UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ACTAVIS ELIZABETH LLC,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**Civil Action No. 09-362 (RMC)**
	)	
UNITED STATES FOOD & DRUG ADMINISTRATION, *et al.*,	)	
	)	
Defendants.	)	
	)	

MEMORANDUM OPINION

Actavis Elizabeth LLC seeks judicial review of a decision of the United States Food and Drug Administration awarding five years of market exclusivity to Intervenor-Defendant Shire Pharmaceuticals Inc. for the manufacture of lisdexamfetamine dimesylate ("LDX"), currently marketed by Shire's subsidiary in the United States under the trade name Vyvanse®. Actavis disagrees with the agency's conclusion that LDX is a "new chemical entity" within the meaning of the Federal Food, Drug, and Cosmetic Act ("Act"), 21 U.S.C. § 301 *et seq*., as amended. Actavis, FDA, and Shire each moves for summary judgment.[1] For the reasons explained herein, the Court will grant summary judgment to FDA and Shire, and will deny summary judgment to Actavis.

I. FACTS

On February 23, 2007, FDA approved Shire's new drug application for LDX to treat

[1] FDA also moves to dismiss for failure to state a claim. *See* Dkt. # 30. Because matters outside the pleadings have been presented to the Court, the motion must be treated as one for summary judgment. *See* Fed. R. Civ. P. 12(d). The motion to dismiss will therefore be denied.

Attention Deficit Hyperactivity Disorder. FDA awarded Shire five years of market exclusivity pursuant to § 355(j)(5)(F)(ii) of the Act and FDA's interpreting regulations, 21 C.F.R. § 314.108. FDA determined that LDX is a "new chemical entity" within the meaning of the Act because LDX contains a previously approved molecule with a covalent, non-ester amide derivative.[2] With certain limited exceptions, FDA's determination precludes it from accepting abbreviated new drug applications for generic versions of LDX for five years following February 23, 2007, that is, until February 23, 2012.

On January 29, 2009, Actavis submitted an abbreviated new drug application for a generic version of LDX. FDA declined receipt of Actavis's application on February 6, 2009, based on its grant of five years of market exclusivity to Shire. That same day, Actavis submitted a position paper to FDA arguing that the agency should reconsider its decision that LDX is a "new chemical entity." On February 24, 2009, Actavis filed this lawsuit alleging that FDA had erroneously determined that LDX is a "new chemical entity" and that FDA should not have refused its application for a generic version of LDX.

FDA determined that the issues raised by Actavis should be considered administratively and opened a public docket on April 13, 2009, to receive comments from interested parties on the relevant legal and regulatory issues. On October 23, 2009, FDA issued a final decision

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[2] A covalent bond is formed when two atoms share a pair of electrons. A noncovalent bond is a bond between atoms that does not involve the sharing of pairs of electrons. Esters contain a type of covalent bond, called an ester bond, that links an oxygen atom to a central atom, such as a carbon atom or a phosphorous atom, wherein the central atom also is double bonded to an oxygen atom. Amides contain a type of covalent bond, called an amide bond, that links a nitrogen atom to a central atom, such as a carbon atom or a phosphorous atom, wherein the central atom also is double bonded to an oxygen atom. *See* Pl.'s Mem. in Supp. of Mot. for Summ. J. [Dkt. # 18] at 5.

affirming its original determination to grant Shire five years of market exclusivity. FDA concluded that the LDX molecule in Vyvanse® was a "new chemical entity" because:

> Lisdexamfetamine consists of dextroamphetamine bonded covalently to lysine through an amide bond. Lisdexamfetamine is a prodrug that is metabolically converted to produce dextroamphetamine, which is responsible for the drug's activity. Under FDA's regulation at 21 CFR § 314.108, a non-ester covalently bonded molecule is considered the active moiety of a drug and, if not previously approved, it will be considered a new chemical entity entitled to 5 years of exclusivity. A non-ester that requires metabolic conversion to produce a previously approved active moiety is considered a new chemical entity. Because lisdexamfetamine is a non-ester covalently bonded molecule, and because it requires metabolic conversion to produce dextroamphetamine, lisdexamfetamine is a new chemical entity and is thus entitled to 5 years of exclusivity.

A.R. 1782.[3]

On October 6, 2009, Actavis amended its complaint to challenge FDA's October 23, 2009, final decision. All parties move for summary judgment. Oral argument on the motions was held on February 17, 2010.

II. LEGAL STANDARDS

A. SUMMARY JUDGMENT

Under Rule 56 of the Federal Rules of Civil Procedure, summary judgment must be granted when "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c); *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247 (1986). Moreover, summary judgment is properly granted against

[3] "Prodrugs" are drugs that "are themselves pharmacologically inactive compounds that are converted into biologically active substances in a variety of ways, including by hydrolysis of ester or amide linkages, or by other metabolic processes." A.R. 1798-99.

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).

In ruling on a motion for summary judgment, the court must draw all justifiable inferences in the nonmoving party's favor and accept the nonmoving party's evidence as true. *Anderson*, 477 U.S. at 255. A nonmoving party, however, must establish more than "the mere existence of a scintilla of evidence" in support of its position. *Id.* at 252. In addition, the nonmoving party may not rely solely 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. *Id.* at 675. If the evidence "is merely colorable, or is not significantly probative, summary judgment may be granted." *Anderson*, 477 U.S. at 249-50 (citations omitted).

