

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022051Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**VERAMYST EXCLUSIVITY
DETERMINATION**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 21, 2012

FROM: Keith O. Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

SUBJECT: Addendum to Veramyst (fluticasone furoate) New Chemical Entity (NCE)
Exclusivity Determination

TO: NDA 022051 Veramyst (fluticasone furoate) Nasal Spray
GlaxoSmithKline

Attached is the May 29, 2012 letter that denied the request from GlaxoSmithKline that Veramyst (fluticasone furoate) be granted 5 years of NCE exclusivity.

An NCE is a drug that contains no previously approved active moiety. FDA's regulatory definition of active moiety has for eighteen years categorically excluded ester appendages, regardless of the *in vivo* activity of the particular ester at issue. Veramyst (fluticasone furoate) is comprised of an active moiety, fluticasone, which is modified with an ester bonded appendage. Before approving Veramyst, the Agency approved products that contain fluticasone modified with a different ester (fluticasone propionate). Under the Agency's interpretation of its regulations, the active moiety in these products is also fluticasone. Therefore, Veramyst contains a previously approved active moiety, fluticasone. Accordingly, in its May 29 letter, FDA determined that Veramyst is not a NCE and therefore is not entitled to 5-year NCE exclusivity.

No change in the publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) is needed; any 3-year period of Hatch-Waxman exclusivity for which Veramyst (fluticasone furoate) Nasal Spray may have been eligible has expired and therefore is now a moot issue.

Attachment



NDA 022051

William M. Zoffer
Vice President, R&D Legal Operations
GlaxoSmithKline
P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Mr. Zoffer:

GlaxoSmithKline ("GSK" or "you") has requested that the Food and Drug Administration ("FDA" or "Agency") grant five years of New Chemical Entity ("NCE") exclusivity for Veramyst (fluticasone furoate) ("Veramyst"). Notwithstanding the Agency's previous approval of several drug products containing fluticasone propionate ("FP") and notwithstanding Agency regulations that state that appended ester portions of a molecule should not be considered when determining what constitutes an active moiety,¹ you assert that Veramyst does not contain a previously approved active moiety because fluticasone furoate (FF), the active ingredient in Veramyst, is a stable ester of fluticasone, and the whole molecule (including the ester appendage) is responsible for Veramyst's therapeutic effect.

We have carefully reviewed the submissions you have made to the Agency on this issue, and additional relevant materials. For the reasons set forth below, we have determined that Veramyst is not a NCE and will not be granted five years of exclusivity.

I. Summary

Your argument appears to be premised on the contention that Veramyst's furoate ester appendage "remains an integral and functional part of the drug substance as it exerts its pharmacological effect at the local site of action."² Therefore, according to GSK, the entire molecule, including the ester appendage, is the active moiety. In your view, this makes Veramyst eligible for NCE exclusivity since FDA has not previously approved a drug containing FF. Under the Agency's interpretation of the Federal Food, Drug, and Cosmetic Act ("FD&C Act" or "the Act") and its regulations, however, an esterified molecule is considered to contain the same active moiety as the de-esterified molecule.³ Thus, the active moiety in Veramyst is fluticasone. Several products containing fluticasone in the form of FP were approved before Veramyst obtained marketing approval.⁴ It is true that FP is a different molecule than FF.

¹ See 21 C.F.R. 314.108(a) (defining active moiety as, among other things, "excluding those appended portions of the molecule that cause the drug to be an ester").

² William M. Zoffer, Letter to Badrul A. Chowdhury, Director, Division of Pulmonary and Allergy Drug Products, FDA, at 1 (May 30, 2007) [hereinafter Zoffer letter I].

³ See FDA, Vyvanse Exclusivity Decision Letter, Docket No. FDA-2009-N-0184, Doc. 0034, at 9-14 (Oct. 23, 2009) [hereinafter Vyvanse letter] (interpreting and applying the active moiety definition at 21 C.F.R. § 314.108(a)).

