

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206544Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206544

SUPPL #

HFD # 170

Trade Name MorphaBond

Generic Name morphine sulfate extended-release tablets

Applicant Name INSPIRION DELIVERY TECHNOLOGIES, LLC (IDT)

Approval Date, If Known September 21, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 019516

MS Contin and multiple NDAs and ANDAs, multiple various dosage forms listed in the Orange Book

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1

Study M-ARER-002, a single-center, randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover study to investigate the human abuse-liability of Morphabond

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support

the effectiveness of a previously approved drug product?

Investigation #1 YES NO
Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study M-ARER-002, a single-center, randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover study to investigate the human abuse-liability of Morphabond

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 115822 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Director, DAAAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CHRISTOPHER M HILFIGER
10/02/2015

SHARON H HERTZ
10/02/2015

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

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

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

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 bioavailability¹⁵ 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

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

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 drug²² 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

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

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

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 bioavailability [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. Embeda³⁷

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

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 potential⁴⁵ 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 (b) (4) which are intended to contribute to AD properties. Withh l d i F ll b4 (CCI/TS) (b) (4)

⁴³ See Embeda Labeling approved Aug. 30, 2009. (b) (4)

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.

(b) (4) (b) (4)
(b) (4) This is intended to maintain the ER characteristics even if the tablet is physically manipulated by crushing (b) (4) If the tablet is physically manipulated and placed in liquid, (b) (4) 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

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 Digitally signed by Sanjay Sitlani A
DN: c US, o U S Government ou HHS
ou FDA ou People on Sanjay Sitlani A
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Date: 2015.10.02.12:16:56 -0400

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

/s/

CHRISTOPHER M HILFIGER
10/02/2015

SHARON H HERTZ
10/02/2015
I concur.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206544 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: MorphaBond Established/Proper Name: morphine sulfate extended-release Dosage Form: tablets		Applicant: INSPIRION DELIVERY TECHNOLOGIES LLC Agent for Applicant (if applicable):
RPM: Christopher Hilfiger		Division: DAAAP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>9/21/2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 9/21/2015
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	04/02/2015 03/16/2015
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None 3/17/2015 DMPP/PLT (DRISK): <input type="checkbox"/> None 09/04/2015 OPDP: <input type="checkbox"/> None 09/11/2015 SEALD: <input type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 09/14/2015
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Morphine ARER is not a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, IDT is exempt from the requirement for an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients under the Pediatric Research Equity Act (PREA) (21 USC 355c).	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 2, 2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	08/19/2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Pg.17 of the clinical review dated 08/19/2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A 07/17/2015
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 07/28/2015
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/16/2015
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested 04/07/2015

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 09/02/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/16/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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

/s/

CHRISTOPHER M HILFIGER
10/07/2015



NDA 206544

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Inspirion Delivery Technologies, LLC
c/o Cardinal Health Regulatory Sciences
7400 West 110th Street
Commerce Plaza II, Suite 300
Overland Park, KS 66210

ATTENTION: Debra Aub Webster, Ph.D.
Director, Executive Consultant

Dear Dr. Webster:

Please refer to your New Drug Application (NDA) dated and received November 21, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended-release Tablets, 15mg, 30 mg, 60 mg, and 100 mg.

We also refer to your correspondence, dated and received January 29, 2015, requesting review of your proposed proprietary name, Morhabond.

We have completed our review of the proposed proprietary name, Morhabond and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 29, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. For any other information regarding this application, contact Christopher Hilfiger, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

TODD D BRIDGES
04/02/2015

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, January 15, 2015 10:15 AM
To: Webster, Debra
Subject: RE: NDA 206544 Information request

Received and sent to the reviewers. Thank you for your reply.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Thursday, January 15, 2015 9:38 AM
To: Hilfiger, Christopher
Subject: FW: NDA 206544 Information request

Dear Chris,
Could you please confirm receipt of the email below that I sent yesterday?
Thank you.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile
debra.webster@Cardinalhealth.com

From: Webster, Debra
Sent: Wednesday, January 14, 2015 8:31 AM
To: 'Hilfiger, Christopher'
Subject: RE: NDA 206544 Information request

Dear Chris,
Thank you for your email.

Regarding the oral liking study (M-ARER-003), as indicated in section 2.2 of the NDA 206544, the protocol for this study is being revised and the study has not yet initiated.

The Pharmacy Manual for study M-ARER-002 can be found on page 140 of Appendix 16.1.1 Protocol or Amendment in Section 5.3.4.1 of the NDA under the M-ARER-002 leaf.

