DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 08/19/2016

TO: Targiniq (Oxycodone Hydrochloride and Naloxone Hydrochloride) ER tablets (new drug application (NDA) 205777)
Troxyca (Oxycodone Hydrochloride and Naltrexone Hydrochloride) ER capsules (NDA 207621)

FROM: CDER Exclusivity Board Jay Sattari 8/19/16

THROUGH: Sharon Hertz, MD, Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

SUBJECT: Whether 3-Year Exclusivity for Targiniq (Oxycodone Hydrochloride and Naloxone Hydrochloride) ER tablets (NDA 205777) blocks the approval of Troxyca (Oxycodone Hydrochloride and Naltrexone Hydrochloride) ER tablets (NDA 207621)

SUMMARY

This memorandum addresses whether the unexpired 3-year exclusivity for NDA 205777 for Targiniq extended-release (ER) tablets (Targiniq), a fixed-combination[1] that contains two active ingredients with the active moieties oxycodone and naloxone, blocks the approval of the 505(b)(2) NDA for Troxyca ER capsules (Troxyca) (NDA 207621), a fixed-combination that contains two active ingredients with the active moieties oxycodone and naltrexone.

The Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER), in consultation with CDER's Division of Anesthesia, Analgesia, and Addiction Products (DAAAP

[1] A drug containing two or more active ingredients in a single dosage form will be referred to as a fixed-combination in this memorandum, and a drug containing a single active ingredient will be referred to as a single-entity drug.

or Division) and other components of FDA, concludes that Targiniq's 3-year exclusivity for the conditions of approval of NDA 205777 is tied to its specific combination of active moieties, oxycodone and naloxone. The Board thus recommends that any 3-year exclusivity for Targiniq should not block the approval of Troxyca because Troxyca has a different combination of active moieties, oxycodone and naltrexone.[2]

I. LEGAL BACKGROUND

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the Federal Food, Drug & Cosmetic (FD&C) Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs). Because Targiniq and Troxyca are 505(b)(2) NDAs, the remaining discussion will focus primarily on the 505(b)(2) pathway.

1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[3] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.[4] One basis for FDA not approving a 505(b)(1) NDA is that there is a lack of substantial evidence that the drug product is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.[5]

2. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[6] amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs

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[2] This memorandum only discusses whether the 3-year exclusivity for Targiniq should block the approval of the Troxyca NDA, and does not address the full scope of Targiniq's exclusivity nor whether Troxyca is eligible for its own period of exclusivity or the scope of any such exclusivity. This memorandum does not address naturally derived mixtures or other complex products.

[3] See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include: a full list of the articles used as components of the proposed drug product; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. Id.

[4] See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

[5] See section 505(d)(5) of the FD&C Act.

[6] Public Law 98-417 (1984).

and ANDAs, respectively.[7] The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[8] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[9]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the "full reports" requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[10] Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as its own studies, published reports of studies to which the applicant has no right of reference, the Agency's findings of safety and/or effectiveness for one or more previously approved drugs, or a combination of these and other sources to support approval.[11]

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[7] Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously-approved conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

[8] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[9] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

[10] Section 505(b)(2) of the FD&C Act provides for approval of an application:

> for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

As defined at 21 CFR 314.3, "*Right of reference or use* means the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary."

[11] See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA's transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity (NCE),[12] and, in some instances, may describe a drug product with substantial differences from a listed drug.[13] When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can *bridge*[14] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability[15] of the two products, or other appropriate scientific information.

FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process,[16] the 505(b)(2) Draft Guidance, and previous citizen petition responses.[17] FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. FDA's interpretation of section 505(b)(2) avoids requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval, with no corresponding benefit to the public health. In addition, the conduct of duplicative studies may raise ethical concerns because it could subject human beings and animals to medically or scientifically unnecessary testing. The 505(b)(2) pathway permits sponsors and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the drug on which the 505(b)(2) application seeks to rely.[18]

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[12] See 21 CFR 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 [FD&C Act]").

[13] In October 1999, the Agency issued a draft guidance for industry entitled "Applications Covered by Section 505(b)(2)" (505(b)(2) Draft Guidance) which states that "[a] 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference." 505(b)(2) Draft Guidance at 3, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[14] The "bridge" in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

[15] Bioavailability data provide an estimate of the amount of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug. See, e.g., FDA's Guidance for Industry: "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" (March 2014) (BA/BE NDA/IND Guidance), at 3.

[16] See Abbreviated New Drug Application Regulations, 54 FR 28872 (July 10, 1989); Abbreviated New Drug Application Regulations, 57 FR 17950 (April 28, 1992); Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 FR 50338 (October 3, 1994).

[17] See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

[18] 21 CFR 314.54(a) states that "[A 505(b)(2)] application need contain only that information needed to support the modification(s) of the listed drug."

B. Exclusivity Under the FD&C Act and Fixed-Combinations

The Hatch-Waxman Amendments provide incentives for pharmaceutical innovation in the form of 3-year and 5-year NCE exclusivity to protect qualified drugs submitted under section 505(b) from competition from certain 505(b)(2) NDAs and ANDAs for varying periods of time depending on the factual circumstances. Although our decision here relates specifically to 3-year exclusivity, we provide background first on 5-year NCE exclusivity for contextual purposes, followed by background on 3-year exclusivity, and then apply the framework to fixed-combinations.

1. 5-Year NCE Exclusivity

The longest and most protective period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity described at section 505(c)(3)(E)(ii) of the FD&C Act.[19] Under this section, a 5-year exclusivity period is provided 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 [section 505(b)]."[20] This exclusivity generally has been interpreted to prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug.[21] Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

FDA's regulations at 21 CFR 314.108 implement the statutory exclusivity provisions. Under FDA's interpretation of the statute, embodied in the regulations, a drug that contains an NCE

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[19] A parallel provision can be found at section 505(j)(5)(F)(ii).