⁴ One such product is GSK's Flovent, which was approved on March 27, 1996 under NDA 020548.

Nevertheless, because FP is also an ester of fluticasone, its active moiety is also fluticasone. Accordingly, FDA concludes that Veramyst contains a previously approved active moiety, namely fluticasone. Based on this analysis, Veramyst is not a NCE and your request for five years of exclusivity is denied.

II. Factual and Procedural Background

A. GSK's original request for NCE exclusivity

GSK submitted NDA 022051 for FF on June 28, 2006. As part of NDA 022051, GSK submitted a request that FDA award NCE exclusivity for Veramyst because FF is "a unique molecular entity that exhibits distinct functional effects [compared to the previously approved fluticasone ester, FP]."⁵ In support of this assertion, GSK argued that "neither [FF] nor [FP] is metabolized to fluticasone. . . . [Therefore,] the entire molecule, including the ester group, is the active moiety."⁶ In addition, GSK argued that FF should be considered a NCE based on the observation that it differs from FP in "such fundamental physical properties" as "molecular weight, melting point, and crystalline structure."⁷ According to GSK, FF's ester appendage resulted in Veramyst exhibiting increased affinity to the target receptor compared to FP, which accounted for the differences between the pharmacokinetics of the two molecules. Finally, GSK accorded significance to the observation that FF and FP "are metabolized to *different* inactive acid metabolites and share no common metabolites."⁸

FDA approved NDA 022051 for Veramyst on April 27, 2007, for the daily treatment of symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older. Sections 505(c) and (j) of the FD&C Act provide for 3 years or 5 years of marketing exclusivity for certain drugs approved in NDAs, depending upon the characteristics of the drug and the type of information needed to support its approval. At the time of approval, the Agency did not classify Veramyst as a NCE. The Division Director's approval memo noted that "fluticasone is already approved for the treatment of allergic rhinitis."⁹ In addition, the exclusivity summary answered "Yes" to the question "Has FDA previously approved under section 505 of [the FD&C Act] any drug product containing the same active moiety as the drug under consideration?" and listed NDA 020548, for Flovent (fluticasone propionate), as one of the previously approved applications that contained the same active moiety as Veramyst.¹⁰

GSK sued Sandoz, Inc. on December 23, 2011, based on Sandoz' submission of an Abbreviated New Drug Application ("ANDA") referencing Veramyst.¹¹

⁵ Exclusivity request, Module 1.3.5.3 of NDA 022051, at 1.

⁶ *Id.* at 2.

⁷ *Id.*

⁸ *Id.* at 4 (emphasis in original).

⁹ Badrul A. Chowdhury, Division Director's Memorandum at 16 (April 27, 2007).

¹⁰ Veramyst Exclusivity Summary at 2,3 available at

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022051s000_AdminCorres_P1.pdf.

¹¹ *GlaxoSmithKline Intellectual Property Management LTD v. Sandoz Inc.*, No. 11-1284 (D. Del.).

B. Further arguments by GSK

After the approval of NDA 022051, GSK requested that FDA revisit its exclusivity decision and expanded on its initial claim of NCE status for Veramyst.¹² In support of its claim that “the furoate ester group is not simply ‘an appended portion’ of the molecule that ‘causes the drug to be an ester,’ but rather contributes importantly and distinctively to the ‘pharmacological action of the drug substance,’”¹³ GSK asserted that “the furoate ester group remains present at the target receptor, and this presence results in action on the molecular level that distinguishes Veramyst [from FP]”¹⁴ because “FF more fully occupies a lipophilic pocket in the receptor than FP . . . resulting in stronger binding and an unusually high receptor affinity.”¹⁵ GSK referred to the Veramyst labeling statement that indicated that FF exhibited a binding affinity that was approximately 1.7 times that of FP. In addition, GSK highlighted other functional differences between the two molecules, such as “a longer duration of functional activity” and “greater accumulation . . . in epithelial cells” for FF compared to FP.¹⁶