B. APA

Under the Administrative Procedure Act ("APA"), 5 U.S.C. § 551 *et seq.*, "[a]gency action made reviewable by statute and final agency action for which there is no other adequate remedy in a court are subject to judicial review." 5 U.S.C. § 704. The APA requires a reviewing court to set aside an agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Id.* § 706(2)(A); *Tourus Records, Inc. v. DEA*, 259 F.3d 731, 736 (D.C. Cir. 2001). However, a reviewing court is "not to substitute its judgment for that of the agency." *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 416 (1971).

When reviewing an agency's interpretation of its own organic statute, a court must undertake a two-step analysis as set forth in *Chevron U.S.A. Inc. v. Natural Resources Defense*

Council, Inc., 467 U.S. 837 (1984). First, a court must determine whether "Congress has directly spoken to the precise question at issue" and if so the court must "give effect to the unambiguously expressed intent of Congress." 467 U.S. at 842-43. To decide whether Congress has addressed the precise question at issue, a court must analyze the text, purpose, and structure of the statute. *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 124 (D.C. Cir. 2006).

If the statute is silent or ambiguous on the question, the court must proceed to the second step of the *Chevron* analysis and determine whether the agency's interpretation is based on a permissible construction of the statute. *Chevron*, 467 U.S. at 843. When an agency's interpretation of a statute is challenged at step two, 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." *Pauley v. BethEnergy Mines, Inc.*, 501 U.S. 680, 702 (1991). "The court need not conclude that the agency's construction was the only one it permissibly could have adopted to uphold the construction, or even the reading the court would have reached if the question initially had arisen in a judicial proceeding." *Chevron*, 467 U.S. at 844 n.11. If the agency's statutory construction is permissible, then the court must defer to the agency's interpretation. *Id.*

III. ANALYSIS

The Act awards five years of market exclusivity to drugs "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application . . . ." 21 U.S.C. § 355(j)(5)(F)(ii). The term "active ingredient" is not defined in the statute. By regulation, FDA has interpreted "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application" to mean a "new chemical entity." *See* 21 C.F.R. § 314.108(a). "New chemical entity" is defined by FDA to mean "a drug that

contains no active moiety that has been approved by FDA in any other application . . . ." *Id.* FDA defines "active moiety" as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." *Id.* Accordingly, under FDA's interpretation of the Act, a previously approved molecule that differs only by an ester or salt derivative is not a "new chemical entity" whereas a previously approved molecule with a covalent, non-ester derivative is a "new chemical entity." Applying this construction of the Act to LDX, FDA determined that LDX is a "new chemical entity" because LDX contains a previously approved molecule with a covalent, non-ester amide derivative.

Actavis argues that "FDA's covalent/noncovalent derivative distinction is contrary to Congressional intent because it effectively reads a structural requirement into the statute" and that the term "active ingredient" "must be interpreted to be the molecule that actually provides the therapeutic effect." Pl.'s Mem. in Opp'n to Mots. for Summ. J. ("Pl.'s Opp'n") [Dkt. # 32] at 3. However, Congress did not define "active ingredient" in the statute and Actavis identifies no statutory language that compels its interpretation of the term. Indeed, the Court of Appeals for the District of Columbia Circuit already has concluded that the statutory language "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application" is ambiguous. *See Abbott Labs. v. Young*, 920 F.2d 984, 987 (D.C. Cir. 1990) ("The parenthetical phrase ('including any ester or salt of *the* active ingredient') can refer to *either* the active ingredient of the original approved drug *or* to the active ingredient in the new drug, depending on how 'the' in the parenthetical and the words surrounding the parenthetical — 'no active

ingredient . . . of which has been approved' — [are] interpreted.") (emphasis in original). While the court was concerned with the ambiguity of the language inside the parenthetical, it specifically recognized that the meaning of the parenthetical phrase depended on how "the words surrounding the parenthetical — 'no active ingredient . . . of which has been approved' — [are] interpreted." *Id.* Thus, the court acknowledged that the words surrounding the parenthetical which are in contest here also are ambiguous. *See, e.g., AFL-CIO v. FEC*, 333 F.3d 168, 173 (D.C. Cir. 2003) ("A statute is considered ambiguous if it can be read more than one way."). At *Chevron* step one, this Court's review is limited to determining whether "the statute unambiguously forecloses the agency's interpretation, and therefore contains no gap for the agency to fill . . . ." *Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 982-83 (2005). The Act plainly does not unambiguously foreclose FDA's interpretation.

