balance between expediting generic drug applications and protecting the interests of the original drug manufacturers.") (citing H.R.REP. NO. 98-857, pt. 1, at 15 (1984), *reprinted in* 1984 U.S.C.C.A.N. (98 Stat. 1585) 2647, 2648).

While AstraZeneca is thus correct to point out that Congress provided exclusivity rights "as an incentive for pioneer companies to engage in expensive clinical research," Pl.'s Reply at 1, granting exclusivity to Table 2 would disrupt the "careful balance" Congress crafted. Adopting AstraZeneca's interpretation, where every change approved in a supplemental application receives exclusivity, would increase the potential for companies to receive whole-product exclusivity and bar generic competition altogether for labeling changes unrelated to

innovations in drug use. *See* Defs.' Mem. at 36. As the FDA notes, AstraZeneca's interpretation would result in an "unwarranted evergreening of exclusivity," Defs.' Reply at 10, allowing AstraZeneca to retain a monopoly over production of a drug by periodically updating safety information in their labeling. This risk is particularly worrisome given the FDA's practice that "modifications to product labeling usually occur in concert with other [regulatory] actions being taken." AR 883 (FDA Consultative Review, dated Mar. 27, 2012, to OGD). AstraZeneca's interpretation would create a perverse incentive for pharmaceutical companies to drag out their presentation of vital safety data to the FDA in order to bar generic competition beyond the periods determined acceptable by Congress. While Congress was no doubt concerned that pharmaceutical manufacturers have incentives to continue research and development in order to discover vital new drugs, Congress plainly did not intend for these manufacturers to retain exclusivity into perpetuity.

The legislative history makes clear that the sponsors of the Hatch-Waxman Amendments, Senator Orrin Hatch and Representative Henry Waxman, envisioned that three-year exclusivity would be granted for significant changes, such as approvals for new therapeutic uses and new patient populations. *See* 130 CONG. REC. 24,425 (1984) (Statement of Rep. Henry Waxman) (three-year exclusivity is intended to "encourage drugmakers to obtain FDA approval for significant therapeutic uses of previously approved drugs"); *see also* 130 CONG. REC. 23,766 (1984) (Statement of Senator Orrin Hatch) (three-year exclusivity is intended to protect "some changes in strength, indications, and so forth . . . ."). These sponsors' statements support the FDA's decision to consistently grant exclusivity for changes resulting from studies supporting efficacy supplements, such as in the cases of Meridia, Travatan, Rapamune, and Colcrys, but not

to grant exclusivity for Table 2, which involves general "warnings or other similar risk information" applicable to all indications for the drug. *See* AR 1529 (59 Fed. Reg. 50,357).

The legislative history thus supports the FDA's reasonable conclusion that Table 2 is not entitled to exclusivity under 21 U.S.C. § 355(j)(5)(F)(iv).

IV. CONCLUSION

For the foregoing reasons, AstraZeneca's Motion for Summary Judgment, ECF No. 21, is DENIED, and the FDA's Motion for Summary Judgment, ECF No. 26, is GRANTED. An Order consistent with this Memorandum Opinion was issued on June 28, 2012.

DATED: July 5, 2012

/s/ *Beryl A. Howell*
BERYL A. HOWELL
United States District Judge