As requested by Vaishali Jarral of DMEPA, we are planning on submitting to the NDA the Request for Review of Proprietary Name with the conditionally approved proprietary name, MorphaBond and revised labels and labeling, in the last week of January.

Please let me know if this email is a sufficient response or I need to submit this formally to the NDA.

If there is anything else you need please let me know.

Thank you.

Regards,

Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax [REDACTED] ^{(b) (6)} mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Tuesday, January 13, 2015 10:02 AM
To: Webster, Debra
Subject: NDA 206544 Information request

Dear Dr. Aub Webster,

I have the following information requests for you:

1. We had provided guidance in the past regarding the conduct of oral liking study (M-ARER-003) IDT's Morphine Sulfate ARER tablet. We notice that the results of this study M-ARER-003 were not submitted to the NDA. Provide information on the status of this study (completed, discontinued, etc.).
2. Provide the pharmacy manual from Inspirion for the intranasal HAP study M-ARER-002 under NDA 206544 (IND [REDACTED] ^{(b) (4)}).

Sincerely,
Christopher Hilfiger
Regulatory Project Manager

Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Friday, February 06, 2015 11:52 AM
To: Webster, Debra
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond)
Attachments: No Filing Review Issues Identified (COR-NDAFILE-05)(COR-SNDAFILE-05)(COR-BLAFI-05)(COR-SBLAFI-05).pdf - Adobe Acrobat Pro.pdf

Sorry for the delay, I have been very busy.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Friday, February 06, 2015 11:35 AM
To: Hilfiger, Christopher
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond)

Hi Chris,
I am trying to plan for coverage during some upcoming travel. Can you give me an indication of when we might expect the 74-day letter? We had anticipated receiving this on February 3.
If you could please let me know that you received this email it would be most appreciated.

Thank you!

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile
debra.webster@Cardinalhealth.com

From: Webster, Debra
Sent: Wednesday, February 04, 2015 8:40 AM

To: Hilfiger, Christopher (Christopher.Hilfiger@fda.hhs.gov)
Subject: IDT NDA 206544 Morphine ARER (MorphaBond)

Hi Chris,
Just touching base to see when we can expect the 74-day letter regarding IDT's NDA that was submitted November 21, 2014. By our calculations we were expecting this yesterday.
Can you please confirm when we receive the FDA's response?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile
debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Monday, February 09, 2015 10:45 AM
To: Webster, Debra
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond)

Dear Debra,

See section 9.2 of the label below.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022321s016lbl.pdf

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Hilfiger, Christopher
Sent: Friday, February 06, 2015 11:52 AM
To: 'Webster, Debra'
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond)

Sorry for the delay, I have been very busy.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Friday, February 06, 2015 11:35 AM
To: Hilfiger, Christopher
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond)

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Thank you!

Regards,

Debra



Debra Aub Webster, PhD

Director, Executive Consultant

Regulatory Sciences

Specialty Solutions

7400 W 110th St, Suite 300, Overland Park, KS 66210

913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile

debra.webster@Cardinalhealth.com

From: Webster, Debra

Sent: Wednesday, February 04, 2015 8:40 AM

To: Hilfiger, Christopher (Christopher.Hilfiger@fda.hhs.gov)

Subject: IDT NDA 206544 Morphine ARER (MorphaBond)

Hi Chris,

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Can you please confirm when we receive the FDA's response?

Regards,

Debra



Debra Aub Webster, PhD

Director, Executive Consultant

Regulatory Sciences

Specialty Solutions

7400 W 110th St, Suite 300, Overland Park, KS 66210

913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile

debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Tuesday, February 10, 2015 8:42 AM
To: Webster, Debra
Cc: Stefan Aigner (stefan.aigner@inspirionrx.com); 'Matthew Iverson'
Subject: RE: IDT NDA 206544

Dear Debra,

I will discuss your point of view with the Division management. However, two things I wanted you to be aware of:

1. This EMBEDA label was approved 6/3/2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022321s012lbl.pdf It does not contain the (b) (4) language in the currently approved label (Section 9.2)
2. I did not completely or clearly explain how a priority review status would be available to you. If a sponsor conducts studies for an (b) (4) drug that compares their drug to a currently approved (b) (4) drug priority review status could be available.