[20] Section 505(c)(3)(E)(ii) of the Act provides:

> 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 which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) [of this section] 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 subsection (b) [of this section] 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 clause (iv) of subsection (b)(2)(A) [of this section]. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) 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 approval of the subsection (b) application.

See also section 505(j)(5)(F)(ii).

[21] An applicant may submit an ANDA or 505(b)(2) NDA after 4 years under specific circumstances described in section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act that are not at issue here.

will qualify for 5 years of NCE exclusivity. If a drug does not contain an NCE, it will not be eligible for 5-year NCE exclusivity, but it may be eligible for 3-year exclusivity.[22]

The Agency's regulations define *new chemical entity* to mean "a drug[23] that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the [FD&C Act]."[24] *Active moiety* in turn 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.[25]

FDA's interpretation of the 5-year NCE exclusivity provisions has focused on the specific chemical structure of the active moiety under consideration;[26] FDA concluded that the term "active ingredient," as used in the phrase "active ingredient (including any salt or ester of the active ingredient)," refers to the active moiety. FDA adopted a chemical structure-driven approach based upon certain reasonable, generally applicable scientific principles regarding the anticipated characteristics of different types of molecules, which can be applied consistently to different types of drugs.[27] Under this approach, the Agency does not need to determine the

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[22] Describing the 5-year NCE exclusivity provisions, Representative Waxman stated:

> [T]he amendment provides a 5-year period of exclusive market life for drugs approved for the first time after enactment of the legislation. This provision will give the drug industry the incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains.

130 Cong. Rec. 24425 (1984) (statement of Rep. Waxman) (emphasis added). Representative Waxman contrasted this to 3-year exclusivity (which would be available for drugs that did not qualify for the longer period of exclusivity given to a new chemical entity) as follows:

> [A] 3-year period of exclusive market life is afforded to non-new chemical entities approved after enactment of the bill which have undergone new clinical studies essential to FDA approval.

Id. (emphasis added). See also 130 Cong. Rec. 23765 (1984) (statement of Sen. Hatch).

[23] In FDA's guidance for industry entitled, "New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products" (Oct. 2014) (Fixed-Combination NCE Guidance), FDA explains that under its current thinking, the word "drug" in this phrase refers to the drug substance, not the drug product as FDA had previously interpreted the statute. We note that the terms "drug substance" and "active ingredient" are used interchangeably for purposes of this memorandum. See definition of *drug substance* at 21 CFR 314.3(b) and definition of *active ingredient* at 21 CFR 210.3(b)(7).

[24] 21 CFR 314.108(a).

[25] Id.

[26] See, e.g., Abbreviated New Drug Application Regulations, 54 FR 28872, 28897-28898 (July 10, 1989) ("1989 Proposed Rule").

[27] See, e.g., Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 FR 50338, at 50358 (Oct. 3, 1994) ("1994 Final Rule") (concluding that the definition of active moiety should exclude chelates, clathrates, and other noncovalent derivatives because they generally do not affect the active moiety of a drug product).

precise molecule or molecules responsible for the pharmacological action in vivo to determine eligibility for 5-year NCE exclusivity.

Thus, in determining the eligibility for 5-year NCE exclusivity for a single-entity drug, FDA conducts a structure-based analysis on the active ingredient, and if the active ingredient contains an active moiety that the Agency has not previously approved, the drug will be eligible for 5-year exclusivity. Such exclusivity will block any application that contains the active moiety protected by 5-year NCE exclusivity.

2. 3-Year Exclusivity

The Hatch-Waxman Amendments also provide for a 3-year period of exclusivity for certain drugs that are not eligible for 5-year NCE exclusivity. The statute and regulations for 3-year exclusivity describe which original NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval by that exclusivity.

For original NDAs, section 505(c)(3)(E)(iii) of the FD&C Act states:[28]

> *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 subsection (b) [of this section] for the conditions of approval of such drug in the approved 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] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[29]

The first clause (italicized) in section 505(c)(3)(E)(iii), often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. As noted in Section I.B.1, in the 5-year NCE exclusivity context, FDA has interpreted the term "active ingredient" in the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean active moiety. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for single-entity drugs that are not eligible for 5-year NCE exclusivity (because they contain an active moiety "that has been

[28] A parallel provision applies 3-year exclusivity to ANDAs. See section 505(j)(5)(F)(iii) of the FD&C Act.

[29] See Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4)(iv) (similarly stating that if an application submitted under section 505(b) contains new clinical investigations that were essential to approval and conducted or sponsored by the applicant, the Agency "will not make effective for a period of 3 years after the date of approval of the application a 505(b)(2) application or an [ANDA] for the conditions of approval of the original application . . . .").

approved in another application") are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA's implementing regulations further interpret certain aspects of the statutory language regarding eligibility for 3-year exclusivity. Among other things, they define the terms *clinical investigation,*[30] *new clinical investigation,*[31] and *essential to approval.*[32]

The second clause in section 505(c)(3)(E)(iii) (underlined), often referred to as the bar clause, describes which 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity. The Agency's interpretation of the bar clause and thus a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) generally involves two aspects. One aspect of the scope inquiry focuses on the drug at issue. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause. The "drug" in the eligibility clause refers to "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application," that is, the drug which includes a previously approved active moiety. FDA interprets this cross reference to mean that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity.[33] Another aspect of the scope inquiry focuses on the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant informs the "conditions of approval" relevant to 3-year exclusivity.[34]

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[30] "Clinical investigation" is defined as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects." 21 CFR 314.108(a).

[31] "New clinical investigation" is defined as "an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 CFR 314.108(a).

[32] "Essential to approval" means "with regard to an investigation, that there are no other data available that could support approval of the application." 21 CFR 314.108(a).

