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

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TO: MorphaBond (morphine sulfate) extended-release tablets file (NDA 206544)

FROM: CDER Exclusivity Board

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

SUBJECT: Scope of 3-Year Exclusivity for MorphaBond (NDA 206544)

SUMMARY

MorphaBond (morphine sulfate) extended-release (ER) tablets (MorphaBond) is the first FDA-approved, single-entity morphine product with claims in the labeling related to deterring abuse via the intranasal and intravenous routes.[1] New drug application (NDA) 206544 for MorphaBond was approved on October 2, 2015. The only clinical investigation (other than bioavailability studies) submitted in MorphaBond's NDA was a human abuse liability (HAL) study (Study M-ARER-002), which assessed the drug's abuse potential by the intranasal route of administration. Based on this HAL study, MorphaBond was approved with labeling that describes certain properties of the product that are expected to reduce abuse by the intranasal route.

In light of a pending action for an application for another morphine sulfate ER tablet product with AD claims in the proposed labeling,[2] the Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER) is assessing the scope of 3-year exclusivity for MorphaBond resulting from Study M-ARER-002 to determine the effect of its exclusivity on the approval of the subsequent application. FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) has not been updated to include a description of MorphaBond's

[1] NDA 206544 Division Director Review (Oct. 2, 2015) (Division Director Review), at 2.
[2] NDA 208603 for Arymo (morphine sulfate) ER tablets was submitted on December 14, 2015.

exclusivity; the Orange Book currently states that, "There is no unexpired exclusivity for this product in the Orange Book database."[3]

This memorandum describes the scope of MorphaBond's 3-year exclusivity. The Board, in consultation with CDER's Division of Anesthesia, Analgesia, and Addiction Products (DAAAP or Division) and other components of FDA, concludes that the scope of MorphaBond's exclusivity is labeling describing the expected reduction of abuse of single-entity ER morphine by the intranasal route of administration due to physicochemical properties.[4] This memorandum will use the term, "labeling describing intranasal AD properties," as a shorthand description of this scope. MorphaBond's exclusivity will expire on October 2, 2018, 3 years after the date of the original approval. The Board recommends that the Orange Book be amended to describe the exclusivity code for MorphaBond as: "M-XXX, labeling describing the expected reduction of abuse of single-entity extended-release morphine by the intranasal route of administration due to physicochemical properties."[5]

A discussion of the Board's rationale follows.

I. LEGAL AND REGULATORY 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 MorphaBond is a 505(b)(2) application, 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.[6] 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*.

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[3] *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, available at http://www.accessdata.fda.gov/scripts/cder/ob/.

[4] For purposes of this memorandum, the terms "physicochemical properties" and "physical/chemical barriers" are used interchangeably.

[5] The Board notes generally that the scope of exclusivity should be determined by the nature of the clinical studies done to gain approval of the NDA, not by the exclusivity code that is used as shorthand to describe that approval in the Orange Book.

[6] 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.

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, and it meets other applicable requirements.[7] 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.[8]

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

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[9] 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.[10] 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.[11] 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.[12]

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.[13] 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

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

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

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

[10] 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.

[11] 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.

[12] 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).

[13] 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."

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.[14]

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity (NCE),[15] and, in some instances, may describe a drug product with substantial differences from a listed drug.[16] 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*[17] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability[18] 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.[19] 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

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[14] 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)

[15] 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").

[16] 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.

[17] 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.

[18] 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.

[19] 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).

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.[20]

B. Three-Year Exclusivity Under the FD&C Act

An application for a drug containing a previously approved active moiety is generally eligible for 3 years of exclusivity if the statutory and regulatory standards are satisfied. The availability of a 3-year exclusivity period for an NDA is described in sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act. 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. The statute states:

> *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.[21]

The first clause (italicized) in section 505(c)(3)(E)(iii) of the FD&C Act, often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. 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")[22] are eligible for 3-year exclusivity if they include new clinical investigations

[20] 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."

[21] 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 . . . .").

[22] The longest and most protective period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity. See section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act. A 5-year exclusivity period is

(other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant.

The second clause in section 505(c)(3)(E)(iii) of the FD&C Act (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 steps. One step 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. The second step 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 conducted or sponsored by the applicant determines the "conditions of approval" for which certain subsequent applications are barred.