If you want to talk to me about this today, that is possible. I am free most of the day with the exception of noon to 1 PM. It is unlikely I will have spoken to the Division management by then.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Monday, February 09, 2015 4:13 PM
To: Hilfiger, Christopher
Cc: Stefan Aigner (stefan.aigner@inspirionrx.com); 'Matthew Iverson'
Subject: IDT NDA 206544
Importance: High

Hi Chris,

Thank you for speaking with me today. As you mentioned you were meeting today please find below our preliminary thoughts on review status. This issue is very important to IDT and we will provide a more in-depth document shortly.

You indicated that IDT's NDA 206544 was not granted priority review because it was considered a follow-on to the approved Embeda, which has (b) (4) features. However, Embeda is a combination product with 2 listed active ingredients in the FDA Orange Book and IDT's MorphaBond (Morphine ARER) is not and achieves (b) (4) without exposing the patient to additional risk. We therefore believe that it should be considered as a first-in-class (b) (4) formulation of extended-release morphine and eligible for a priority review. Additionally, in response to IDT's Type C meeting question:

Will the Division confirm that an expedited review for the Morphine ARER tablet product will occur during the NDA filing review?

The FDA response was: As a product with proposed abuse-deterrent features, this NDA will be eligible for a priority review.

This meeting was held on July 2, 2013, at which time the product labeling for Embeda already contained (b) (4) language. At the time of filing of this NDA Embeda was not and still is not commercially available. IDT's quantitative marketing research indicates some prescribers are hesitant to prescribe antagonist-containing products.

Thank you for presenting this information to the reviewers.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
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debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Friday, April 03, 2015 1:23 PM
To: Webster, Debra
Subject: IDT NDA 206544 Morphine ARER (MorphaBond) Information request

Dear Debra,

Please address the following items.

1. The proposed dissolution acceptance criteria at 2 hours; (b) (4)% for 30 mg and (b) (4)% for 15 mg are too wide, therefore, not acceptable without an established IVIVC.

You need to revisit the overall dissolution profile data and revise the acceptance criteria at 2 hours for each of the 30 and 15 mg tablet strengths and submit the revised acceptance criteria to the Agency for review. The final determination on the dissolution acceptance criteria for all the four strengths proposed will be made upon NDA review based on the totality of dissolution data submitted.

2. In the alcohol dose dumping report, the Figure Nos. 17-20 in M3.2.P.2 need clarification/revisions since there are only 5 curves in each graph, but 6 legends shown; a bold blue legend for 40% alcohol is unclear or undefined.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
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Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Hilfiger, Christopher
Sent: Monday, February 09, 2015 10:45 AM
To: 'Webster, Debra'
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond)

Dear Debra,

See section 9.2 of the label below.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022321s016lbl.pdf

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Hilfiger, Christopher
Sent: Friday, February 06, 2015 11:52 AM
To: 'Webster, Debra'
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond)

Sorry for the delay, I have been very busy.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Friday, February 06, 2015 11:35 AM
To: Hilfiger, Christopher
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond)

Hi Chris,
I am trying to plan for coverage during some upcoming travel. Can you give me an indication of when we might expect the 74-day letter? We had anticipated receiving this on February 3.
If you could please let me know that you received this email it would be most appreciated.

Thank you!

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
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913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

From: Webster, Debra
Sent: Wednesday, February 04, 2015 8:40 AM

To: Hilfiger, Christopher (Christopher.Hilfiger@fda.hhs.gov)
Subject: IDT NDA 206544 Morphine ARER (MorphaBond)

Hi Chris,

Just touching base to see when we can expect the 74-day letter regarding IDT's NDA that was submitted November 21, 2014. By our calculations we were expecting this yesterday.
Can you please confirm when we receive the FDA's response?

Regards,

Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
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7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax [REDACTED] ^{(b) (6)} mobile
debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, April 16, 2015 9:47 AM
To: Webster, Debra
Subject: RE: IDT NDA 206544 re: request for information

Your statement:

Can you tell me if you have from any of the other review divisions?

is not clear to me.

Additionally, Luz Rivera is female.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Tuesday, April 14, 2015 4:08 PM
To: Hilfiger, Christopher
Subject: IDT NDA 206544 re: request for information

Hi Chris,

As per my email to L. Riveria, on which I copied you, we are preparing the responses to the requests for information in his email of April 8, 2015. His email also included the 2 questions that were in your prior request as per your email of April 3, 2015, so we will prepare this as a single submission both by email on April 21 as requested and will follow up with the official submission to the NDA as soon as possible thereafter.