[33] See Letter from Janet Woodcock, M.D., Director, CDER, FDA to William H. Carson, M.D., President & CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. and Ralph S. Tyler, Esq., Venable L.L.P. (Oct. 5, 2015) (Docket No. FDA-2015-P-2482), aff'd *Otsuka Pharmaceutical Co., Ltd., et al v. FDA*, Case No. 1:15-cv-01688-KBJ (D.D.C. July 28, 2016) (upholding FDA's interpretation of section 505(c)(3)(E)(iii) that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity) (currently pending appeal).

[34] FDA considered, in the context of a single-entity drug, the meaning of the phrase "conditions of approval of such drug in the approved subsection (b) application" in a recent decisional letter regarding whether Astellas' 3-year exclusivity for its tacrolimus drug, Astagraf XL, blocks approval of Veloxis' tacrolimus drug, Envarsus XR. See Letter from R. Albrecht, FDA to M. McGuinness, Veloxis Pharmaceuticals, Inc., Jan. 12, 2015 (Veloxis Letter), aff'd Veloxis Pharmaceuticals, Inc. v. FDA, No. 14-cv-2126, 2015 U.S. Dist. LEXIS 77559 (D.D.C. June 12, 2015)("Veloxis Court Decision"). In the Veloxis Letter, FDA considered both aspects of the scope inquiry in determining whether approval of Envarsus XR was blocked. Although not a subject of dispute, it was clear that in interpreting the phrase "conditions of approval of such drug in the subsection (b) application," FDA considered the conditions of approval for tacrolimus, which was the single active moiety for the two products at issue. In the Veloxis Letter, FDA repeatedly stated that the exclusivity for Astagraf XL covered "a once-daily, extended-release

Thus, in the case of an application submitted for a single-entity drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval (i.e., the conditions of approval for which new clinical investigations were essential).

For supplements to approved NDAs, section 505(c)(3)(E)(iv) of the FD&C Act states:

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

Although the statute and regulations use different words to describe 3-year exclusivity for an original NDA and a supplement to an NDA, FDA has taken a consistent approach to both types of applications in determining eligibility for 3-year exclusivity and scope. The eligibility clause in section 505(c)(3)(E)(iv) (italicized) corresponds to the eligibility clause in section 505(c)(3)(E)(iii) of the FD&C Act, except, among other things, in section 505(c)(3)(E)(iv), the word "supplement" is substituted for the word "application" in section 505(c)(3)(E)(iii). As with an original NDA, a supplement may be eligible for 3-year exclusivity if it contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the supplement that were conducted or sponsored by the applicant submitting the supplement.

The bar clause of section 505(c)(3)(E)(iv) (underlined) describes 3-year exclusivity as blocking approval of a 505(b)(2) application for "a change approved in the supplement." Although this language is not identical to the phrase "conditions of approval of such drug in the approved subsection (b) application" used in section 505(c)(3)(E)(iii), in determining the scope of exclusivity and which applications are barred, there are likewise two aspects of the inquiry. One aspect of the inquiry focuses on the drug at issue. Under FDA's longstanding policy regarding which changes are eligible to be approved in a supplement (as opposed to requiring a full, new original application), any change in the active ingredient (and thus any change in active moiety)

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dosage form of tacrolimus for prophylaxis of organ rejection for use in de novo kidney transplant patients." FDA did not consider other single-entity drugs that contained a different active moiety in determining whether Envarsus XR's approval would be blocked. Because the active moiety was the same for the two products at issue, FDA then considered the scope of the new clinical investigations essential to the approval conducted or sponsored by the applicant to determine the "conditions of approval of such drug" and thus the scope of exclusivity.

may only be made through a new, original application, not a supplement.[35] In other words, a change approved in a supplement must be a change in conditions of approval for the same drug (active moiety) approved in the original NDA. Thus, in order to determine that a 505(b)(2) NDA is blocked because it seeks approval for a "change approved in a supplement" during another applicant's 3-year exclusivity period, FDA interprets the 505(c)(3)(E)(iv) language such that the 505(b)(2) NDA must be for a drug with the same active moiety as the drug with exclusivity.

If the 505(b)(2) application for a single-entity drug seeks approval for the same drug (active moiety) to which exclusivity has attached, then the second aspect of the scope inquiry applies. To determine whether the 505(b)(2) NDA is barred, FDA must also determine what exclusivity-protected change was approved in the supplement. To do so, FDA examines the conditions of approval supported by the new clinical investigations (other than bioavailability studies) that were essential to approval of the supplement. If the 505(b)(2) NDA for a single-entity drug is for the same drug for the same exclusivity-protected change approved in the supplement, it will be blocked.

3. *5-Year NCE Exclusivity, 3-Year Exclusivity, and Fixed-Combinations*

The 5-year NCE exclusivity and 3-year exclusivity statutory and regulatory provisions apply not only to single-entity drugs, but also to fixed-combinations. When FDA evaluates a fixed-combination to determine eligibility for 5-year NCE exclusivity, it conducts a structure-based chemistry analysis to determine whether any of the individual active ingredients in the fixed-combination contains an active moiety that has never previously been approved. If the fixed-combination contains an active ingredient that includes a previously unapproved active moiety, that active ingredient is considered an NCE, and 5-year NCE exclusivity attaches to the previously unapproved active moiety. In such a case (with certain exceptions not relevant here) applications for drugs containing that active moiety are barred from submission for a period of 5 years.[36]

As noted in Section I.B, FDA considers eligibility for 3-year exclusivity only if it has determined that 5-year NCE exclusivity is not available. Thus, if after conducting its structure-based chemistry analysis, FDA determines that no active ingredient in the fixed-combination contains an active moiety that has not been previously approved, (i.e., it determines that no 5-year NCE exclusivity will attach), the Agency will then proceed with determining eligibility of the fixed-combination for 3-year exclusivity. In analyzing eligibility for 3-year exclusivity for a fixed-combination, the Agency determines whether the fixed-combination or a change to the fixed-combination is supported by new clinical investigations (other than bioavailability studies) essential to approval of the application for the fixed-combination (or the supplement to the application for the fixed-combination) and were conducted or sponsored by the applicant.

