

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022088Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS PART 2**

TORISEL 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 Sciences
Center for Drug Evaluation and Research

SUBJECT: Addendum to Torisel (temsirolimus) New Chemical Entity (NCE) Exclusivity Determination

TO: NDA 022088 – Torisel (temsirolimus) Injection
Wyeth Pharmaceuticals Inc.

Attached is the May 29, 2012 letter that discusses the reasons that Torisel (temsirolimus) is not eligible for NCE exclusivity. Sandoz requested that the Agency reconsider whether Torisel (temsirolimus) was eligible for 5 years of NCE exclusivity. The Agency reconsidered this determination and issued the attached letter.

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. Temsirolimus is comprised of a previously approved active moiety, sirolimus, which is modified with an ester bonded appendage. Because temsirolimus's ester-bonded appendage is excluded from its active moiety, it contains a previously approved active moiety, sirolimus. The Agency, therefore, incorrectly considered temsirolimus to be a NCE entitled to 5 years of exclusivity. Torisel's NCE exclusivity award has been rescinded, as it was granted in error. Though it seems that Torisel would have been eligible for 3 years of exclusivity, the issue is moot because Torisel has already enjoyed more than 3 years of exclusivity.

In light of this conclusion, the 5-year NCE exclusivity designation has been removed from the publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

Attachment



NDA 022088

Kurt. R. Karst, Counsel for Sandoz
Hyman, Phelps & McNamara, P.C.
700 13th Street N.W., Suite 1200
Washington D.C. 20005-5929

Dear Mr. Karst:

Sandoz has requested that the Food and Drug Administration ("FDA" or "Agency") reconsider its grant of five years of New Chemical Entity ("NCE") exclusivity for Torisel (temsirolimus) injection ("Torisel"). Sandoz asserts that Torisel contains a previously approved active moiety because it is an ester of a previously approved active moiety.

We have carefully reviewed the submissions made to the Agency on this issue, the exclusivity record for New Drug Application ("NDA") 022088, and additional relevant materials. For the reasons set forth below, we have determined that Torisel was erroneously granted five years of NCE exclusivity.

I. Summary

The Torisel Exclusivity Summary of May 30, 2007 indicated "No" to the question "Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as [temsirolimus]?"¹ As Sandoz has pointed out, FDA has previously approved another product containing the same active moiety. Specifically, Rapamune (sirolimus) has been previously approved under section 505 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act or the Act").² Temsirolimus is an ester of sirolimus. Under the Agency's interpretation of the FD&C Act and its regulations, an esterified molecule is considered to contain the same active moiety as the de-esterified molecule.³ Accordingly, FDA now concludes that the answer to the question of whether Torisel contains the same active moiety as a previously approved drug should have been "Yes". Based on this analysis, temsirolimus is not a NCE and Torisel should not have been granted five years of exclusivity.

FDA rescinds Torisel's NCE exclusivity as of the date of this letter. It is likely that Torisel would instead have been eligible for three years of exclusivity;⁴ however, we need not address that issue here because Torisel has already enjoyed more than three years of exclusivity.

¹ See 21 C.F.R. § 314.108(a) (defining "new chemical entity" as "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.").

² FDA approved Rapamune (sirolimus) Oral Solution (NDA 021083) on September 15, 1999.

³ See 21 C.F.R. § 314.108(a) (defining "active moiety" as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester . . ., responsible for the physiological or pharmacological action of the drug substance.").

⁴ See Section 505(j)(5)(F)(iii) of the FD&C Act and the discussion in section III.B., *infra*.

II. Factual and Procedural Background

A. Approval of Torisel

FDA approved NDA 022088 for Torisel on May 30, 2007 for the treatment of advanced renal cell carcinoma. 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 classified Torisel as a NCE entitled to five years of exclusivity beginning on the date of approval under 21 C.F.R. § 314.108. Torisel's exclusivity period was due to expire on May 30, 2012.

B. The challenge to Torisel's NCE exclusivity

On June 9, 2011, Sandoz challenged Torisel's NCE status and exclusivity, arguing that temsirolimus is an ester derivative of a previously approved active moiety, sirolimus, and therefore not entitled to five years of NCE exclusivity.⁵ The Agency then sought input from Pfizer, Torisel's current sponsor, which was received on July 5, 2011.⁶ Pfizer argued that Torisel was entitled to five years of exclusivity despite being an ester of a previously approved active moiety because of its distinctive properties.⁷ Subsequently, on July 28, 2011, and August 5, 2011, FDA received two more communications from the parties responding to each other's assertions.

