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

DATE: 10/01/2015

TO: Embeda Extended-Release (ER) Capsules (new drug application (NDA) 022321)
MorphaBond ER Tablets (NDA 206544)

FROM: CDER Exclusivity Board

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

SUBJECT: Whether 3-Year Exclusivity for Embeda (Morphine Sulfate /Naltrexone Hydrochloride) ER Capsules (NDA 022321) blocks the approval of MorphaBond (Morphine Sulfate) ER Tablets (NDA 206544)

SUMMARY

This memorandum addresses whether the unexpired 3-year exclusivity for a supplement to the NDA for Embeda ER Capsules (Embeda), a fixed-combination drug product that contains two active ingredients with the following active moieties: morphine and naltrexone (NDA 022321), blocks the initial approval of the 505(b)(2) NDA for MorphaBond ER Tablets (MorphaBond), a single-entity drug with the following active moiety: morphine (NDA 206544).[1]

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 or Division) and other components of FDA, concludes that Embeda's 3-year exclusivity for the change approved in supplement (S-016) to the Embeda NDA is tied to the combination of active moieties in Embeda, and thus recommends that 3-year exclusivity for Embeda should not block the approval of MorphaBond.[2]

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

[2] This memorandum only discusses whether the 3-year exclusivity for Embeda should block the approval of the

I. LEGAL BACKGROUND

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the 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 Embeda and MorphaBond 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 and ANDAs, respectively.[7] The Hatch-Waxman Amendments reflect Congress's efforts to

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MorphaBond NDA, and does not address the scope of Embeda's exclusivity nor whether MorphaBond is eligible for its own period of exclusivity or the scope of any such exclusivity. Because the two active ingredients in Embeda are synthetically produced and each contains only a single active moiety, in the remainder of this memorandum we will refer only to the active moiety of these active ingredients instead of using a more cumbersome phrase (e.g., "a single-entity active ingredient containing [name of active moiety] as an active moiety"). This memorandum does not address naturally derived mixtures which may contain one or more active ingredients each of which may contain more than one active moiety.

[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).

[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),

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]

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

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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)

[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").

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, the 505(b)(2) Draft Guidance, and previous citizen petition responses.[16] 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.[17]

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

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[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, 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).

[17] 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."

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, such as the one at issue here.

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.[18] 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)]."[19] 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.[20] 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 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.[21]

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

[19] 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).

[20] Id. (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).

[21] 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

The Agency's regulations define *new chemical entity* to mean "a drug[22] 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]."[23] *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.[24]

FDA's interpretation of the 5-year NCE exclusivity provisions has focused on the specific chemical structure of the active moiety under consideration;[25] 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.[26] FDA adopted a chemical structure-driven

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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).

[22] 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).

[23] 21 CFR 314.108(a).

[24] Id.

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

[26] A recent district court decision has questioned FDA's interpretation of the 5-year NCE exclusivity provision in the context of a naturally derived mixture containing a new active ingredient with one or more previously approved active moieties. See *Amarin Pharms. Ir. Ltd. v. FDA*, No. 14-cv-00324, 2015 WL 3407061 (D.D.C. May 28, 2015). In the *Amarin* decision, FDA applied its regulation and interpreted the phrase "active ingredient" in the 5-year NCE provision at section 505(c)(3)(E)(ii) to mean "active moiety." Based on this interpretation, FDA had concluded that the active ingredient of the previously approved naturally-derived mixture at issue in that case contained the same active moiety as in Amarin's drug. FDA had further concluded that Amarin's drug was not eligible for 5-year NCE exclusivity. The court held that under the circumstances of that case, the statutory language required FDA to determine whether the active ingredient in Amarin's drug had been previously approved, not whether it contained a previously approved active moiety. See id. The case has been remanded to FDA for proceedings consistent with the opinion and FDA is considering the best means of implementing the court's ruling on remand. Although FDA did not appeal, there is currently a pending motion to intervene in that case, filed by Watson, an ANDA applicant that seeks to appeal the *Amarin Pharms* decision. Also, FDA has not yet issued a decision on remand; thus the scope and effect of the court's ruling have not yet been determined. Given the posture of the *Amarin Pharms* case, until FDA has clarified its interpretation on remand, for ease of reference in this decision, we will interpret the statutory

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 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

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language "active ingredient" to refer to the active moiety or combination of active moieties of the drug products at issue, not the active ingredient or combination of active ingredients. We note that any ultimate decision on the interpretation of the statutory term "active ingredient" at issue in the *Amarin Pharms* case would not affect the result of this decision because Embeda is a drug containing a combination of two active moieties and two active ingredients and thus is a distinctly different drug than MorphaBond which contains only one active moiety and one active ingredient. Thus, the active ingredient/active moiety distinction would not affect the outcome here.