505(b)(2) NDAs are barred from approval by 3-year exclusivity for an original application if

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[35] See FDA's guidance for industry entitled "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees", at 3 (Bundling Guidance) ("Every different active ingredient or combination of two or more different active ingredients should be submitted in a separate original application.").

[36] See Fixed-Combination NCE Guidance at 8.

they are seeking approval for "the conditions of approval of such drug." In the case of a fixed-combination, when determining which applications are seeking approval for "the conditions of approval of such drug" and thus have the potential to be blocked, FDA generally focuses its inquiry to applications that contain the same combination of active moieties as in the fixed-combination. This is because the clinical investigations that earn exclusivity must be submitted to the application for the combination, and necessarily support approval of the combination described in the application (or of a change to that combination).[37] Thus, the conditions of approval of *such drug* necessarily encompass the conditions of approval of the particular combination of active moieties of the drug for which the application was submitted and for which new clinical investigations were essential.

Similarly, applications are barred from approval by 3-year exclusivity for a supplement if they are seeking approval for the "change approved in the supplement." As noted in Section I.B.2, FDA interprets 3-year exclusivity for a supplement to provide the same protection as 3-year exclusivity for an original application. Thus, in determining whether a 505(b)(2) NDA is seeking approval for a "change approved in the supplement" to a fixed-combination and is therefore blocked by 3-year exclusivity for the supplement, FDA similarly focuses its inquiry to applications that contain the same combination of active moieties as in the fixed-combination and examines the scope of the new clinical investigations essential to the approval and that were conducted or sponsored by the applicant. If the 505(b)(2) NDA is seeking approval for a fixed-combination with a different combination of active moieties than the combination with exclusivity, it is not seeking approval for a change approved in the supplement and therefore cannot be blocked.

[37] FDA regulations generally require that the combination as a whole be shown to be safe and effective and that each drug in the fixed-combination be shown to contribute to efficacy. It is not adequate for a sponsor to demonstrate only that the individual components are safe and effective. See 21 CFR 300.50.

II. FACTUAL BACKGROUND

A. Targiniq[38]

Purdue Pharma L.P.'s (Purdue's) NDA for Targiniq ER tablets (NDA 205777) was approved by FDA on July 23, 2014. Targiniq is a fixed-combination comprising two active moieties: oxycodone (from the active ingredient oxycodone HCl) and naloxone (from the active ingredient naloxone HCl). Targiniq ER tablets are intended for oral administration every 12 hours, and are available in dosage strengths (oxycodone/naloxone milligrams (mg)) 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg.[39]

Oxycodone is a μ-opioid receptor agonist (with some activity at the κ and δ receptors) with the primary therapeutic action of analgesia. Oxycodone has been marketed for over 80 years. Oxycodone is an active moiety in several marketed drug products used for the treatment of pain, including as a single-entity product[40] and in combination with acetaminophen or non-steroidal anti-inflammatory drugs.[41]

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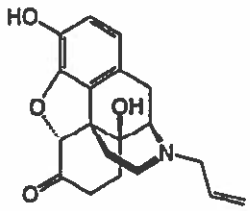
[38] There are other drug products containing oxycodone with unexpired exclusivity. OxyContin (oxycodone HCl) ER tablets (OxyContin) (NDA 022272) is a single-entity drug that contains one active ingredient with the active moiety oxycodone. On August 13, 2015, FDA approved a supplement (S-027) to the OxyContin NDA. That approval included labeling changes regarding the use of OxyContin in the pediatric population. S-027 qualified for 3-year exclusivity which will expire on August 13, 2018. Xtampza ER (oxycodone) ER capsules (NDA 208090) is a single-entity drug that contains one active ingredient with the active moiety oxycodone. On April 26, 2016, FDA approved the NDA for Xtampza ER, and the NDA qualified for 3-year exclusivity which will expire on April 26, 2019. Xartemis XR (oxycodone HCl and acetaminophen) ER tablets (NDA 204031) is a fixed-combination that contains two active ingredients with the active moieties oxycodone and acetaminophen. On March 11, 2014, FDA approved an original 505(b)(2) NDA for Xartemis XR, and the NDA qualified for 3-year exclusivity which will expire on March 11, 2017. We do not need to address the full scope of any applicable exclusivity for OxyContin, Xtampza ER, or Xartemis XR to recommend that any exclusivity for OxyContin, Xtampza ER, and Xartemis XR should not block the approval of the Troxyca NDA. The first aspect of the scope inquiry as described in Section I.B is determinative. OxyContin and Xtampza ER contain only a single active moiety (oxycodone), whereas Troxyca contains a combination of active moieties (oxycodone and naltrexone). Because Troxyca is a fixed-combination whereas OxyContin and Xtampza ER are single-entity drugs, any approval of Troxyca is not an approval for the "change approved in the supplement" for which OxyContin has exclusivity or for the "conditions of approval of such drug in the approved subsection (b) application" for which Xtampza ER has exclusivity. Also, Xartemis XR contains a combination of two active moieties (oxycodone and acetaminophen), whereas Troxyca contains a different combination of two active moieties (oxycodone and naltrexone). Because Troxyca does not contain the same combination of active moieties approved in Xartemis XR, any approval of Troxyca is not an approval for the "conditions of approval of such drug in the approved subsection (b) application" for which Xartemis XR has exclusivity. Therefore, we recommend that any applicable exclusivity for OxyContin, Xtampza ER, or Xartemis XR should not block the approval of Troxyca. We need not analyze the second aspect of the scope inquiry as described in Section I.B. In addition, we need not examine whether any additional drug products containing naloxone have unexpired exclusivity because Troxyca does not contain the active moiety naloxone.