Although neither the statute nor the regulations defines the phrase *conditions of approval* for purposes of determining the scope of 3-year exclusivity,[23] the preamble to FDA's proposed rule governing exclusivity (1989 Proposed Rule)[24] provides the Agency's interpretation. It makes clear FDA's view that 3-year exclusivity covers the innovative change that is supported by the new clinical investigations:

> Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.[25]

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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)]." 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. Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

[23] 21 CFR 314.108(a) and 314.108 (b)(4)(iv).

[24] See generally, Abbreviated New Drug Application Regulations, 54 FR 28872 (July 10, 1989) (1989 Proposed Rule).

[25] 1989 Proposed Rule at 28896-97.

FDA thus interprets the scope of exclusivity to be related to the scope of the underlying *new clinical investigations* that were essential to the approval. Exclusivity does not extend beyond the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential. Courts have upheld FDA's view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year exclusivity.[26]

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).

FDA's regulation on 3-year exclusivity mirrors the statutory framework.[27] In this regulation, FDA defined *clinical investigation* as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects."[28] The Agency defined *new clinical investigation*, in relevant part, 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."[29] *Essential to approval* is defined as "with regard to an investigation, that there are no other data available that could support approval of the NDA."[30] Finally, the regulations define *conducted or sponsored by the applicant*, in relevant part, as "that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the

[26] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 115-24 (D.D.C. 2015); *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement'"); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) ("[T]he Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . ."). Although the latter two cases involved the parallel statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.
[27] 21 CFR 314.108(b)(4).
[28] 21 CFR 314.108(a).
[29] Id.
[30] Id.

applicant or the applicant's predecessor in interest, provided substantial support for the investigation."[31]

C. Labeling of Abuse-Deterrent Opioids

On January 24, 2006, FDA published a final rule describing the "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," which revised the content and format requirements to make labeling easier to access, read, and use.[32] This final rule is commonly referred to as the Physician Labeling Rule (PLR). PLR format refers to labeling that meets the content and format requirements at 21 CFR §§ 201.56(d) and 201.57.

Section 9 of the labeling under PLR describes information on the drug's abuse and dependence, as appropriate.[33] Relevant here, section 9.2 of the labeling "must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used."[34]

In April 2015, the Agency issued *Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling* (AD Opioids Guidance), which is intended to assist industry in developing new formulations of opioid drugs with AD properties.[35] Among other things, the AD Opioids Guidance explains the Agency's current thinking on including information in a drug's labeling on its AD properties based on premarket studies.

The Agency recommends that a sponsor's development program generally include three types of premarket studies to evaluate the AD properties of an opioid product:

- Laboratory-based in vitro manipulation and extraction studies (Category 1), "to evaluate the ease with which the potentially [AD] properties of a formulation can be defeated or compromised;"[36]
- Pharmacokinetic studies (Category 2), "to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration;"[37]

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[31] Id.
[32] 71 Fed. Reg. 3922.
[33] 21 CFR 201.57(c)(10).
[34] 21 CFR 201.57(c)(10)(ii).
[35] FDA, Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling, (April 2015), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf. The guidance is intended to assist sponsors who wish to develop opioid drug products with potential AD properties, and describes the categories of premarket studies a sponsor should conduct to seek inclusion of information on a product's AD properties.
[36] Id. at 6.
[37] Id. at 8.

- Clinical abuse potential studies (also referred to HAL studies) (Category 3), for assessing the impact of potentially AD properties.[38]

FDA advises sponsors to propose labeling that sets forth the results of Category 1, 2, and 3 studies (and any postmarket studies (Category 4), if available) and appropriately characterize the AD properties of the product.[39] Information on AD properties should be described in Section 9.2 of the proposed labeling. Labeling regarding abuse deterrence should describe the product's specific AD properties and the specific routes of abuse that the product has been developed to deter.[40] Specific recommendations on how to describe the results of the premarket studies are found in Section VI of the AD Opioids Guidance.

The AD Opioids Guidance also lists the seven categories of current AD formulations, including Physical/Chemical Barriers, described below:

> Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.[41]

II. FACTUAL BACKGROUND

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 pruritus, and physical dependence. Morphine has been marketed in the United States since at least 1832 as morphine sulfate, its sulfate salt form.[42,43] An extended-release tablet form of morphine sulfate has been approved since 1987 in the approval of MS Contin (NDA 019516). MS Contin is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time, and is approved in the following strengths of ER morphine sulfate: 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg.