C. Temsirolimus is an ester derivative of sirolimus

There is no dispute that temsirolimus is an ester of sirolimus, as shown in Figure 1, below. In its July 5, 2011 letter, Pfizer submitted several scientific arguments supporting its assertion that temsirolimus should be considered a NCE despite being an ester of a previously approved active moiety. The basic premise of Pfizer's argument appears to be that temsirolimus exhibits different physicochemical and pharmacokinetic properties than sirolimus,⁸ *i.e.*, it is "a stable, modified ester of sirolimus that persists in the blood after intravenous administration."⁹ In support of this argument, Pfizer presents evidence that both temsirolimus and sirolimus can be measured in the blood at various time points after the administration of a single intravenous dose of temsirolimus, which suggests that the ester bond that differentiates temsirolimus from sirolimus is not rapidly cleaved *in vivo*.¹⁰ Observable blood levels of un-metabolized temsirolimus is not surprising, as enhanced resistance to chemical and enzymatic cleavage of sterically hindered esters, such as temsirolimus, is well known. Ultimately, however, whether and to what extent the ester bond that differentiates temsirolimus from sirolimus dissociates upon administration is not relevant to the determination of temsirolimus's NCE status. As an ester derivative of a previously approved active moiety, temsirolimus is ineligible for NCE status.

⁵ Kurt R. Karst, Letter on behalf of Sandoz, Inc.

⁶ Jeffrey P. Kushan, Letter on behalf of Pfizer, Inc. [Kushan letter].

⁷ *Id.* at 2-3.

⁸ *E.g., id.* at 2, 8.

⁹ *Id.* at 1.

¹⁰ Joseph Boni, et al., *Pharmacokinetic Profile of Temsirolimus with Concomitant Administration of Cytochrome P450-inducing Medications*, 47 J. Clinical Pharmacology 1430, 1436 (2007).

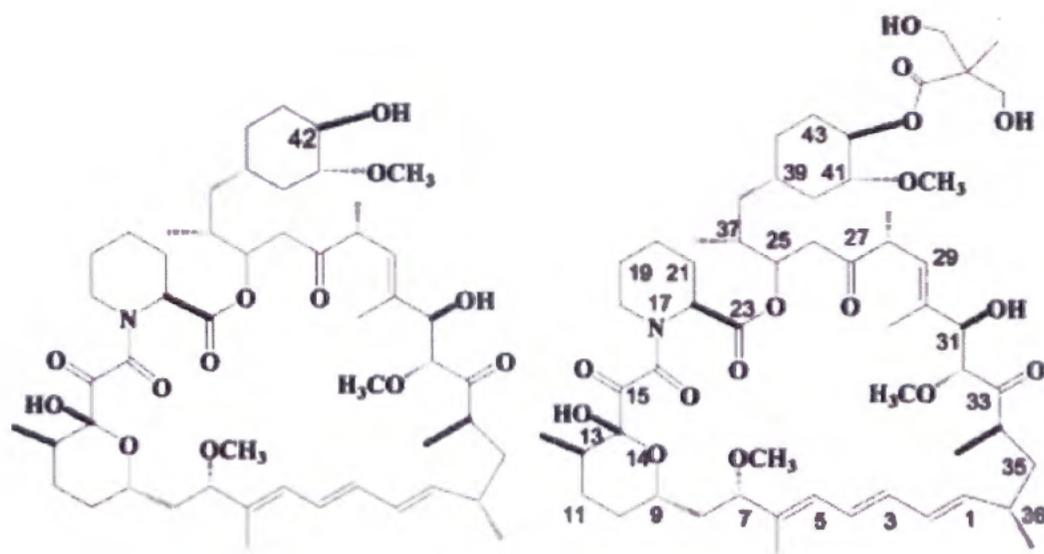


Figure 1. Sirolimus (left) and its ester derivative, temsirolimus (right).¹¹ Temsirolimus contains an ester bonded appendage at carbon 42, whereas sirolimus contains an alcohol at the same position. Apart from that difference, the two molecules are identical.

After due consideration, taking into account the arguments of the parties, the applicable statutory and regulatory authorities, the Agency's recent evaluation of and determination with regards to NCE exclusivity,¹² as well as the court's acceptance of FDA's position in the subsequent litigation,¹³ the Agency concludes that Torisel contains the same active moiety as that of the previously approved drug, Rapamune (sirolimus) oral solution, notwithstanding Pfizer's argument that temsirolimus has "distinct and independent therapeutic effects *in vivo* relative to sirolimus."¹⁴

III. Statutory and Regulatory Background¹⁵

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.¹⁶ One pathway under section 505(b) provides for approval of NDAs that are supported entirely by investigations either

¹¹ Ping Cai, Rushung Tsao, and Mark E. Ruppen, *In Vitro Metabolic Study of Temsirolimus: Preparation, Isolation, and Identification of the Metabolites*, 35 Drug Metabolism and Disposition 1554, 1555 (2007).