[39] NDA 205777, Targiniq Cross Discipline Team Leader (CDTL) Review at 2 (July 14, 2014). See also Targiniq Product Labeling approved July 23, 2014.

[40] See, e.g., OxyContin ER tablets (NDA 022272), Oxaydo tablets (NDA 202080), and numerous generic versions.

[41] See, e.g., Percocet tablets (currently marketed under numerous ANDAs) and Percodan tablets (NDA 007337).

Naloxone, (5R,9R,13S,14S)-17-Allyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one (molecular formula, $C_{19}H_{21}NO_4$),[42] is a nonselective[43] opioid receptor antagonist that markedly attenuates or completely blocks the subjective effects of opioids such as oxycodone through reversible, competitive binding at μ-opioid receptors. Naloxone can exert an effect anywhere there are opioid receptors such as in the brain, spinal cord, and peripheral organs (e.g., intestine, heart, kidney, and lungs). Naloxone will precipitate withdrawal symptoms in subjects physically dependent on opioids. Naloxone is a congener of oxymorphone with no opioid agonist properties of its own. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.[44] The structure of naloxone is shown below.



Naloxone was first approved on April 13, 1971 as Narcan (NDA 016636), a parenteral product to reverse the effects of opioid overdose. When administered orally, the absolute bioavailability of naloxone is less than 2% due to extensive first-pass metabolism in the liver. Naloxone has since been approved as two additional single-entity products[45] and in combination with pentazocine to deter parenteral abuse.[46] Naloxone is also approved in combination with buprenorphine for maintenance treatment for opioid dependence.[47]

Targiniq was approved by FDA for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate"[48] on July 23, 2014. The 505(b)(2) NDA for Targiniq relied, in part, on FDA's previous finding of safety and effectiveness for Narcan and cross-referenced Purdue's OxyContin (oxycodone HCl) products – original OxyContin (NDA 20553) and reformulated OxyContin (NDA 022272). Targiniq is a fixed-combination comprising the active moieties oxycodone and naloxone. The extended-release mechanism of Targiniq is matrix-controlled with stearyl alcohol and ethylcellulose N45 as rate controlling excipients.[49]

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[42] In Targiniq naloxone is present as its HCl salt form.

[43] In some cases, naloxone shows greater selectivity for the μ-opioid receptor than the δ- or κ-opioid receptor.

[44] In contrast, naltrexone differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group.

[45] See Evzio (NDA 205787) and Narcan Nasal Spray (NDA 208411).

[46] See Talwin NX (NDA 018733).

[47] See, e.g., Suboxone (NDA 020733) and Bunavail (NDA 205637).

[48] Targiniq falls within the class of drugs that are part of the Extended-Release/Long-Acting (ERLA) Opioid Risk Evaluation and Mitigation Strategy (REMS), and the indication is the same as that for other ERLA products. Targiniq CDTL Review at 2.

[49] NDA 205777, Targiniq Controlled Substances Staff (CSS) Review at 8 (June 24, 2014).

The intent of the addition of naloxone to the Targiniq formulation is to provide abuse-deterrent (AD) properties as described in NDA 205777.[50] The principal mechanism underlying the AD properties of Targiniq is the effectiveness of the 2:1 oxycodone:naloxone ratio in blocking the subjective reinforcing effects of oxycodone administered by the intranasal and intravenous routes and potentially precipitating withdrawal.[51] As shown by in vitro studies, the difficulty involved in separating naloxone from oxycodone also contributes to Targiniq's AD properties. Targiniq is not formulated (i) to be resistant to crushing; (ii) to resist, upon crushing, compromise of the controlled-release properties of oxycodone or naloxone;[52] or (iii) to gel upon exposure to an aqueous environment, as there are no gelling agents in the formulation.[53]

Purdue demonstrated the efficacy of Targiniq in a single, adequate, and well-controlled clinical trial, Study ONU3701. This clinical trial was conducted as a Phase 3 randomized, double-blind, placebo-controlled, parallel-arm enriched design study in opioid-experienced patients with chronic low back pain who required around-the-clock opioids in a range of 20 mg to 160 mg morphine equivalents.[54]

This study was necessitated by the inclusion of naloxone in Targiniq. Specifically, the Division advised Purdue that as a 505(b)(2) applicant relying on the Agency's finding of safety and efficacy for Narcan, with cross-reference to Purdue's original OxyContin and reformulated OxyContin NDAs, it would need to conduct a clinical trial demonstrating efficacy if detectable levels of naloxone in systemic circulation were noted.[55] Among other concerns, the Agency was concerned about the potential impacts of naloxone on the analgesic efficacy of oxycodone[56] (in particular whether the presence of naloxone could interfere with analgesic efficacy), and recognized the possibility that patients treated with Targiniq may be at risk for adverse events due to the presence of naloxone, specifically opioid withdrawal.[57] Study ONU3701 was prospectively designed to evaluate efficacy and to assess the occurrence of opioid withdrawal symptoms in subjects treated with Targiniq compared to placebo.

Purdue also conducted certain studies to evaluate the AD properties of Targiniq. For instance, Purdue conducted several human abuse potential studies (Studies ONU1003, ONU1004,

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[50] Targiniq CDTL Review at 2-3; NDA 205777, Targiniq Clinical Review at 8 (June 18, 2014); NDA 205777, Targiniq Summary Review at 3 (July 23, 2014).

[51] Targiniq Summary Review at 26, citing Targiniq CSS Review at 3.

[52] Simple crushing of the tablets results in rapid and complete compromise of the controlled release properties of oxycodone and naloxone.

[53] Targiniq CSS Review at 3.

[54] Targiniq Clinical Review at 9.

[55] Targiniq CDTL Review at 19.

[56] Targiniq PIND 70851, Meeting Minutes for February 24, 2009, Pre-IND Meeting at 8. See also, Targiniq PIND 70851, Written Response from FDA to Purdue (August 19, 2011) at 1-2.