Can you tell me if you have from any of the other review divisions?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
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debra.webster@Cardinalhealth.com

APPEARS THIS WAY ON ORIGINAL

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, April 16, 2015 9:52 AM
To: Webster, Debra
Subject: RE: IDT NDA 206544 re: request for information

No comments from the other reviewers yet.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Thursday, April 16, 2015 9:51 AM
To: Hilfiger, Christopher
Subject: RE: IDT NDA 206544 re: request for information

Thank you for that clarification!

I was trying to ask if you have heard from any of the other review disciplines as to whether they have any questions!
Sorry for the confusion.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
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7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Thursday, April 16, 2015 8:47 AM
To: Webster, Debra
Subject: RE: IDT NDA 206544 re: request for information

Your statement:

Can you tell me if you have from any of the other review divisions?

is not clear to me.

Additionally, Luz Rivera is female.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
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10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Tuesday, April 14, 2015 4:08 PM
To: Hilfiger, Christopher
Subject: IDT NDA 206544 re: request for information

Hi Chris,

As per my email to L. Riveria, on which I copied you, we are preparing the responses to the requests for information in his email of April 8, 2015. His email also included the 2 questions that were in your prior request as per your email of April 3, 2015, so we will prepare this as a single submission both by email on April 21 as requested and will follow up with the official submission to the NDA as soon as possible thereafter.

Can you tell me if you have from any of the other review divisions?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
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debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, May 14, 2015 3:57 PM
To: Webster, Debra
Subject: IDT NDA 206544 Morphine ARER (MorphaBond) Information request

Dear Debra,

Can you provide the following information?

1. In Study M-ARER-007, one subject who received 15 mg M-ARER developed abdominal pain, and withdrew from the study. Provide narrative of this subject.
2. In 2.7.4.3 of submission, Clinical laboratory Evaluations, you listed subjects who experienced 8 clinically laboratory events. Provide the abnormal laboratory value.
3. In 2.7.4.4 of submission, Vital Signs, Physical Findings, and Other Observational Related to Safety, you listed 5 subjects who developed abnormal vital signs. Provide the value of the abnormal vital signs.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
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10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, June 11, 2015 2:43 PM
To: 'Webster, Debra'
Subject: IDT NDA 206544 Morphine ARER (MorphaBond) request

Dear Debra,

Revise the bottle labels such that the current drug product name of “(morphine sulfate extended-release tablets)” reads as “(morphine sulfate) extended-release tablets”.

Note that only the established name should be included in the parenthesis.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Monday, July 20, 2015 10:06 AM
To: 'Webster, Debra'
Subject: RE: Inspirin Delivery Technologies NDA 206544 MorphaBond

Yes.

That will be helpful

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Monday, July 20, 2015 10:01 AM
To: Hilfiger, Christopher
Subject: RE: Inspirin Delivery Technologies NDA 206544 MorphaBond

Dear Chris,
Thank you. As before can we submit by email by the 24th and follow up with the formal submission a week later?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
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debra.webster@Cardinalhealth.com



Convention: June 15-17, 2015
Exhibition & Networking: June 15-16, 2015
Pennsylvania Convention Center
Philadelphia, PA

Exhibitor
#BIO2015

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From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Monday, July 20, 2015 8:59 AM

To: Webster, Debra
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The newly approved group REMS. We are requesting the items to be submitted by 7/24/15.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Monday, July 20, 2015 9:27 AM
To: Hilfiger, Christopher
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris,
Do you want word files of the REMS we submitted with the NDA or revised as per the newly approved group REMS?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
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debra.webster@Cardinalhealth.com



December 1-3, 2015
Exhibitions & Partnering: June 15-18, 2015
Pennsylvania Convention Center
Philadelphia, PA

Exhibitor
#BIO2015

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From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Monday, July 20, 2015 7:11 AM
To: Webster, Debra
Subject: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The reviewers are requesting word versions of your REMS doc and materials. Please provide these as soon as possible.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation-II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Monday, July 20, 2015 9:59 AM
To: 'Webster, Debra'
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The newly approved group REMS. We are requesting the items to be submitted by 7/24/15.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Monday, July 20, 2015 9:27 AM
To: Hilfiger, Christopher
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris,
Do you want word files of the REMS we submitted with the NDA or revised as per the newly approved group REMS?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
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7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com



Conventions: June 15-18, 2015
Exhibitors & Partners: June 15-18, 2015
Philadelphia Convention Center
Philadelphia, PA

Exhibitor
#BIO2015

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From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Monday, July 20, 2015 7:11 AM