¹² FDA, Vyvanse Exclusivity Decision Letter, Docket No. FDA-2009-N-0184, Doc. 0034 (Oct. 23, 2009) [Vyvanse letter].

¹³ *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760 (D.C. Cir. 2010).

¹⁴ Kushan letter, *supra* note 6, at 1.

¹⁵ The discussion that follows in subsections III.A.-D., *infra*, substantially mirrors the same discussion in the Vyvanse letter, *supra* note 12, at 4-8.

¹⁶ Section 505(b)(1) of the FD&C Act.

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 abbreviated new drug applications (“ANDAs”) for approval of generic versions of listed drugs.¹⁷ A listed drug is a drug product with an effective approval under section 505(c).¹⁸ 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.¹⁹

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).²⁰ This exclusivity generally prevents FDA from accepting²¹ a 505(b)(2) application or ANDA that contains the protected

¹⁷ Section 505(j) of the FD&C Act.

¹⁸ 21 C.F.R. § 314.3(b).

¹⁹ Section 505(j)(2) of the FD&C Act.

²⁰ 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 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.

²¹ Note 20, *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.

drug (active moiety) for a 5-year period from the date of approval of the protected drug.²² 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.²³ 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.²⁴

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 period of 5 years from the date of approval of the first approved new drug application. . . .²⁵

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."²⁶ "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)

²² Sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act.

²³ 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.

²⁴ Sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act.

²⁵ 21 C.F.R. § 314.108(b)(2).

²⁶ *Id.* § 314.108(a).

of the molecule, responsible for the physiological or pharmacological action of the drug substance.²⁷

“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.²⁸

Active ingredient²⁹ 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.³⁰

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 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.³¹

²⁷ *Id.*

²⁸ 21 C.F.R. § 314.3(b).

²⁹ An “inactive ingredient” means any component other than an active ingredient. 21 C.F.R. § 210.3(b)(8).

³⁰ 21 C.F.R. § 210.3(b)(7).

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

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.³²

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 covalently bonded molecule that would not be considered an active moiety is an ester.³³ 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.

³² 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.

³³ 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).

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.³⁴

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.³⁵ Lisdexamfetamine is composed of a dextroamphetamine moiety and a lysine appendage covalently linked via an amide bond.³⁶ 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."³⁷

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."³⁸ 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.³⁹

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, 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.⁴⁰ 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)

³⁴ 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.

³⁵ Vyvanse Letter, *supra* note 12, at 3.

³⁶ *Id.*

³⁷ *Id.* at 13.

³⁸ *Id.* at 9.

³⁹ *See id.* at 13-15.

⁴⁰ *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.")

of the drug are attributable to that molecule or to the molecule minus the covalently bonded portion.⁴¹

FDA acknowledged that some non-ester covalent bonds may behave more like an ester bond, and vice versa.⁴² However, in part because of the “difficulty in determining precisely which molecule, or portion of a molecule, is responsible for a drug’s effects,”⁴³ 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.⁴⁴ 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.⁴⁵

V. Exclusivity for Torisel

Under the interpretation described above, it is evident that the Agency’s grant of NCE for Torisel was incorrect.⁴⁶ Pfizer’s focus on Torisel’s alleged unique properties 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, noting that the parties made conflicting claims about the scientific data.⁴⁷ After a full and reasoned discussion, FDA affirmed its chemical-structure based interpretation of the applicable statutory and regulatory provisions.

⁴¹ *Id.* at 16.

⁴² *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).

⁴³ *Id.* at 16.

⁴⁴ *Actavis, supra* note 13, at 765. (“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.”).

⁴⁵ *Id.* at 766 (internal quotation marks and citations omitted).

⁴⁶ The determination of Torisel’s NCE status predated the Vyvanse letter, *supra* note 12.