[57] Targiniq Summary Review at 20, citing CDTL Review at 30-35.

ONU1007, and ONU1008) to assess Targiniq's resistance to abuse by intravenous (IV), intranasal, and oral administration.[58]

Targiniq has 3-year exclusivity which will expire on July 23, 2017. The exclusivity is denoted in the Orange Book as "new combination" (NC). FDA has concluded that some of the clinical studies submitted in the Targiniq NDA qualified for 3-year exclusivity because they were new clinical investigations essential to approval of the NDA and were conducted by Purdue.[59] However, we need not determine the full scope of that exclusivity to recommend that Targiniq's exclusivity should not block approval of Troxyca as discussed below.

B. Troxyca[60]

NDA 207621 for Troxyca ER capsules was submitted by Pfizer, Inc. (Pfizer) on December 19, 2014. Pfizer is seeking approval of Troxyca for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Troxyca is a fixed-combination comprising two active moieties: oxycodone (from the active ingredient oxycodone HCl) and naltrexone (from the active ingredient naltrexone HCl). The product is intended for oral administration every 12 hours, and is available in dosage strengths (oxycodone/naltrexone mg) of 10 mg/1.2 mg; 20 mg/2.4 mg; 30 mg/3.6 mg; 40 mg/4.8 mg; 60 mg/7.2 mg; and 80 mg/9.6 mg.

Naltrexone, (5α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one (molecular formula, $C_{20}H_{23}NO_4$)[61] is a nonselective opioid receptor antagonist that markedly

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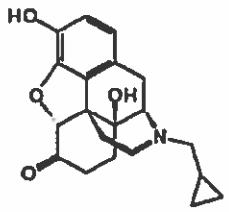
[58] Targiniq CSS Review, generally. See also, Targiniq Clinical Review at 106, Targiniq Summary Review at 30-32.

[59] FDA intends to reach a decision on these matters during the ordinary course of making exclusivity decisions in relation to other applications for combinations of oxycodone and naloxone as appropriate. Such a determination would require the Agency to identify the new clinical investigations that were essential to approval and to determine the conditions of approval resulting from those new clinical investigations.

[60] There are other fixed-combinations containing naltrexone with unexpired exclusivity. Embeda (morphine sulfate and naltrexone HCl) ER capsules (NDA 022321) is a fixed-combination that contains two active ingredients with the active moieties morphine and naltrexone. FDA approved the original NDA for Embeda on August 13, 2009. On October 17, 2014, FDA approved a supplement (S-016) to the Embeda NDA. That approval included labeling changes regarding the AD properties of Embeda. S-016 qualified for 3-year exclusivity which will expire on October 17, 2017. Contrave (naltrexone HCl and bupropion HCl) ER tablets (NDA 200063) is a fixed-combination that contains two active ingredients with the active moieties naltrexone and bupropion. On September 10, 2014, FDA approved an original 505(b)(2) NDA for Contrave, and the NDA qualified for 3-year exclusivity which will expire on September 10, 2017. We do not need to address the full scope of any applicable exclusivity for Embeda or Contrave to recommend that any exclusivity for Embeda and Contrave should not block the approval of the Troxyca NDA. The first aspect of the scope inquiry as described in Section I.B is determinative. Embeda contains a combination of two active moieties (morphine and naltrexone) and Contrave contains a combination of two active moieties (naltrexone and bupropion), whereas Troxyca contains a different combination of two active moieties (oxycodone and naltrexone). Because Troxyca does not contain the same combination of active moieties approved in Embeda or Contrave, any approval of Troxyca is not an approval for the "change approved in the supplement" for which Embeda has exclusivity or for the "conditions of approval of such drug in the approved subsection (b) application" for which Contrave has exclusivity. Therefore, we recommend that any applicable exclusivity for either Embeda or Contrave should not block the approval of Troxyca. We need not analyze the second aspect of the scope inquiry as described in Section I.B.

attenuates or completely blocks the subjective effects of opioids such as oxycodone through reversible, competitive binding at μ-opioid receptors. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties.[62] Naltrexone will precipitate withdrawal symptoms in subjects physically dependent on opioids.[63] Structurally, naltrexone is a congener of oxymorphone with no opioid agonist properties of its own. It differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group.[64] The structure of naltrexone is shown below.



Naltrexone was first approved as Naltrexone HCl on November 20, 1984 (Revia Tablets; NDA 018932)[65] for the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. With regard to treating opioid dependence, naltrexone has since been approved as a single-entity product (Vivitrol; NDA 021897 approved on April 13, 2006). Naltrexone has also been approved as part of a fixed-combination with morphine sulfate intended to provide AD properties (Embeda; NDA 022321 approved on August 13, 2009).

NDA 207621 for Troxyca was submitted pursuant to section 505(b)(2) of the FD&C Act, and relies, in part, on FDA's findings of safety and effectiveness for Roxicodone (oxycodone HCl) (NDA 021011) and Revia (naltrexone HCl) (NDA 018932). Pfizer also cross-referenced its NDA 022321 for Embeda (morphine sulfate and naltrexone HCl).

In contrast with naloxone, naltrexone is generally well-absorbed orally, and is bioavailable to a greater extent. Like naloxone, naltrexone is subject to significant first pass metabolism in the liver; however, its absolute oral bioavailability is estimated to range from 5 to 40%[66] in contrast to the less than 2% observed with naloxone.[67] Therefore, when naltrexone is used in an AD opioid formulation, it needs to be sequestered so that it does not result in withdrawal symptoms in patients. Troxyca is thus formulated with barrier layers including a sequestering membrane intended to sequester the naltrexone.

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[61] In Troxyca naltrexone is present as its HCl salt form.

[62] NDA 207621, Troxyca Clinical Review at 19 (Sep. 14, 2015).

[63] Id.