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[38] Id. at 9.
[39] Id. at 22.
[40] Id.
[41] AD Opioids Guidance at 3.
[42] See E. Kremer and G. Sonnendecker, *Kremers and Urdang's History of Pharmacy*, 4th ed., American Institute of the History of Pharmacy (1976), at 327; P. Gahlinger, *Illegal Drugs: A Complete Guide to their History, Chemistry, Use and Abuse*, Penguin Books (2004), at 25-26.
[43] 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 abbreviated new drug applications (ANDAs).

On September 21, 2014, Inspirion Delivery Technologies LLC (Inspirion) submitted NDA 206544 for MorphaBond (morphine sulfate) ER tablets.[44] The MorphaBond application was submitted pursuant to section 505(b)(2) of the FD&C Act, relying on the Agency's finding of safety and effectiveness for MS Contin. Inspirion established a bridge between MorphaBond and MS Contin by comparative bioavailability studies, demonstrating that reliance on MS Contin was scientifically justified for the approval of MorphaBond.[45] The company sought approval of MorphaBond for the same indication and strengths as MS Contin, except for the 200 mg strength. Because Inspirion sought approval of a product (MorphaBond) that was the same as MS Contin with respect to active ingredient, dosage form, route of administration, strengths, indication, and dosing recommendations, and was demonstrated to be bioequivalent to MS Contin, Inspirion was not required to conduct clinical investigations (other than bioavailability studies) to support the safety and effectiveness of its product.

Unlike the MS Contin applicant, however, Inspirion sought approval of claims in MorphaBond's labeling describing AD potential derived from the drug product's physicochemical properties.[46] Consistent with the AD Opioids Guidance,[47] Inspirion conducted several Category 1 (in vitro manipulation and extraction) studies to evaluate the ease with which the product's physical/chemical barriers can be defeated or compromised.[48] The studies showed that MorphaBond could be ground into a fine powder with only a coffee grinder, but not two spoons, a pill crusher, a mortar and pestle, a hammer, a knife, or a cheese grater, while MS Contin tablets were easy to crush into a fine powder using any tool.[49] The studies also showed that it was not possible to obtain a sufficient amount of morphine sulfate in solution that could be aspirated into a syringe from intact, ground, or cut MorphaBond for abuse by the intravenous route of administration, in contrast to the relative ease of doing so with MS Contin.[50]

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[44] Throughout the summary basis of approval, MorphaBond is referred to as either "Morphine ARER" (Abuse Resistant Extended Release) or "IDT-001".

[45] 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 and effectiveness of MorphaBond was supported by data from six clinical pharmacology studies. See NDA 206544 Clinical Review (Aug. 19, 2015) (Clinical Review), at 8, 22-23.

[46] MorphaBond includes an (b) (4), all of which are intended to contribute to AD properties. Specifically, the compressed core tablet is comprised of excipients that (b) (4)

The (b) (4)

NDA 206544 Cross-Discipline Team Leader (CDTL) Review (Sept. 15, 2015), at 2. As explained in section III, however, the Board does not believe that the scope of MorphaBond's exclusivity is defined by the specific formulation or specific technology used to deter abuse.

[47] AD Opioids Guidance at 6-8.

[48] Division Director Review at 13.

[49] Id.

[50] Id. at 14-15.

Additionally, Inspirion submitted one combined Category 2/3 (pharmacokinetic and HAL) study evaluating the drug's abuse potential by the intranasal (IN) route (Study M-ARER-002).[51] Study M-ARER-002 was a double-blind, double-dummy, 4-way crossover study, conducted in non-dependent recreational opioid users to investigate the AD properties of MorphaBond following nasal administration of crushed MorphaBond. The primary objective of the study was to determine the abuse potential of crushed MorphaBond, 60 mg, administered intranasally and intact MorphaBond, 60 mg, administered orally, both relative to crushed MS Contin, 60 mg, administered intranasally.[52] The intact oral tablets were included as a reference for evaluating abuse potential after manipulation and administration via the intranasal route. The primary analysis was a comparison of Drug Liking visual analog scales (VAS) between IN crushed MorphaBond and IN crushed MS Contin.