GSK asserted that FP represents the case where the clause that excludes “appended portions” in FDA’s active moiety definition comes into conflict with the “responsible for physiological or pharmacological action” clause in the same regulation.¹⁷ In other words, GSK alleged that, because the ester portion of FP (and FF) remains attached to fluticasone as the drug exerts its pharmacological effect, it must be included in a consideration of what part of the molecule is “responsible for the physiological or pharmacological action of the drug substance” and cannot be excluded as the earlier phrase requires.¹⁸ This apparent conflict, GSK claimed, could be resolved by not considering the regulation as requiring the exclusion of appended ester portions in every case, but rather, only where the ester appendage does *not* “confer all or part of a drug’s therapeutic action.”¹⁹ Referring to the single instance where FDA classified a stable ester as a “new molecular entity,”²⁰ GSK claimed that there was “precedent” for its position that Veramyst should be treated differently from other esters.²¹

In addition, GSK pointed to other authorities’ definitions of active moiety which do not exclude ester appendages,²² referred to a 1972 Agency statement made in the context of the Drug Efficacy Study Implementation Process concerning identical, related and similar drug products,²³ and argued that the expense that GSK incurred in developing Veramyst qualifies it as an innovative compound deserving of five-year exclusivity.²⁴

¹² Zoffer letter I; Letter from William M. Zoffer, Vice President, Assistant General Counsel of GSK, to Elizabeth Dickinson, Office of the Chief Counsel (November 14, 2007) [hereinafter Zoffer letter II].

¹³ Zoffer letter I at 2.

¹⁴ *Id.*

¹⁵ *Id.* at 4.

¹⁶ *Id.*

¹⁷ Zoffer letter II at 1-2 (citing 21 U.S.C. (sic) § 314.108(a)).

¹⁸ *Id.* at 2.

¹⁹ *Id.*

²⁰ This molecule was approved before FDA finalized the regulations at issue here.

²¹ *Id.*

²² *Id.* (citing, e.g., U.S. Pharmacopeia).

²³ *Id.* at 2-3 (citing 37 Fed. Reg. 23185 where FDA seems to have recognized that some salts, esters and isomers can produce a different effect than their base compounds).

²⁴ *Id.* at 3-4.

III. Statutory and Regulatory Background²⁵

A. New Drug Applications and Abbreviated New Drug Applications

Section 505(b) of the FD&C Act establishes the approval requirements for NDAs. To be approved, an application submitted under 505(b) must, among other things, be supported by investigations showing the drug product to be safe and effective.²⁶ One pathway under section 505(b) provides for approval of NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference (a “stand-alone NDA”). The 1984 Drug Price Competition and Patent Term Restoration Act (“Hatch-Waxman Amendments”) provided an alternate pathway under subsection 505(b)(2) for approval of an NDA for which some or all of the safety and efficacy investigations relied upon for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (a “505(b)(2) application”). Like a stand-alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act. Drugs approved under both types of NDAs are eligible for exclusivity under relevant provisions of the FD&C Act.

The Hatch-Waxman Amendments also provide for submission of ANDAs for approval of generic versions of listed drugs.²⁷ A listed drug is a drug product with an effective approval under section 505(c).²⁸ The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA’s previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to repeat the studies conducted to support approval of the listed drug. To rely on such a finding, the ANDA applicant must show that, among other things, its proposed drug product is the same as the listed drug with respect to active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling, and that its product is bioequivalent to the listed drug.²⁹

B. Five-Year and Three-Year Marketing Exclusivity

In addition to establishing the abbreviated drug approval pathways in sections 505(b)(2) and 505(j) of the FD&C Act, the Hatch-Waxman Amendments provided incentives for pharmaceutical innovation in the form of marketing exclusivity to protect qualified drug products approved under section 505(c) from competition for certain periods. Under the statute, a 5-year exclusivity period is provided for drug products that do not contain a previously approved active ingredient (including any ester or salt of the active ingredient).³⁰ This exclusivity generally

²⁵ The discussion that follows in subsections III.A.-D., *infra*, substantially mirrors the same discussion in the Vyvance letter, *supra* note 3, at 4-8.