⁴⁷ Vyvanse letter, *supra* note 12, at 16-17. (“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. . . . For example, the parties do not agree upon what effect, if any, inclusion of lisdexamfetamine (instead dextroamphetamine) has on activity of the drug *in vivo*. Actavis asserts that lisdexamfetamine is merely a carrier

The same considerations that resulted in the rejection of Actavis's arguments regarding Vyvanse apply with full force here. The ester-bonded moiety in temsirolimus is eventually cleaved in the body to yield sirolimus as a "major metabolite."⁴⁸ The parties have submitted different views on what effect the conversion of temsirolimus to sirolimus has, if any, on the activity of the drug *in vivo*. For example, Sandoz points out that a Wyeth (Pfizer) publication states that "[c]linically relevant pharmacokinetic (PK) exposure to i.v. temsirolimus is considered to be a composite of both temsirolimus and sirolimus."⁴⁹ "While this debate is interesting,"⁵⁰ it also serves to further illuminate the drawbacks of an activity-based approach and the merits of FDA's categorical interpretation. FDA need not, indeed should not, carry out an examination of whether and to what extent temsirolimus or any of its metabolites, such as sirolimus, furnish Torisel's pharmacological effect.

Pfizer makes several additional assertions in favor of retaining Torisel's NCE status. First, it points to the extensive studies that it has carried out to demonstrate the safety and effectiveness of Torisel as a basis for classifying the drug as an NCE. Second, it asserts that FDA has recognized certain "stable esters" as an exception to its categorical approach. Third, it cites to a judicial interpretation of the patent term extension provisions of the Hatch-Waxman Amendments to argue that temsirolimus is a NCE under the "plain meaning of the statute." None of these arguments are convincing.

First, the amount of research that a sponsor invests in a drug is not determinative of that 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.⁵¹ 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.

Second, although FDA may have granted NCE exclusivity to a stable ester in 1991, that approval occurred before FDA finalized the applicable regulation, and FDA has since adhered to its structure-based approach that does not evaluate the activity of the ester.⁵² Moreover, it is not clear in this case whether temsirolimus is "stable" because it is at least partially de-esterified *in vivo*, yielding sirolimus as a major metabolite.⁵³

used to deliver dextroamphetamine to the site of action, and thus has no physiological or pharmacological effect. Shire, in turn asserts that studies have shown that by covalently bonding dextroamphetamine to lysine, it has created a molecule that - without the use of excipients or mechanical formulation - has the characteristics and pharmacokinetics of a sustained release formulation of dextroamphetamine. Each party has its experts.") (citations omitted).

⁴⁸ *Temsirolimus*, 5 *Drugs R&D* 363, 364 (2004).

⁴⁹ JP Boni, et al., *Differential effects of ketoconazole on exposure to temsirolimus following intravenous infusion of temsirolimus*, 98 *British J. of Cancer* 1797, 1797 (2008).

⁵⁰ Vyvanse letter, *supra* note 12, at 17.

⁵¹ Compare section 505(j)(5)(F)(ii) of the Act with section 505(j)(5)(F)(iii) of the Act.

⁵² See Vyvanse letter, *supra* note 12, at 9 n.14.

⁵³ See note 48, *supra*.

Finally, Pfizer's "plain meaning" argument relies on the Federal Circuit's interpretation of a different, albeit similar, statutory provision.⁵⁴ That interpretation of "active ingredient" is inapplicable because it does not pertain to the statutory provisions that govern FDA's determination of NCE exclusivity. The controlling judicial interpretation of "active ingredient" as that phrase appears in the relevant provisions of the FD&C Act is the D.C. Circuit's *Actavis* decision, discussed above.⁵⁵

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. Temsirolimus is comprised of a previously approved active moiety, sirolimus, that is modified with an ester bonded appendage. Because temsirolimus's ester-bonded appendage is excluded from its active moiety, it contains a previously approved active moiety, sirolimus. The Agency therefore incorrectly considered temsirolimus to be a NCE entitled to five years of exclusivity.

Torisel's NCE exclusivity award is hereby rescinded as it was granted in error.⁵⁶ Though it seems that it would have been eligible for three years of exclusivity instead, the issue is moot because Torisel has already enjoyed more than three 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: Jeffrey P. Kushan, Counsel for Pfizer
Elizabeth Dickinson, Chief Counsel, FDA/OCC

⁵⁴ See *Photocure ASA v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010) (interpreting 35 U.S.C. §156(a) & (f)).

⁵⁵ See *Actavis*, *supra* note 13, at 764 n.6 (discussing, but not adopting, the Federal Circuit's interpretation of "active ingredient" in *Photocure*).

⁵⁶ See *Macktal v. Chao*, 286 F.3d 822, 825-26 (5th Cir. 2002) ("[I]t is generally accepted that in the absence of a specific statutory limitation, an administrative agency has the inherent authority to reconsider its decisions.") (collecting cases).

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