To: Webster, Debra
Subject: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The reviewers are requesting word versions of your REMS doc and materials. Please provide these as soon as possible.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Monday, July 20, 2015 8:11 AM
To: 'Webster, Debra'
Subject: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The reviewers are requesting word versions of your REMS doc and materials. Please provide these as soon as possible.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Tuesday, July 07, 2015 11:17 AM
To: 'Webster, Debra'
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Thanks. This was forwarded to the reviewers.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Monday, July 06, 2015 5:19 PM
To: Hilfiger, Christopher
Cc: Matthew Iverson
Subject: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris,

As requested, please find attached to this email a zip folder containing IDT's response to your email dated June 25, 2015. The patient narrative is provided in section 1.11.3 Efficacy information amendment and the response to questions regarding product labeling in section 1.11.4 Multiple module information amendment. The revised draft labeling text is provided in section 1.14.1.3 Draft labeling text and the revised annotated labeling is provided in section 1.14.1.2. Please note, for consistency, the label has also been revised to reflect FDA's prior request regarding bottle labels that was submitted to the NDA in SN0005.

This request for information will be formally submitted to NDA 206544 via the ESG this week.
If there is any further information you require please let me know.

In addition, thank you for your telephone message regarding the REMS. We had anticipated that we would likely need to resubmit and will wait for further direction from you as to the appropriate timing for resubmitting the REMS.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
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debra.webster@Cardinalhealth.com

APPEARS THIS WAY ON ORIGINAL

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, June 25, 2015 6:54 PM
To: 'Webster, Debra'
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond) information request

Email is ok

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Thursday, June 25, 2015 2:28 PM
To: Hilfiger, Christopher
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond) information request

Hi Chris,
Thank you for this communication. Is it acceptable to reply by email to you by July 6th and follow up with a formal submission to the NDA?
Given the holiday next week it will be difficult to meet that date for a formal submission.
Thank you.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
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913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com



Convention: June 15-18, 2015
Exhibition: Pre-travel to June 15, 2015
Philadelphia Convention Center
Philadelphia, PA

Exhibitor
#8102615



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From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Thursday, June 25, 2015 1:05 PM
To: Webster, Debra
Subject: IDT NDA 206544 Morphine ARER (MorphaBond) information request

Dear Debra,

I have the following requests for information. If possible reply to me by July 6, 2015.

1. In ISS Table 18, there is one case treated with morphine ARER (Study M-ARER-005) who developed abdominal discomfort that was associated with the SMQ perforation, ulcer hemorrhage, obstruction, nonspecific findings/procedures in the SOC for GI disorders. The Investigator considered the event to be related to treatment with naltrexone. Provide the narrative of the case who treated with study product in Study M-ARER-005.
2. Please provide clarification on how the ^{(b) (4)} for drug liking were ^{(b) (4)} as stated in the footnote in Table 1 under Section 9.2 of the proposed label for NDA 206544 (page 19 of 33 of the proposed label).
3. Please replace the ^{(b) (4)} in your proposed label and the percentage reduction computation should follow the current FDA's Guidance for Industry "Abuse-Deterrent Opioids — Evaluation and Labeling" (April, 2015). We recommend the following formula for the calculation:

$$\% \text{reduction} = \begin{cases} \frac{a_i - t_i}{a_i - 50} \times \left(1 - \frac{p_i - 50}{50} \right) \times 100\%, & \text{if } p_i > 50; \\ \frac{a_i - t_i}{a_i - 50} \times 100\%, & \text{if } p_i \leq 50. \end{cases}, \quad i = 1, 2, \dots, n$$

BEST AVAILABLE
COPY

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, June 25, 2015 2:05 PM
To: 'Webster, Debra'
Subject: IDT NDA 206544 Morphine ARER (MorphaBond) information request

Dear Debra,

I have the following requests for information. If possible reply to me by July 6, 2015.

1. In ISS Table 18, there is one case treated with morphine ARER (Study M-ARER-005) who developed abdominal discomfort that was associated with the SMQ perforation, ulcer hemorrhage, obstruction, nonspecific findings/procedures in the SOC for GI disorders. The Investigator considered the event to be related to treatment with naltrexone. Provide the narrative of the case who treated with study product in Study M-ARER-005.
2. Please provide clarification on how the ^{(b)(4)} for drug liking were ^{(b)(4)} as stated in the footnote in Table 1 under Section 9.2 of the proposed label for NDA 206544 (page 19 of 33 of the proposed label).
3. Please replace the ^{(b)(4)} in your proposed label and the percentage reduction computation should follow the current FDA's Guidance for Industry "Abuse-Deterrent Opioids — Evaluation and Labeling" (April, 2015). We recommend the following formula for the calculation:

$$\% \text{reduction} = \left\{ \begin{array}{ll} \frac{c_i - t_i}{c_i - 50} \times \left(1 - \frac{p_i - 50}{50} \right) \times 100\%, & \text{if } p_i > 55; \\ \frac{c_i - t_i}{c_i - 50} \times 100\%, & \text{if } p_i \leq 55. \end{array} \right\}, \quad i = 1, 2, \dots, n$$