[64] In contrast, naloxone differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

[65] Upon approval, Revia received 5-year NCE exclusivity.

[66] Revia Labeling (revised Oct. 3, 2013), Clinical Pharmacology Section (Pharmacokinetics – Absorption).

[67] Id.

Specifically, Troxyca is formulated as a hard gelatin capsule filled with individual pellets containing rate-controlling excipients and oxycodone separated from the naltrexone inner core by a barrier layer.[68] If the intact capsule (or sprinkled pellets) is ingested orally, oxycodone is released with an extended-release profile to provide analgesia, while naltrexone largely remains sequestered. However, upon crushing or chewing the capsule or the pellets, naltrexone is released, resulting in antagonism of the pharmacodynamic effects of oxycodone, including drug liking and high.[69]

To support the approval of the Troxyca NDA, Pfizer conducted two Phase 3 efficacy and safety studies to assess whether sequestered naltrexone could potentially compromise the analgesic effects of oxycodone or safety due to systemic exposure of a small amount of naltrexone that escapes the inner core. Pfizer also conducted three human abuse liability studies to assess the AD properties of the formulation.[70]

III. DISCUSSION

A. Three-Year Exclusivity for Targiniq Does Not Block Approval of the 505(b)(2) NDA for Troxyca

The issue addressed in this memorandum is whether the 3-year exclusivity for Targiniq, a fixed-combination containing the active moieties oxycodone and naloxone, will block the approval of the 505(b)(2) NDA for Troxyca, a fixed-combination containing the active moieties oxycodone and naltrexone. We conclude that it should not.

Targiniq is a fixed-combination that contains two active ingredients (oxycodone HCl and naloxone HCl), which contain oxycodone and naloxone as active moieties. In 2014, at the time of approval of the original NDA for Targiniq, FDA determined that no active ingredient (neither oxycodone HCl nor naloxone HCl) contained an active moiety that had not been previously approved, and thus no 5-year NCE exclusivity attached. FDA has since proceeded with determining eligibility for 3-year exclusivity and concluded that Targiniq has 3-year exclusivity. As explained in Section I.B. above, the conditions of approval of *such drug* necessarily encompass the particular combination of active moieties for which the application was submitted and for which new clinical investigations were essential. The conditions of approval for Targiniq are for the drug containing the combination of active moieties – oxycodone and naloxone. That exclusivity expires on July 23, 2017. Thus, the exclusivity-protected conditions of approval only bar approval of other 505(b)(2) NDAs for drugs containing the same combination of active moieties approved in Targiniq and that otherwise seek approval for the same exclusivity-protected conditions of approval as Targiniq. Because Troxyca does not

[68] Troxyca Clinical Review at 12-13. (b) (4)

[69] Troxyca Clinical Review at 12-13, 21. See also, NDA 207621, Troxyca CSS Review at 2 (Sep. 16, 2015).

[70] Troxyca Clinical Review at 22. Pfizer also conducted five pharmacodynamic studies to assess the dose ratio for oxycodone to naltrexone.

contain the same combination of active moieties approved in Targiniq, any approval of Troxyca is not an approval for the "conditions of approval of such drug in the approved subsection (b) application" for which Targiniq currently has exclusivity and no additional inquiry is required. Therefore, we recommend that the exclusivity awarded to Targiniq should not block approval of Troxyca.[71]

B. The Board's Recommendation that Targiniq's 3-Year Exclusivity Should Not Block Approval of Troxyca Is Consistent with FDA Regulations, Congressional Intent, and the Targiniq Approval

The Board's recommendation that 3-year exclusivity for Targiniq should not block approval of Troxyca is consistent with the Agency's regulations regarding fixed-combinations and with the approval of the Targiniq NDA. FDA regulations generally require that the combination as a whole be shown to be safe and effective and that each component (drug) in the fixed-combination be shown to contribute to efficacy.[72] Generally, it is not adequate for a sponsor to demonstrate only that the individual components are safe and effective. The regulation describes "special cases" (or examples) of the general rule regarding when a sponsor must demonstrate that each component (drug) in a combination contributes to the combination's claimed effect. These examples include when a component is added to the combination: "(1) [t]o enhance the safety or effectiveness of the principal active component;" and "(2) [t]o minimize the potential for abuse of the principal active component."[73]

Targiniq is one of these special cases. Targiniq was approved as a 505(b)(2) application that relied, in part, on a cross-reference to two applications for previously approved single-entity oxycodone products (original and reformulated OxyContin) and on the Agency's finding of safety and effectiveness for a single-entity naloxone product (Narcan). For the initial approval of Targiniq, however, it was not sufficient for the sponsor to rely only on studies or findings of safety and efficacy for drugs containing the individual active moieties oxycodone and naloxone alone. Rather, the sponsor needed to conduct an adequate and well-controlled efficacy study to demonstrate that detectable levels of naloxone in systemic circulation do not interfere with analgesic efficacy.[74] Moreover, the sponsor needed to investigate how the presence of naloxone as the antagonist to oxycodone affects the AD properties of the combination product. Both components are therefore integral to the safety and effectiveness of Targiniq and it follows that the conditions of approval for Targiniq necessarily include the fact that it contains the combination of oxycodone and naloxone. This is consistent with FDA's conclusion that the conditions of approval for Targiniq supported by new clinical investigations relate to the

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[71] If both Targiniq and Troxyca contained the same combination of the two active moieties oxycodone and naloxone, we would need to assess further the scope of exclusivity of Targiniq. We need not reach this aspect of the scope of inquiry here, however, because Targiniq and Troxyca do not contain the same combination of active moieties. Rather, Targiniq contains a combination of oxycodone and naloxone, a characteristic that distinguishes it from Troxyca, which contains oxycodone and naltrexone.

[72] See 21 CFR 300.50.

[73] 21 CFR 300.50(a)(2).