[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).

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

> 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 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) 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. Thus, 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. Another aspect of the scope inquiry focuses on the scope of 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

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[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 . . . .").

[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."

conducted or sponsored by the applicant determines the "conditions of approval" for which certain subsequent applications are barred.[33]

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

[33] 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 Envarsus XR covered "a once-daily, extended-release 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 by Astagraf XL's exclusivity. 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.

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 change approved in the supplement." Although this language is not identical to the phrase "conditions of approval of such drug" 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) may only be made through a new, original application, not a supplement.[34] 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, 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.[35]

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

[34] 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.").

[35] See Fixed Combination NCE Guidance at 8.

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 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 limits 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).[36] 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 II.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 a supplement" to a fixed-combination and is therefore blocked by 3-year exclusivity for the supplement, FDA similarly limits 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 not seeking approval for a fixed-combination with the same combination of active moieties as the combination with exclusivity, it is not seeking approval for a change approved in the supplement and therefore cannot be blocked.

II. FACTUAL BACKGROUND

A. Embeda[37]

Alpharma Pharmaceuticals LLC's (Alpharma's) original NDA for Embeda ER Capsules (NDA 022321) was approved by FDA on August 30, 2009. It is a fixed-combination comprising two

[36] 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.

[37] This section focuses on Embeda's exclusivity since there are no other drugs containing morphine with any remaining exclusivity listed in the Orange Book.

active moieties: morphine (from the active ingredient morphine sulfate) and naltrexone (from the active ingredient naltrexone HCl). Embeda ER capsules contain pellets of morphine sulfate and naltrexone HCL in a 25:1 (or 100:4) ratio.[38]

Morphine is an opioid drug that acts predominantly at the μ-opioid receptor. It is a full agonist, binding with and activating these receptors at sites in the periaqueductal and periventricular grey matter, the ventromedial medulla and the spinal cord to produce analgesia. Apart from its predominant therapeutic effect of analgesia, however, morphine also produces a wide spectrum of pharmacologic effects. These effects include dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered cardiovascular circulatory dynamics, histamine release with pruritis, and physical dependence.[39]

Naltrexone is an opioid antagonist that markedly attenuates or completely blocks the subjective effects of opioids through reversible, competitive binding at μ-opioid receptors. In subjects who are physically dependent on opioids, naltrexone will precipitate withdrawal symptoms.[40]

Embeda is indicated 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. Embeda was approved by FDA as a 505(b)(2) NDA that relied, in part, on FDA's previous finding of safety and effectiveness for a single-entity naltrexone product (Revia), a cross-reference to Alpharma's previously approved single-entity morphine product (Kadian), as well as other studies conducted by Alpharma. Alpharma conducted, among other studies, an adequate and well-controlled efficacy study to demonstrate that the small amount of exposure to naltrexone does not negatively affect the analgesic efficacy of the fixed-combination.[41] In 2009, FDA approved the fixed-combination containing two active moieties as safe and effective. Embeda qualified for 3-year exclusivity upon its initial approval.[42]

Embeda was the first approved morphine-containing product intended by the sponsor to have abuse-deterrent (AD) properties. Embeda is a capsule comprising individual pellets containing morphine sulfate with a sequestered naltrexone HCl inner core and rate controlling excipients. If the intact capsule is ingested orally, morphine is released in a controlled manner to provide pain relief, while the opioid antagonist naltrexone largely remains sequestered. However, crushing, dissolving, or chewing of the capsule or the pellets, will result in the rapid release of morphine

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[38] NDA 022321, Cross Discipline Team Leader (CDTL) Review at 1 (July 16, 2009). See also Embeda Product Labeling approved Oct. 17, 2014.

[39] Morphine has been marketed in the United States since at least 1827 as morphine sulfate, its sulfate salt form; numerous approved injectable and oral formulations (solutions, tablets, ER tablets, ER capsules) of morphine sulfate are currently marketed in the United States under both NDAs and ANDAs.

[40] Naltrexone was first approved as Naltrexone HCl on November 20, 1984 (Revia Tablets; NDA 018932), at which time it received 5-year NCE exclusivity.

[41] Embeda CDTL Review at 3, 6, 7, 10; see also 21 CFR 300.50.