Sincerely,
 Christopher Hilfiger
 Regulatory Project Manager
 Division of Anesthesia, Analgesia, and Addiction Products
 Office of Drug Evaluation II
 Center for Drug Evaluation and Research
 10903 New Hampshire Avenue
 Building 22, Room 3240
 Silver Spring, MD 20933-0002
 (P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Friday, June 12, 2015 3:37 PM
To: 'Webster, Debra'
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond) request

Dear Debra,

The Division has had our mid-cycle meeting for your product and have nothing to report back at this time. Regarding the labelling, submit it shortly (10 days) so that the reviewers may complete their reviews.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Friday, June 12, 2015 11:27 AM
To: Hilfiger, Christopher
Subject: RE: IDT NDA 206544 Morphine ARER (MorphaBond) request

Dear Chris

Thank you for this feedback. Does this need to be submitted immediately or just to be fixed when we submit the final labeling? Also can you tell me if the mid cycle review meeting has been held and when we might expect comments resulting from that meeting?

Thanks
Debra

Sent via the Samsung Galaxy Note® 4, an AT&T 4G LTE smartphone

----- Original message -----

From: "Hilfiger, Christopher" <Christopher.Hilfiger@fda.hhs.gov>
Date: 06/11/2015 11:43 AM (GMT-08:00)
To: "Webster, Debra" <debra.webster@cardinalhealth.com>
Subject: IDT NDA 206544 Morphine ARER (MorphaBond) request

Dear Debra,

Revise the bottle labels such that the current drug product name of [REDACTED] reads as "(morphine sulfate) extended-release tablets".

(b) (4)

Note that only the established name should be included in the parenthesis.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, July 23, 2015 10:55 AM
To: 'Webster, Debra'
Subject: Urgent Request - Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

During review of your NDA submission, we have determined that the level of (b) (4) associated with the maximum theoretical daily dose of 2 g/day of morphine ARER (b) (4) that are present in approved FDA oral products. As discussed previously, the safety of the (u) (4) polymeric backbone, which consists of ethyl acrylate and methyl methacrylate copolymer, appears to be addressed in your NDA submission. However a safety justification for the (b) (4) cannot be located in your NDA submission. As the levels of (b) (4) exceeds those levels in FDA-approved oral products, submit as soon as possible a comprehensive safety assessment of (b) (4) that supports the safety of this (b) (4) at the level associated with the MTDD of morphine ARER of 2 g/day.

Please response as soon as possible, via email, to this request. You may submit the information to your NDA after sending it to me.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Hilfiger, Christopher
Sent: Monday, July 20, 2015 10:06 AM
To: 'Webster, Debra'
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Yes.

That will be helpful

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Monday, July 20, 2015 10:01 AM
To: Hilfiger, Christopher
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris,
Thank you. As before can we submit by email by the 24th and follow up with the formal submission a week later?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile
debra.webster@Cardinalhealth.com



Conventions: June 15-18, 2015
Exhibitors & Partnering: June 15-18, 2015
Philadelphia Convention Center
Philadelphia, PA

Exhibitor
#BIO2015



BEST AVAILABLE COPY

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Monday, July 20, 2015 8:59 AM
To: Webster, Debra
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The newly approved group REMS. We are requesting the items to be submitted by 7/24/15.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Monday, July 20, 2015 9:27 AM
To: Hilfiger, Christopher
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris,

Do you want word files of the REMS we submitted with the NDA or revised as per the newly approved group REMS?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | [REDACTED] ^{(b)(6)} mobile
debra.webster@Cardinalhealth.com



Convention: June 15-18, 2015
Exhibitors & Networking: June 15-18, 2015
Pharmaceutical Convention Center
Philadelphia, PA

Exhibitor
#BIO2015

BEST AVAILABLE COPY

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Monday, July 20, 2015 7:11 AM
To: Webster, Debra
Subject: Inspirin Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The reviewers are requesting word versions of your REMS doc and materials. Please provide these as soon as possible.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, July 30, 2015 8:34 AM
To: 'Webster, Debra'
Cc: 'Matthew Iverson'
Subject: RE: Urgent Request - Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

I have received all of your email submissions.