²⁶ Section 505(b)(1) of the FD&C Act.

²⁷ Section 505(j) of the FD&C Act.

²⁸ 21 C.F.R. § 314.3(b).

²⁹ Section 505(j)(2) of the FD&C Act.

³⁰ Section 505(j)(5)(F)(ii) of the FD&C Act provides, in relevant part, as follows:

If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the

prevents FDA from accepting³¹ a 505(b)(2) application or ANDA that contains the protected drug (active moiety) for a 5-year period from the date of approval of the protected drug.³² If an action for patent infringement is brought within one year following four years after the original approval date, any thirty-month stay shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of the original approval.³³ The exclusivity does not block acceptance and review of stand-alone NDAs containing the same active moiety.

The Act also provides for a 3-year period of exclusivity. This is available for drug products that contain a previously approved active ingredient (including any ester or salt of the active ingredient), when that application includes new clinical investigations essential to the approval of the application and conducted or sponsored by the applicant.³⁴ This marketing exclusivity prevents FDA from approving 505(b)(2) applications and ANDAs for the same conditions of approval for 3 years from the date of approval of the protected drug.³⁵

C. FDA's Regulations Governing Five-Year Exclusivity

The regulation at 21 C.F.R. § 314.108 implements the statutory exclusivity provisions. In this regulation, FDA has interpreted the relevant sections of the FD&C Act to preclude the Agency from accepting ANDAs for drugs that contain the same active moiety as in a previously approved new chemical entity. The regulation provides:

If a drug product that contains a new chemical entity was approved. . . in an application submitted under section 505(b) of the act, no person may submit a[n] . . . abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a

approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii).

See section 505(c)(3)(E)(ii) of the FD&C Act.

³¹ Note 30, *supra*. An applicant may submit an ANDA or 505(b)(2) application after 4 years if the application includes a paragraph IV certification to a patent listed in the Orange Book for the reference listed drug.

³² Sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act.

³³ *Id.* (last sentence).

³⁴ Section 505(j)(5)(F)(iii) of the FD&C Act provides

If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

See section 505(c)(3)(E)(iii) of the FD&C Act.

³⁵ Sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act.

period of 5 years from the date of approval of the first approved new drug application. . . .³⁶

The Agency has defined “new chemical entity” to mean “a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.”³⁷ “Active moiety” is defined as:

[T]he 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 a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.³⁸

“Drug substance” is further defined as

[A]n active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use [sic] in the synthesis of such ingredient.³⁹

Active ingredient⁴⁰ is defined as

[A]ny component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.⁴¹

Thus, under FDA’s interpretation of the statute embodied in the regulations, a drug that is a new chemical entity will receive 5 years of exclusivity. If a drug product does not contain a new chemical entity (i.e., it contains any previously approved active moiety), it may be eligible for 3 years of exclusivity, but not for 5 years of exclusivity.

D. FDA’s interpretation of its regulations on NCE Exclusivity

FDA’s interpretation of the NCE exclusivity provisions has consistently focused on the specific chemical structure of the drug under consideration. In the 1989 preamble to the proposed regulation defining a NCE, the Agency explained that it interpreted the statutory requirement that, to receive 5 years of exclusivity, a drug must contain no previously approved “active ingredient (including any ester or salt of the active ingredient)” to mean that the drug must not contain any previously approved active moiety. FDA based its interpretation on the statutory

³⁶ 21 C.F.R. § 314.108(b)(2).

³⁷ *Id.* § 314.108(a).

³⁸ *Id.*

³⁹ 21 C.F.R. § 314.3(b).

⁴⁰ An “inactive ingredient” means any component other than an active ingredient. 21 C.F.R. § 210.3(b)(8).