Study M-ARER-002 demonstrated that IN administration of crushed MorphaBond resulted in a substantially lower response to Drug Liking, High, and Take Drug Again, compared to crushed MS Contin.[53] The responses to crushed and intact oral MorphaBond were very similar (see Appendix A for labeling describing the study results). According to the Division Director Review, "the results of the in vitro assessments of syringeability and low volume extraction, and the results of the intranasal human abuse liability study demonstrate that MorphaBond has characteristics that are likely to deter intravenous and intranasal abuse as compared to MS Contin."[54] A description of the AD properties demonstrated by the in vitro and HAL studies is included in Section 9.2 of the MorphaBond labeling (see Appendix A).[55]

MorphaBond was approved on October 2, 2015, as the first single-entity ER morphine product with labeling describing intranasal and intravenous AD properties.[56] The Exclusivity Summary lists Study M-ARER-002 as the only new clinical investigation essential to approval of MorphaBond's application.[57]

III. DISCUSSION

An application for a drug containing a previously approved active moiety is eligible for 3-year exclusivity if the approval of the application is supported by at least one (1) new (2) clinical investigation (other than a bioavailability study) (3) that is conducted or sponsored by the applicant and is (4) essential to the approval of the application.[58] Study M-ARER-002 is the only clinical investigation in the MorphaBond application that meets this standard.[59] Study M-

[51] Id. at 15.
[52] CDTL Review at 22-23.
[53] Division Director Review at 20.
[54] Id.
[55] MorphaBond Prescribing Information (Oct. 2, 2015), Section 9.2 Abuse, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206544lbl.pdf.
[56] See id., Section 9.2 Abuse ("The data from the clinical study, along with support from in vitro data, also indicate that MORPHABOND has physicochemical properties that are expected to reduce abuse by the intranasal route of administration.").
[57] See NDA 206544 MorphaBond Exclusivity Summary (Oct. 2, 2015) (Exclusivity Summary).
[58] The approval of an NDA or supplement to an NDA includes approval of labeling submitted in the NDA or supplement. 21 CFR 314.50.
[59] See Exclusivity Summary.

ARER-002 is considered a new clinical investigation under 21 CFR 314.108(a) because it has not been previously relied upon by the Agency to support approval of an application. The study is considered a clinical investigation under this regulation because it is an experiment other than a bioavailability study[60] in which drug products (MorphaBond and MS Contin) were administered or dispensed to human subjects. Study M-ARER-002 was "essential to approval" of the MorphaBond application within the meaning of 21 CFR 314.108 because, as described above, the study demonstrated that MorphaBond has physicochemical properties that are expected to reduce abuse by the intranasal route of administration as described in the product's labeling, and there are no other data available that could support labeling describing deterrence of abuse by this route. Finally, Inspirion is the sponsor of Study M-ARER-002.[61] Thus, MorphaBond is eligible for 3-year exclusivity on the basis of Study M-ARER-002, submitted to support the approval of the MorphaBond NDA.[62]

As explained in Section I, FDA interprets the scope of exclusivity to be related to the scope of the underlying new clinical investigations that are essential to the approval of the application (or supplement). Exclusivity does not extend beyond the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential. Here, Study M-ARER-002, the only clinical investigation that is not a bioavailability study, demonstrated that MorphaBond could be labeled with an abuse deterrence claim related to intranasal abuse under the principles described in the AD Opioids Guidance. The study demonstrated that, as a result of physicochemical properties affecting the crushability of MorphaBond, intranasal administration of crushed MorphaBond resulted in a substantially lower response to Drug Liking, High, and Take Drug Again measures, compared to crushed MS Contin. Based on Study M-ARER-002, MorphaBond became the first single-entity ER morphine product approved with labeling describing intranasal AD properties. Accordingly, the scope of Morphabond's exclusivity is limited to the condition of approval supported by Study M-ARER-002: labeling describing the expected reduction of abuse of a single-entity ER morphine by the intranasal route of administration due to physicochemical properties. We describe below the reasons for adopting this approach.