[42] FDA's *Approved Drugs and Therapeutic Equivalence Evaluations* (the Orange Book) listed the exclusivity code for Embeda as "new combination exclusivity".

and naltrexone; the naltrexone reduces the euphoria or "high" associated with the morphine. Alpharma submitted certain studies to support the purported AD properties as part of the original Embeda NDA. Upon approval of the original NDA, Embeda's labeling included a description of certain studies regarding AD properties of Embeda in Section 12.2 (Pharmacodynamics).[43] FDA's reviews of the original Embeda NDA reflect a view that the inclusion of this information was not tantamount to a finding that Embeda had AD properties; consistent with FDA policy at the time, the product labeling included certain caveats as well.[44]

On September 17, 2013, Alpharma submitted a supplement (S-016) to the Embeda NDA (NDA 022321). The supplement included a reanalysis of human abuse potential[45] studies that had been previously submitted in the original NDA in addition to data from other human abuse potential studies of the combination drug that had not been previously submitted. FDA approved S-016 on October 17, 2014. That approval included certain labeling changes, including labeling changes regarding the AD properties of Embeda. FDA concluded at the time that some of these studies qualified for 3-year exclusivity because they were new clinical investigations essential to the approval of the supplement and were conducted by Alpharma. Accordingly, S-016 was granted 3-year exclusivity by FDA which will expire on October 17, 2017.

We are currently evaluating the scope of Embeda's 3-year exclusivity.[46] However, we need not complete that analysis to recommend that Embeda's exclusivity should not block approval of MorphaBond as discussed below.

B. MorphaBond

The NDA for MorphaBond ER Tablets (NDA 206544) was submitted by Inspirion Delivery Technologies LLC (Inspirion) on September 21, 2014. MorphaBond only contains one active ingredient (morphine sulfate) and one active moiety (morphine). MorphaBond ER Tablets include a (b) (4) tablet. 1 Page(s) of Draft Labeling have been Withheld in Full b4 (CCI/TS) which are intended to contribute to AD properties (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[43] See Embeda Labeling approved Aug. 30, 2009

[45] These studies are also referred to as human abuse liability studies.

[46] FDA intends to identify the clinical investigations that can be considered "new" for purposes of exclusivity and to determine the precise scope of changes resulting from those new clinical investigations in light of (1) certain other changes made at the time of approval of S-016, and (2) changes made based on evolving policies regarding labeling for abuse deterrent drugs. These and other factors may help inform an appropriate exclusivity code for Embeda in the Orange Book. We intend to reach a decision on those matters during the ordinary course of making exclusivity decisions in relation to other applications for combinations of morphine and naltrexone as appropriate.

[47] Cross-Discipline Team Leader (CDTL) Review, NDA 206544 (Sept. 15, 2015), at 2.

[redacted] This is intended to maintain the ER characteristics even if the tablet is physically manipulated by crushing [redacted] If the tablet is physically manipulated and placed in liquid, [redacted] becomes highly viscous, thereby reducing the ability to administer it in a syringe.

MorphaBond is indicated 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. The application was submitted pursuant to section 505(b)(2) of the FD&C Act, relying upon the Agency's finding of safety and effectiveness for MS Contin (morphine sulfate) ER Tablets (NDA 019516, approved on May 29, 1987). Inspirion was not required to conduct efficacy trials to support the approval of MorphaBond. Inspirion conducted comparative bioavailability studies to demonstrate that it is scientifically appropriate for the MorphaBond NDA to rely for approval on FDA's finding of safety and effectiveness for the MS Contin NDA; the safety of the product was also supported by data from six clinical pharmacology studies.[48] Inspirion also submitted one human intranasal abuse potential study, which supports labeling providing that "MorphaBond has properties that are expected to reduce abuse or misuse via the intranasal route of administration as the extended-release characteristics were largely maintained even after extensive manipulation of the formulation."[49]

III. DISCUSSION

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

The issue addressed in this memorandum is whether the 3-year exclusivity for Embeda (i.e., a fixed-combination containing two active ingredients with two active moieties) will block the approval of the 505(b)(2) NDA for MorphaBond (i.e., a single-entity drug with one active moiety). We conclude that it should not.

Embeda is a fixed-combination that contains two active ingredients (morphine sulfate and naltrexone hydrochloride), which contain morphine and naltrexone as active moieties. In 2009, at the time of approval of the original NDA for Embeda, FDA determined that no active ingredient (neither morphine sulfate nor naltrexone hydrochloride) contained an active moiety that had not been previously approved, and thus no 5-year NCE exclusivity attached. FDA thus proceeded with determining eligibility for 3-year exclusivity and concluded that 3-year exclusivity attached at that time. As explained in section I.B. above, the conditions of approval of *such drug* necessarily encompassed the particular combination of active moieties in Embeda for which the application was submitted and for which new clinical investigations were essential. That exclusivity expired in August 2012.

Subsequently, Alpharma submitted S-016 and received approval of that supplement in 2014. FDA concluded at that time that S-016 included some new clinical investigations essential to the

[48] The clinical pharmacology studies were conducted in normal volunteers who were naltrexone-blocked.