⁴¹ 21 C.F.R. § 210.3(b)(7).

language and on the definition of “new molecular entity” or “Type 1” drug in FDA’s IND/NDA classification scheme (used to classify new drugs by chemical type and therapeutic significance), which was in effect when Congress was considering the Hatch-Waxman Amendments. FDA stated that its interpretation of the 5-year exclusivity provision was consistent with the legislative history, which showed that Congress was aware of FDA’s drug classification scheme and did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds.⁴²

Under the drug classification scheme, a “new molecular entity” is a compound containing an entirely new (i.e., never previously approved) active moiety. FDA elaborated on the definition of active moiety, as follows:

The “active moiety” in a drug is 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 a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance. A drug product will thus not be considered a “new chemical entity” entitled to 5 years of exclusivity if it contains a previously approved active moiety, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative has not been previously approved. A compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety is considered a “new molecular entity,” however, and will be considered a new chemical entity entitled to 5 years of exclusivity. FDA will consider whether a drug contains a previously approved active moiety on a case-by-case basis.⁴³

In proposing the regulation, the FDA described the chemical structure of the types of molecules that would be considered to be an active moiety. The preamble explained that salts (including certain specific types of salts) and other derivatives, which —like salts— have some non-covalent character, would not be considered the active moiety of a drug. In addition, and of particular application to the matter at hand, the Agency recognized that the only type of

⁴² 54 Fed. Reg. at 28897-98. (July 10, 1989)

⁴³ 54 Fed. Reg. at 28898. This interpretation had also been described generally in an April 28, 1988 “Dear Industry” letter (“the sixth in a series of letters intended to provide informal notice to all affected parties of developments in the policy and interpretation of the Drug Price Competition and Patent Term Restoration Act of 1984”). In that letter, FDA stated that “[t]he Agency considers a drug product eligible for the five-year period if it contains no active moiety that was previously approved by the Agency.” The letter further stated that:

The “active moiety” in a drug product is the molecule or ion, excluding esterified forms, salts, complexes, chelates, or clathrates of the molecule, responsible for the physiological or pharmacological action of the drug substance. A drug product will not be considered a “new chemical entity” entitled to five years of exclusivity if it contains a previously approved active moiety, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other non-covalent derivative (such as a complex, chelate or clathrates) has not been previously approved. A compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety, however, is considered a “new chemical entity” entitled to five years of exclusivity.

covalently bonded molecule that would not be considered an active moiety is an ester.⁴⁴ At the same time, FDA stated that a molecule with a non-ester bond that requires metabolic conversion (i.e., a pro-drug with a non-ester bond) would be eligible for NCE exclusivity, and specifically noted that this analysis would apply even if the molecule resulting from the metabolic conversion is a previously approved active moiety.

FDA's regulation relies on a relatively straightforward analysis of the chemical structure of the drug when analyzing eligibility for exclusivity. FDA adopted this approach based upon certain reasonable assumptions regarding the activity of different types of molecules, which can be applied to a range of drugs. The regulation provides that, although neither esters nor salts will be a unique active moiety (as recognized in the statutory parenthetical), covalently bonded molecules that are not esters will be considered separate active moieties.⁴⁵

IV. Vyvanse Precedent

In 2009, Actavis challenged FDA's decision to grant NCE exclusivity to Vyvanse, a drug whose active ingredient, lisdexamfetamine, includes dextroamphetamine, a previously approved active moiety.⁴⁶ Lisdexamfetamine is composed of a dextroamphetamine moiety and a lysine appendage covalently linked via an amide bond.⁴⁷ Actavis contended that this covalent modification had no therapeutic impact because the lysine cleaves *in vivo* to release dextroamphetamine, which is responsible for the therapeutic effect of Vyvanse. Based on that observation, Actavis asserted that FDA's regulation, which makes distinctions between covalent and non-covalent bonds and between esters and other covalent bonds "is contrary to the statutory language and legislative history, [and] does not reflect what happens when Vyvanse is administered."⁴⁸