Although neither the regulation, nor the preambles to the 1989 Proposed Rule or the final rule governing exclusivity[63] expressly contemplated how exclusivity would be determined for AD opioids, the preamble to the 1989 Proposed Rule states that, "[i]f the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration."[64] The Board believes that the circumstances of the MorphaBond

[60] Although Study M-ARER-002 measured the pharmacokinetic profile of morphine sulfate following intranasal administration, as described above, the study also measured certain "drug liking" scores. Because the study featured a clinical endpoint intended to measure abuse potential, FDA does not consider it to be a "bioavailability study" within the meaning of section 505(c)(3)(E)(iii) and 21 CFR 314.108(a).

[61] See Exclusivity Summary, confirming that Inspirion was named in Form FDA-1571 filed with FDA as the sponsor of Study M-ARER-002.

[62] As described in Section II, claims for abuse deterrence via the intravenous route in MorphaBond's labeling were supported by several Category 1 (in vitro manipulation and extraction) studies, which are not clinical studies that are eligible for consideration for 3-year exclusivity.

[63] Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 FR 50338, at 50358 (Oct. 3, 1994).

[64] 1989 Proposed Rule, at 28896-97.

approval, while not the same, may be analogized to the approval of a "new use" where the Agency represents in approved labeling its finding that a drug product, for example, is safe and effective to treat a new indication. Similarly, in this instance, approved labeling for MorphaBond represents the Agency's finding that MorphaBond is expected to reduce abuse of single-entity ER morphine by the intranasal route of administration due to physicochemical properties.[65] Accordingly, the Board believes that the exclusivity for MorphaBond should protect labeling describing this claim.[66]

This scope of exclusivity is defined by two primary characteristics: (1) the abuse route (intranasal); and (2) the type of abuse deterrence employed (physicochemical properties). The Board notes that these characteristics are consistent with concepts discussed in the AD Opioids Guidance, which describes the categories of AD products (e.g., physical/chemical barriers, antagonist) and types of abuse routes (e.g., intranasal, intravenous, oral).[67] The Board believes that this scope of exclusivity is also consistent with the applicable statutory and regulatory provisions, and it balances the goals of the Hatch-Waxman Amendments' 3-year exclusivity provisions.

We note that the statute does not expressly describe the scope of exclusivity for 3-year exclusivity, providing FDA discretion to make exclusivity determinations in a manner consistent with the statutory language and intent of Congress. In making its determination that the scope of exclusivity in this instance should be defined as described above, the Board nonetheless considered but declined to adopt both broader and narrower potential approaches to the scope of exclusivity.

A broader scope of exclusivity (for example, one covering abuse deterrence generally) would be inconsistent with the scope of Study M-ARER-002, which was intended only to measure the ability to deter abuse of single-entity ER morphine via the intranasal route due to the drug's physicochemical properties. Likewise, this broader approach to exclusivity would be

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[65] We note that in some cases the Agency has described and represented the scope of exclusivity for a new use (e.g., a new indication) as being the use of the drug for that indication. Some Orange Book exclusivity codes also mirror this practice, while others have expressly described the scope of exclusivity as being related to labeling. *See* Exclusivity Codes and Definitions, http://www.accessdata fda.gov/scripts/cder/ob/results_exclusivity.cfm (defining, for example, code I-91 as "MONOTHERAPY USE FOR HYPERTENSION" and code I-713 as "REVISIONS TO THE LABELING TO PERMIT THE USE OF ZUBSOLV AS INITIAL ('INDUCTION') TREATMENT OF OPIOID DEPENDENCE."). Irrespective of how the exclusivity code is worded, however, FDA generally gives effect to exclusivity for a new use by considering the labeling claim regarding that use to be protected by exclusivity. 1989 Proposed Rule, at 28896-97. Thus, the agency does not have a consistent practice regarding the description of the scope of exclusivity for new uses; given the novel issues regarding AD properties described in labeling, the agency believes the approach outlined in the text is reasonable and appropriate.

[66] We note, however, that even if the scope of exclusivity were found to protect the intranasal AD properties, rather than labeling describing those properties, a subsequent ER morphine sulfate drug product might still be eligible for approval to the extent it sought approval for non-protected conditions of approval. See Letter from R. Albrecht, FDA to M. McGuiness, Veloxis Pharmaceuticals, Inc., at 39-43 (Jan. 12, 2015) (concluding that a scope of exclusivity for Astagraf XL did not block approval of a once-daily dosage form of tacrolimus for a population for which Astagraf XL did not obtain approval).