Having concluded that the phrase "no active ingredient . . . of which has been approved" is ambiguous, the Court must "defer to [FDA's] interpretation of the phrase if it 'is based on a permissible construction of the statute.'" *Nat'l Mining Ass'n v. Kempthorne*, 512 F.3d 702, 709 (D.C. Cir. 2008) (quoting *Chevron*, 467 U.S. at 843). At *Chevron* step two, all that is "ask[ed] of the agency is a reasonable interpretation." *Id.* FDA's interpretation easily satisfies this standard. FDA applied its scientific expertise to identify structural modifications to previously approved molecules that are likely to change the activity of the drug and represent a significant innovation, such as non-ester, covalent derivatives, and those that are not likely to reflect a significant change, such as salts and esters. Actavis faults FDA for creating a bright-line rule on the basis of a chemical entity's structure, but the statute itself draws distinctions based on structure — esters and salts — and the Court cannot say that FDA was unreasonable in also doing so. Nor is FDA's interpretation

unreasonable because Actavis asserts that there are other derivatives in addition to esters and salts, such as amides, that often do not alter the properties of the active moiety. That determination "rests on the 'agency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference' from this court." *Serono Labs. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)). Courts are not "scientists independently capable of assessing the validity of the agency's determination — beyond holding it to the standards of rationality required by the Administrative Procedure Act, 5 U.S.C. § 706(2)(A)." *Id.* at 1327. Actavis has failed to show that FDA's interpretation of the Act is impermissible under this standard. "As long as the agency stays within Congress' delegation, it is free to make policy choices in interpreting the statute, and such interpretations are entitled to deference." *Ariz. Pub. Serv. Co. v. EPA*, 211 F.3d 1280, 1287 (D.C. Cir. 2000) (quotation marks and alteration omitted).

Actavis also argues that FDA's interpretation of the Act is unreasonable because it is contrary to FDA's implementing regulations, which, according to Actavis, "require[] that 'active moiety' be construed to refer to the molecule that travels to and acts on the site of drug action." Pl.'s Opp'n at 8. Actavis argues that while LDX "is comprised of dextroamphetamine bonded to lysine through an amide covalent bond, . . . the molecule providing the therapeutic effect of lisdexamfetamine at the site of drug action — its active moiety — is previously approved dextroamphetamine." *Id.* But that is not how FDA interprets its implementing regulations, and the Court "must give substantial deference to an agency's interpretation of its own regulations." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994). As FDA itself explained:

> FDA interprets and applies 21 CFR § 314.108 so that the relevant inquiry addresses the structure of the molecule that forms the drug substance, and whether that molecule has been previously approved as an active moiety. Whether a molecule will be considered to be responsible for the physiological or pharmacological action of the drug substance depends upon the chemical structure of that molecule, which in turn depends on certain reasonable assumptions FDA had adopted about the activity of these classes of molecules. If the molecules in the drug substance are salts or esters or other non covalent derivatives, the active moiety will be the molecule minus the appendage. If the drug substance is composed of non-ester covalently bonded molecules, the covalently bonded molecule is considered the active moiety.

A.R. 1792. Deference to FDA's interpretation of "active moiety" within the meaning of its implementing regulations "is all the more warranted when, as here, the regulation concerns 'a complex and highly technical regulatory program,' in which the identification and classification of relevant 'criteria necessarily require significant expertise and entail the exercise of judgment grounded in policy concerns.'" *Thomas Jefferson Univ.*, 512 U.S. at 512 (quoting *Pauley*, 501 U.S. at 697). Indeed, FDA noted the "difficulty in determining precisely which molecule, or portion of a molecule, is responsible for a drug's effects" and that "Actavis and Shire make conflicting claims regarding which in vivo effects are meaningful and which molecules or portions of molecules are responsible for those effects." A.R. 1797-98. In light of the difficulty in identifying the precise chemical component responsible for a drug's effects and the hotly disputed scientific data with respect to that issue in this case, the Court finds that FDA reasonably applied its interpretation of its implementing regulations and the Act to conclude that LDX was the "active moiety."

Finally, the Court can quickly dispose of Actavis's contention that FDA's decision was arbitrary and capricious because an outdated *draft* version of FDA's Manual of Policy and Procedure 7500.3 purportedly contradicts the structure-based approach reflected in the agency's

formal regulations. It is beyond cavil that "neither an unreasoned statement in the manual nor allegedly long-standing agency practice can trump a formal regulation with the procedural history necessary to take on the force of law." *Cent. Laborers' Pension Fund v. Heinz*, 541 U.S. 739, 748 (2004). Actavis would have this Court set aside FDA's decision for not complying with an outdated draft of an internal document not having the force of law and superseded by formal regulation. The Court declines to do so. Actavis complains that FDA relied on the draft manual provision with respect to another drug application, but any force that argument otherwise might have had is entirely sapped by the fact that FDA recognized its error in that case and reversed itself. Actavis makes too much of the draft manual provision and FDA's alleged flip-flopping. The official policy of the agency is expressed in the formal regulations, not in any draft manual provision that precedes the promulgation of the regulations.

IV. CONCLUSION

For the foregoing reasons, the Court will grant FDA's and Shire's motions for summary judgment [Dkt. ## 28 & 30], and will deny Actavis's motion for summary judgment [Dkt. # 18]. FDA's motion to dismiss [Dkt. # 30] will be denied. A memorializing Order accompanies this Memorandum Opinion.

Date: March 4, 2010

/s/
ROSEMARY M. COLLYER
United States District Judge