In response, FDA reiterated its position that as it "interprets and applies 21 C.F.R. § 314.108, a non-esterified covalently bonded molecule will be considered an active moiety in a drug."⁴⁹ The Agency noted that it drew a distinction between covalent and non-covalent bonds, as well as between ester bonds and other covalent bonds, stating that it was permissible for FDA to draw such a distinction because the scientific assumption underlying the distinction was a reasonable one.⁵⁰

At its root, Actavis's position was that even though Vyvanse contains an amide bond, it acts similarly to sterically unhindered esters such that the amide bonded portion is quickly cleaved *in vivo* from the "active moiety," i.e. dextroamphetamine. Actavis asserted that because neither lisdexamfetamine nor the amide bonded lysine appendage had any therapeutic effect on their own, dextroamphetamine should be considered the active moiety in Vyvanse. In other words,

⁴⁴ The Agency based this conclusion "on the statutory language." 54 Fed. Reg. at 28897; see section 505(j)(5)(F)(ii) of the FD&C Act, stating that drugs eligible for NCE exclusivity are those "no active ingredient (including any *ester* or salt of the active ingredient) of which has been" previously approved (emphasis added).

⁴⁵ Notably, the Agency did not adopt a rule that eligibility for exclusivity depends specifically upon whether the specific molecule responsible for the therapeutic effect has been previously approved.

⁴⁶ Vyvanse Letter, *supra* note 3, at 3.

⁴⁷ *Id.*

⁴⁸ *Id.* at 13.

⁴⁹ *Id.* at 9.

⁵⁰ See *id.* at 13-15.

Actavis asked FDA to consider how the molecule behaved, rather than relying on its chemical structure to determine whether it qualified for NCE exclusivity.

FDA rejected this argument.⁵¹ In doing so, the Agency reiterated its categorical interpretation of its regulatory scheme: “[W]hen the molecule in a drug is covalently bonded (and a non-ester), the Agency need not determine which aspects of the physiological or pharmacological effect(s) of the drug are attributable to that molecule or to the molecule minus the covalently bonded portion.”⁵²

FDA acknowledged that some non-ester covalent bonds may behave more like an ester bond, and vice versa.⁵³ However, in part because of the “difficulty in determining precisely which molecule, or portion of a molecule, is responsible for a drug’s effects,”⁵⁴ the Agency determined that, for NCE exclusivity purposes, an active moiety is considered to remain the same active moiety when it has been modified only by a non-covalent bond or an ester bond, and is considered to be a different active moiety when it has been modified by any non-ester, covalent bond.

Actavis sought judicial review of the Agency’s response. In the resulting litigation, the D.C. Circuit upheld the Agency’s interpretation.⁵⁵ The court found persuasive the Agency’s response to Actavis’ assertion that Vyvanse acts more like an ester bonded molecule despite having a non-ester covalent bond.

At best, Actavis has offered evidence that some covalent structural changes do not alter the basic properties of the drug in question and that some noncovalent structural changes do. But agencies may employ bright-line rules for reasons of administrative convenience, so long as those rules fall within a zone of reasonableness and are reasonably explained. The FDA has explained that its policy is based in part on the difficulty in determining precisely which molecule, or portion of a molecule, is responsible for a drug’s effects. Nothing in the record establishes that the FDA’s approach is unreasonable.⁵⁶

⁵¹ *Id.* at 15-16. (“Because the covalent bond in lisdexamfetamine is an amide bond (i.e., a non-ester covalent derivative), lisdexamfetamine is considered the active moiety, even if in vivo lisdexamfetamine eventually produces dextroamphetamine, a previously approved active moiety.”).

⁵² *Id.* at 16.