Thanks

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Wednesday, July 29, 2015 3:29 PM
To: Hilfiger, Christopher
Cc: 'Matthew Iverson'
Subject: RE: Urgent Request - Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris,
Please find attached IDT's response to FDA's request for information regarding excipient qualification.
Please note the links are not active in the attached section. Additionally, the header reflects the date the official submission will be made.
If you have any additional questions please let me know.

Could you please confirm receipt? In addition could you confirm you received the prior request for the REMS word files?
Thank you.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | [REDACTED] ^{(b) (6)}mobile
debra.webster@Cardinalhealth.com

From: Webster, Debra
Sent: Thursday, July 23, 2015 12:03 PM
To: 'Hilfiger, Christopher'
Subject: RE: Urgent Request - Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris

Thank you for this communication. We will work quickly to supply the response.

Regards,

Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax (b)(6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Thursday, July 23, 2015 9:55 AM
To: Webster, Debra
Subject: Urgent Request - Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

During review of your NDA submission, we have determined that the level of (b)(4) associated with the maximum theoretical daily dose of 2 g/day of morphine ARER (b)(4) that are present in approved FDA oral products. As discussed previously, the safety of the (b)(4) polymeric backbone, which consists of ethyl acrylate and methyl methacrylate copolymer, appears to be addressed in your NDA submission. However a safety justification for the (b)(4) cannot be located in your NDA submission. As the levels of (b)(4) exceeds those levels in FDA-approved oral products, submit as soon as possible a comprehensive safety assessment of (b)(4) that supports the safety of this (b)(4) at the level associated with the MTDD of morphine ARER of 2 g/day.

Please response as soon as possible, via email, to this request. You may submit the information to your NDA after sending it to me.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Hilfiger, Christopher
Sent: Monday, July 20, 2015 10:06 AM
To: 'Webster, Debra'
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Yes.

That will be helpful

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Monday, July 20, 2015 10:01 AM
To: Hilfiger, Christopher
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris,
Thank you. As before can we submit by email by the 24th and follow up with the formal submission a week later?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
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7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com



Convention: June 15-18, 2015
Exhibitors & Sponsors: June 15-18, 2015
Philadelphia Convention Center
Philadelphia, PA

Exhibitor



BEST AVAILABLE COPY

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Monday, July 20, 2015 8:59 AM
To: Webster, Debra
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The newly approved group REMS. We are requesting the items to be submitted by 7/24/15.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Monday, July 20, 2015 9:27 AM
To: Hilfiger, Christopher
Subject: RE: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Chris,
Do you want word files of the REMS we submitted with the NDA or revised as per the newly approved group REMS?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com



Convention: June 15-18, 2015
Exhibitors & Partners: June 15-18, 2015
Pharmaceutical Convention Center
Philadelphia, PA

Exhibitor
#8/02015



BEST AVAILABLE COPY

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Monday, July 20, 2015 7:11 AM
To: Webster, Debra
Subject: Inspirion Delivery Technologies NDA 206544 MorphaBond

Dear Debra,

The reviewers are requesting word versions of your REMS doc and materials. Please provide these as soon as possible.

Sincerely,
Christopher Hilfiger

Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, August 12, 2015 11:24 AM
To: Mellon, Dan; Huynh, Carlic
Subject: FW: Inspirion Delivery Technologies NDA 206544

See the sponsors response below

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Wednesday, August 12, 2015 10:07 AM
To: Hilfiger, Christopher
Cc: Matthew Iverson
Subject: RE: Inspirion Delivery Technologies NDA 206544

Dear Chris,
Thank you for this information. The excipient manufacturer is in (b) (4) and given the time difference it may not be possible to respond by the end of the day tomorrow. We will make every effort to do so but may not be able to complete this response until Friday.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Wednesday, August 12, 2015 8:30 AM
To: Webster, Debra
Cc: Matthew Iverson
Subject: Inspirion Delivery Technologies NDA 206544

Dear Debra,

Please address the following information request. If possible, by the end of tomorrow so that we may complete the non-clinical review of your NDA.