[67] See AD Opioids Guidance, at 3-4 (description of physical/chemical barriers); id.at 22 ("Labeling language regarding abuse deterrence should describe the product's specific abuse deterrent properties as well as the specific routes of abuse that the product has been developed to deter").

inconsistent with the MorphaBond labeling, which (consistent with the AD Opioids Guidance) describes the specific AD properties and the specific routes of abuse that the product has been demonstrated to deter.[68]

A narrower approach to the scope of exclusivity – for example, exclusivity limited to the specific formulation in MorphaBond, or the specific technology MorphaBond uses to deter intranasal abuse – would be inappropriate in this circumstance.[69] As noted above, this approach to exclusivity is not compelled by the statute: FDA generally has taken the position that exclusivity-protected "conditions of approval" may nevertheless overlap between drugs despite certain differences in formulation or other aspects.[70] Thus, FDA has recognized that the scope of exclusivity for the innovation(s) represented by the approval and supported by clinical studies may reach beyond the specific formulation of the drug product approved in an application or supplement.

Importantly, the Board believes that a specific-formulation or specific-technology scope of exclusivity would be inconsistent with the scope of Study M-ARER-002. In this case, Study M-ARER-002 supported approval of MorphaBond as the first single-entity ER morphine product with labeling describing intranasal AD properties. Thus, the labeling describing the expected reduction of abuse of single-entity ER morphine by the intranasal route of administration due to physicochemical properties is the "innovation"[71] represented by the approval of MorphaBond and supported by a new clinical investigation (Study M-ARER-002, the only clinical investigation (that is not a bioavailability study) submitted to MorphaBond's NDA). In addition, a narrow specific-formulation or specific-technology scope of exclusivity potentially would have a very limited effect on subsequent 505(b)(2) applications and ANDAs (which might propose different formulations and excipients than MorphaBond), potentially undermining the purpose of 3-year exclusivity.[72]

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[68] See supra note 55, MorphaBond Prescribing Information, Section 9.2 Abuse ("The data from the clinical study, along with support from in vitro data, also indicate that MORPHABOND has physicochemical properties that are expected to reduce abuse by the intranasal route of administration.").

[69] The Board previously considered the scope of exclusivity recognized for NDA 022272/S-14 requesting approval of labeling describing AD properties of reformulated OxyContin. Although the Board drafted a memorandum and recommendation for the scope of exclusivity of OxyContin, no ANDA or 505(b)(2) application potentially affected by this exclusivity was ready for final approval during the exclusivity period. Further, the Board's thinking on the issues related to 3-year exclusivity for AD opioids has evolved as reflected in this memorandum.

[70] Letter from R. Albrecht, FDA to M. McGuiness, Veloxis Pharmaceuticals, Inc., at 32-36 (Jan. 12, 2015). In *Zeneca Inc. v. Shalala*, WMN-99-307, 1999 U.S. Dist. LEXIS 12327, at *38-39 (D. Md. Aug. 11, 1999), the court noted that FDA granted exclusivity to the plaintiff for addition of a specific preservative to the drug at issue, and not preservatives generally. The rationale for doing so in that case was that the supportive clinical studies were necessitated by specific concerns related to that specific preservative. This narrower scope of exclusivity was limited to the addition of a specific excipient because the studies that support exclusivity were intended to support the safety of that excipient.

[71] 1989 Proposed Rule, at 28896-97.

[72] Although not at issue here, the Board notes that, if a second product is approved and otherwise meets the requirements for 3-year exclusivity, the scope of exclusivity for such a product with labeling describing intranasal AD properties might be narrower than MorphaBond's exclusivity. In assessing such a product, FDA would analyze the nature of the innovation represented by the subsequent approval, applying the requirements of 21 CFR 314.108 and the principles described in this memorandum.

IV. CONCLUSION

For the reasons described above, the Board recommends that the scope of MorphaBond's exclusivity is labeling describing the expected reduction of abuse of single-entity extended-release morphine by the intranasal route of administration due to physicochemical properties. MorphaBond's exclusivity expires 3 years after the original approval of the application, on October 2, 2018. The Board recommends that the Orange Book be amended to include the exclusivity code for MorphaBond as: "M-XXX, labeling describing the expected reduction of abuse of single-entity extended-release morphine by the intranasal route of administration due to physicochemical properties."

DAAAP concurs with this recommendation.

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Sanjay Sitlani -A

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