⁵³ *See id.* at 15 (“The formation of an ester, unlike other covalently bound groups, is *in almost all cases* designed to be removed before, or just after, absorption by gut or blood esterases; at that point the ester portion is cleaved from the “active moiety,” and only the active moiety travels to, and acts on, the receptor site.”) (citing July 26, 1989 Citizen Petition Response, Docket No. 1987P-0339 at 12 n.5) (emphasis added).

⁵⁴ *Id.* at 16.

⁵⁵ *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 765 (D.C. Cir. 2010) (“FDA’s policy is based on its view that drug derivatives containing non-ester covalent bonds are, on the whole, distinct from other types of derivative drugs such that the former are uniquely deserving of ‘new chemical entity’ status and the resulting five-year exclusivity.”).

⁵⁶ *Id.* at 766 (internal quotation marks and citations omitted).

V. Exclusivity for Veramyst

We conclude that Veramyst is not a NCE under the Agency's interpretation of the statutory scheme and its own regulations described above.⁵⁷ GSK's focus on FF's alleged unique properties and stronger binding activity (compared to FP) is irrelevant to the Agency's categorical exclusion of esters from the types of modifications that are considered to result in a different active moiety. Actavis demanded the same activity-based consideration from FDA with respect to Vyvanse, but the Agency declined. After a full and reasoned discussion, FDA affirmed its chemical-structure based interpretation of the applicable statutory and regulatory provisions.

Here, we reject the contention that FF should be considered a NCE because it differs from the previously approved molecule in "such fundamental physical properties" as "molecular weight, melting point, and crystalline structure."⁵⁸ Every new molecule will almost certainly differ from a previously approved molecule in such "fundamental physical properties." Accepting this contention would therefore result in every new molecule being awarded NCE exclusivity unless it was identical to another previously approved molecule. As discussed above, this is clearly not what Congress intended when it excluded all salts and esters from the types of drugs that would be eligible for NCE exclusivity.

In addition, we refuse to adopt a different definition of active moiety based on the definitions employed by other authorities. The Agency has consistently applied the definition embodied in its own regulations since those regulations were promulgated to implement the Hatch-Waxman Amendments, without a reference to other authorities' definitions of active moiety. Moreover, adopting another definition that does not exclude esters from the active moiety definition would be contrary to the statutory requirement that such appendages be excluded from the types of drugs that would be eligible for NCE exclusivity.⁵⁹

We also reject the contention that the fact that FDA granted NCE exclusivity to a stable ester in 1991 constitutes "precedent." First, that approval occurred before FDA finalized the applicable regulation. Second, as the Agency's response to the Vyvanse matter demonstrates, FDA has since adhered to its structure-based approach that does not evaluate the activity of a molecule.⁶⁰ Similarly, an FDA statement, made forty years ago in a different context, that some esters may lead to different effects than their base compounds does not mean that, when determining whether a molecule is a NCE, such differences are determinative of the outcome under FDA's definition of active moiety. To the extent that it proves anything, such a statement shows that FDA has acknowledged that not every ester is expected to behave in the same manner, which is a consideration that the applicable regulation and the Agency's interpretation of that regulation already take into account.⁶¹

⁵⁷ Although five years have already elapsed since the date of original approval of Veramyst on April 27, 2007, this issue does not appear to be moot because GSK has sued at least one ANDA applicant, Sandoz, within the last year of the five years in which GSK claims it should have been eligible for NCE exclusivity. Under the last sentence of Section 505(j)(5)(F)(ii), if GSK in fact had such NCE exclusivity, any thirty-month stay in that litigation would be extended until October 27, 2014 (seven and one-half years following the original date of approval).

⁵⁸ Exclusivity request, Module 1.3.5.3 of NDA 022051 at 7.

⁵⁹ See note 44, *supra*.

⁶⁰ See Vyvanse letter, *supra* note 3, at 9 n.14.

⁶¹ See note 53, *supra*.