[49] MorphaBond Product Labeling, Section 9.2 Summary.

approval of the supplement and otherwise qualified for 3-year exclusivity. The change approved in the supplement (S-016) for Embeda is the change in conditions of approval for the drug containing the combination of active moieties approved in the Embeda NDA. Thus, the change approved in the supplement only bars approval of other 505(b)(2) NDAs for drugs containing the combination of active moieties approved in Embeda and that otherwise seek approval for the same exclusivity-protected conditions of approval as Embeda. Because MorphaBond does not contain the combination of active moieties approved in Embeda, any approval of MorphaBond is not an approval for the "change approved in the supplement" (i.e., S-016) for which Embeda currently has exclusivity and no additional inquiry is required. Therefore, we recommend that the exclusivity awarded to Embeda for S-016 should not block approval of MorphaBond.[50]

B. The Board's Recommendation that Embeda's 3-Year Exclusivity Should Not Block Approval of MorphaBond Is Consistent with FDA Regulations, Embeda Approval, Policy, Congressional Intent and Other FDA Actions

The Board's recommendation that 3-year exclusivity for Embeda should not block approval of MorphaBond is consistent with the Agency's regulations regarding fixed-combination products and with the approval of the Embeda NDA and supplement (S-016). 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.[51] 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 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."[52]

Embeda is one of these special cases. Embeda was approved as a 505(b)(2) application that relied, in part, on a cross-reference to the application for a previously approved single-entity morphine product (Kadian) and on the Agency's finding of safety and effectiveness for a single-entity naltrexone product (Revia). For the initial approval of Embeda, 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 morphine and naltrexone alone. Rather, the sponsor needed to conduct an adequate and well-controlled efficacy study to demonstrate that the exposure to a small amount of naltrexone does not negatively affect the analgesic efficacy of the morphine in the fixed-combination.[53] FDA's decision to require this study demonstrates that in

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[50] If both Embeda and MorphaBond contained the same combination of the two active moieties morphine and naltrexone, we would need to evaluate the nature of the change approved in the NDA supplement and would need to determine which new clinical investigations were essential to approval of S-016. We need not reach this aspect of the scope of inquiry here, however, because Embeda and MorphaBond do not contain the same combination of active moieties. Rather, Embeda contains a combination of two active moieties, a characteristic that distinguishes it from MorphaBond, which contains only a single active moiety.

[51] See 21 CFR 300.50.

[52] 21 CFR 300.50 (a)(2).

[53] Embeda CDTL Review at 3, 6, 7, 10.

this case the Agency evaluated the efficacy of the drug as a whole, i.e., as a fixed-combination containing two active moieties, in addition to evaluating the data or findings of safety and effectiveness derived from studies of morphine and naltrexone individually.

Similarly, in supplement S-016, the investigations regarding Embeda's AD properties showed that the presence of naltrexone in the combination reduces the potential for abuse of morphine. Both components are therefore integral to the safety and effectiveness of Embeda and it follows that the conditions of approval for Embeda necessarily include the fact that it contains the combination of morphine and naltrexone. This is consistent with FDA's conclusion that the change approved in S-016 supported by new clinical investigations relates to the combination of active moieties; and, consequently, any 3-year exclusivity for Embeda cannot block approval of a drug with only one of the active moieties present in Embeda.[54]

The Board's recommendation in this case is also consistent with the Agency's efforts to foster the development of AD opioid products more generally.[55] Because the science of abuse deterrence is still evolving and the Agency does not yet know which AD technologies will ultimately prove most effective in deterring opioid abuse, the Agency believes that, when the statute and regulations permit it, it is in the interest of public health to encourage development of multiple AD alternatives.[56]

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 there were new clinical investigations essential to approval against approval of drugs with the same combination of active moieties for the same exclusivity-protected use. 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 a use that was not supported by the new clinical investigations essential to approval. It therefore promotes and protects innovation while also encouraging the development of alternative therapies.

[54] The Board's conclusion that the change approved in S-016 supported by new clinical investigations relates to the combination of active moieties is also consistent with FDA's bundling policy for applications. See FDA's Bundling Guidance. That is, any change to a combination of active moieties, including the removal of one moiety in the fixed-combination, would not be permitted in a supplement to an NDA and, instead, would require a new NDA. Thus, any change approved in a supplement would necessarily attach to the combination of active moieties in the fixed-combination.

[55] See FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling, at 2 (Apr. 2015).

[56] See id at 2-3.

IV. CONCLUSION

For all of these reasons, the Board recommends that the 3-year exclusivity for approval of S-016 for Embeda, which contains two active moieties, morphine and naltrexone, should not block approval of MorphaBond, which contains morphine as its single active moiety.

DAAAP concurs with this recommendation.

APPEARS THIS WAY ON ORIGINAL

Sanjay Sitlani -A

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/s/

CHRISTOPHER M HILFIGER
10/02/2015

SHARON H HERTZ
10/02/2015
I concur.