[74] Targiniq CDTL Review at 19, 30-35.

combination of active moieties; and, consequently, any 3-year exclusivity for Targiniq cannot block approval of a drug with a different combination of active moieties than Targiniq.[75]

Further, the Board's recommendation in this case is consistent with the goals of the Hatch-Waxman Amendments. The Board's interpretation of the 3-year exclusivity provisions is intended to encourage and reward innovation by protecting a fixed-combination for which new clinical investigations were essential to approval against approval of drugs with the same combination of active moieties for the same exclusivity-protected condition(s) of approval. The Board's interpretation ensures that 3-year exclusivity for a fixed-combination, if granted, does not block approval of different fixed-combinations (different combinations of active moieties) or of single-entity products. It also ensures that such exclusivity does not block approval of the same fixed-combination (the same combination of active moieties) for condition(s) of approval that were not supported by the new clinical investigations essential to approval. It therefore promotes and protects innovation while also encouraging the development of alternative therapies.

C. Targiniq's 3-Year Exclusivity Does Not Block the Approval of Fixed-Combinations of Oxycodone with Any Opioid Receptor Antagonist

In a letter to the Agency dated September 18, 2015, Purdue claims that Targiniq's 3-year exclusivity blocks other solid oral dosage form oxycodone drug products with agonist/antagonist combination-based AD features, regardless of the specific opioid antagonist utilized and regardless of whether the products are labeled to describe their AD characteristics.[76]

Purdue asserts that Targiniq's AD properties are attributable to the presence of the opioid-receptor antagonist in the product, and the inability to readily separate this component from the agonist oxycodone.[77] As the first oxycodone/antagonist fixed-combination to be shown to have AD properties, Purdue claims that Targiniq confirms the viability of oxycodone/antagonist fixed-

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[75] The Board's recommendation here is consistent with the Agency's decisions on the approvals of NDA 206544 for MorphaBond (morphine sulfate) ER tablets, NDA 207932 for Belbuca (buprenorphine) buccal film, NDA 208411 for Narcan (naloxone) nasal spray, and NDA 204442 for Probuphine (buprenorphine) implant. The Agency determined that the Oct. 2, 2015, approval of the NDA for MorphaBond was not blocked by any unexpired 3-year exclusivity for Embeda (morphine sulfate and naltrexone) ER capsules (NDA 022321). The Agency also similarly determined that the Oct. 23, 2015, approval of the NDA for Belbuca was not blocked by any unexpired 3-year exclusivity for Bunavail (buprenorphine and naloxone) or Zubsolv (buprenorphine and naloxone). The Agency also determined that the Nov. 18, 2015, approval of the NDA for Narcan nasal spray was not blocked by any unexpired 3-year exclusivity for Bunavail (buprenorphine and naloxone), Targiniq (oxycodone and naloxone), or Zubsolv (buprenorphine and naloxone). The Agency determined that the May 26, 2016 approval of the NDA for Probuphine was not blocked by any unexpired 3-year exclusivity for Bunavail (buprenorphine and naloxone) or Zubsolv (buprenorphine and naloxone).

[76] Letter from Peter R. Mathers and Jennifer A. Davidson, Kleinfeld Kaplan & Becker, LLP on behalf of Purdue to Jay Sitlani, Office of Regulatory Policy, CDER, FDA and Kim Dettelbach, Office of Chief Counsel, FDA (Sep. 18, 2015) ("Purdue Letter") at 14. Purdue also argues that 3-year exclusivity for Targiniq blocks the approval of other fixed-combinations containing oxycodone and naloxone for the treatment of pain. Id. at 15-16. We need not address this argument in this memo, as Troxyca is a fixed-combination that contains the active moieties oxycodone and naltrexone.

[77] Id. at 14.

combinations for imparting meaningful AD properties.[78] Purdue thus concludes that exclusivity for this innovation should extend to all combinations of oxycodone with *any* opioid receptor antagonist.[79] Moreover, according to Purdue, Targiniq's status as the first agonist/antagonist oxycodone combination with recognized AD properties, and the related labeling statements about the AD attributes and their expected consequences, both separately constitute innovative conditions of approval for Targiniq.[80] Therefore, Purdue asserts that exclusivity extends to Targiniq's status as the first oxycodone product with agonist/antagonist combination-based AD features, and separately to the related labeling statements describing those features.[81] Under Purdue's proposed reading of Targiniq's exclusivity, final approval of products such as Troxyca could not be made effective until Targiniq's 3-year exclusivity period expires.

Purdue's assertions and arguments are inconsistent with the Agency's regulations and the Targiniq approval. As explained in Section III.A. and III.B., Targiniq's 3-year exclusivity for the conditions of approval of NDA 205777 is tied to the specific combination of its active moieties, oxycodone and naloxone, not merely the combination of oxycodone with *any* antagonist. The conditions of approval for which Targiniq received exclusivity necessarily encompass its particular combination of active moieties for which new clinical investigations were essential.[82]

IV. CONCLUSION

For all of these reasons, the Board recommends that the 3-year exclusivity for approval of NDA 205777 for Targiniq, which contains the two active moieties oxycodone and naloxone, should not block approval of Troxyca, which contains the two active moieties oxycodone and naltrexone.

DAAAP concurs with this recommendation.

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[78] Id.

[79] Id. Emphasis added.

[80] Id.

[81] Id. at 6-7.

[82] The Board's recommendation here that Targiniq's 3-year exclusivity does not block the approval of Troxyca turns on Targiniq and Troxyca having different combinations of active moieties. We therefore do not need to assess the second aspect of the scope inquiry as described in Section I.B. Under the second aspect of the scope inquiry, FDA would need to analyze the conditions of approval supported by the new clinical investigations essential to approval of Targiniq and whether Troxyca was otherwise seeking approval for the exclusivity-protected conditions of approval for Targiniq.

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/s/

DIANA L WALKER
08/19/2016

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08/19/2016