Similarly, we do not agree that the fact that FF may exhibit different, or even improved, pharmacokinetics compared to FP leads to the conclusion that it must be a NCE. As the Agency's Vyvanse response amply illustrates, such activity-based considerations do not have any bearing on the determination whether a drug contains a previously approved active moiety. Accordingly, FDA does not agree that a "stable" ester (as Veramyst may be) creates a tension between the "appended portions" and the "responsible for physiological or pharmacological action" clauses of the active moiety definition. In promulgating and then interpreting the regulations at issue, the Agency rejected an activity-based approach after considering its drawbacks and the merits of a categorical interpretation. Thus, where a molecule contains an ester-bonded appendage, FDA does not inquire whether the ester "confer(s) all or part of a drug's therapeutic action,"⁶² notwithstanding the fact, accepted by FDA, that some esters may in fact confer such activity.

To allow such an inquiry would open up to challenge every exclusivity determination where there was a question of whether the ester bonded appendage conferred even a miniscule amount of novel activity to the drug. As the D.C. Circuit has observed, FDA reasonably adopted this bright-line, chemical-structure-based rule because of the difficulty, in many cases, of determining which molecule, or portion of a molecule, is responsible for a drug's effects.⁶³ Therefore, the fact that FF and FP may not separate from the fluticasone portion of the molecule in this case does not impact the determination, based on the undisputed fact that both FP and FF are esters of fluticasone, that fluticasone is the active moiety in both molecules.

Finally, the amount of research that a sponsor invests in a drug is not a factor for determining a drug's NCE status. Neither the statute, the regulations, nor FDA's interpretation of these authorities acknowledge the amount of data generated by the sponsor as a factor in NCE analysis. At the same time, although Congress did not provide for such a consideration for NCE exclusivity, the consideration of whether a sponsor conducted studies that were necessary for approval is a central factor in awarding three-year exclusivity to a drug.⁶⁴ Its inclusion in the three-year exclusivity provision illustrates that Congress could have included such a factor in the NCE analysis if it wished to, and it is reasonable to conclude that its absence from these provisions means that a drug's NCE status is not affected by the amount of research a sponsor conducted in order to obtain approval.⁶⁵

⁶² Zoffer letter II at 2.

⁶³ *Actavis*, *supra* note 55 at 766.

⁶⁴ Compare section 505(j)(5)(F)(ii) of the Act with section 505(j)(5)(F)(iii) of the Act.

⁶⁵ It appears that the studies that GSK conducted would have been sufficient to obtain three-year exclusivity for Veramyst. See Exclusivity Summary, *supra* note 10 at 3-7; see also Section 505(j)(5)(F)(iii) of the FD&C Act. Regardless, the issue is moot because Veramyst was approved more than three years ago and any such exclusivity would have expired. Unlike the NCE exclusivity issue, where a determination that Veramyst was not eligible for NCE exclusivity can have an effect on 30-month stays of approval in litigation between GSK and ANDA filers even after the expiry of the five-year period, no such scenario is possible under the three-year exclusivity provisions of the FD&C Act.

VI. Conclusion

A NCE is a drug that contains no previously approved active moiety. FDA's regulatory definition of active moiety has for eighteen years categorically excluded ester appendages, regardless of the *in vivo* activity of the particular ester at issue. Hence, Veramyst (fluticasone furoate) is comprised of an active moiety, fluticasone, that is modified with an ester bonded appendage. Before approving Veramyst, the Agency approved products that contain fluticasone modified with a different ester (fluticasone propionate). Under the Agency's interpretation of its regulations, the active moiety in these products is also fluticasone. Therefore, Veramyst contains a previously approved active moiety, fluticasone. Accordingly, FDA determines that Veramyst is not a NCE and is not entitled to five years of exclusivity.

Sincerely,

{See appended electronic signature page}

Keith O. Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

cc: Elizabeth Dickinson, Chief Counsel, FDA/OCC

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEITH O WEBBER
05/29/2012

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA L DOWNS
06/21/2012

KEITH O WEBBER
06/21/2012