Justify why the (b) (4) (b) (4) used in the rat radiolabeled distribution study is an adequate characterization of the potential for systemic absorption of (b) (4) in the (b) (4) (b) (4) used in the manufacture of your drug product.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

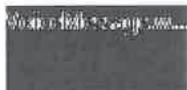
From: Hilfiger, Christopher
Sent: Thursday, August 13, 2015 10:54 AM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: FW: Message from Unknown sender [REDACTED] (b) (6)

Dear Debra,

Can you send your questions to me. I will see if a t-con is possible.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Cisco Unity Connection Messaging System [mailto:unityconnection@fdsla04029.fda.hhs.gov]
Sent: Thursday, August 13, 2015 9:09 AM
To: hilfigerc@fdsla04029.fda.hhs.gov
Subject: Message from Unknown sender [REDACTED] (b) (6)



Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Friday, August 14, 2015 11:36 AM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: Morphabond

Dear Debra,

The Division would like to have a t-con with you next week. I am not sure of the date nor time but the topic will be non-clinical in nature. I will provide questions, and possible dates and times for you next week – likely Monday.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, August 19, 2015 8:22 AM
To: 'Webster, Debra'
Subject: Topic for TC with Inspiron

Dear Debra,

I left a voicemail message on your cell phone.

We would like to discuss the following question with you and your non-clinical colleagues at 9:30 AM EST.

What is known about the release of (b) (4) from the drug product and what is known about the metabolism and absorption of (b) (4)

Please provide a call-in number to me.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, August 19, 2015 11:22 AM
To: 'Webster, Debra'
Subject: RE: Topic for TC with Inspiron

No meeting minutes. We will consider your response adequate for documenting this call.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Wednesday, August 19, 2015 10:57 AM
To: Hilfiger, Christopher
Subject: RE: Topic for TC with Inspiron

Dear Chris,
Thank you for arranging the call today.
I plan on summarizing the discussion in our response, but I am wondering whether you will also be sending FDA meeting minutes of today's teleconference?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Wednesday, August 19, 2015 7:22 AM
To: Webster, Debra
Subject: Topic for TC with Inspiron

Dear Debra,

I left a voicemail message on your cell phone.

We would like to discuss the following question with you and your non-clinical colleagues at 9:30 AM EST.

What is known about the release of (b) (4) from the drug product and what is known about the metabolism and absorption of (b) (4)

Please provide a call-in number to me.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Tuesday, August 25, 2015 10:23 AM
To: 'Webster, Debra'
Subject: RE: IDT MorphaBond NDA 206544 SN0019

Thanks Debra,

Regarding the labelling, the Division is reviewing it and we should have it as scheduled. The PMRs may be a little late due to the non-clinical information submitted and what our research internally yields.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Monday, August 24, 2015 6:43 PM
To: Hilfiger, Christopher
Subject: IDT MorphaBond NDA 206544 SN0019

Dear Chris,

Please find attached the response to the questions discussed at last week's teleconference. Please note the links are not active in the attached.

Please let me know if you need anything else. We plan to submit this officially the NDA on Friday.

Can you also tell me if we are still on track to receive the labeling and, if necessary, any postmarketing commitment requests by August 31, 2015 as indicated in the Day 74 letter?

Thanks!

Regards,

Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Friday, August 28, 2015 2:34 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: NDA 206544 - MorphaBond Comments

Dear Debra,

I have the following comments. Submit your changes to your NDA as soon as possible.

Container Labels

1. Add the proposed proprietary name on the container labels for evaluation.
2. Add updated NDC numbers on the container labels for evaluation.
3. Relocate the medication guide statement to appear under the strength presentation on the principal display panel. To ensure that the proprietary name and the established name are the most prominent information on the label, move the NDC number, proprietary name, established name, and strength up toward the top of the label to increase their prominence.
4. Relocate the statement "Swallow tablets whole. Do not break, crush, dissolve or chew" to the principal display panel to improve the prominence of important administration information and to mitigate the risk of wrong technique errors.
5. Relocate the dosage form to appear outside of the parenthesis and use title case to increase the prominence of it to mitigate potential confusion with other immediate release oral morphine products.

For example:

Morphabond
(morphine sulfate) Extended-release Tablets

6. Decrease the font size of the CII symbol to ensure that the proprietary name, established name, and strength are the most prominent information on the label.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

APPEARS THIS WAY ON ORIGINAL

9

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Tuesday, September 01, 2015 12:27 PM
To: 'Webster, Debra'
Subject: NDA 206544 - Label
Attachments: TO_SPONSORdraft-labeling-text8.31.15.docx

Dear Debra,

Attached is your label. Please review the edits and return in track changes with comments as needed. If possible, return to me by 9/4/2015.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, September 02, 2015 1:58 PM
To: 'Webster, Debra'
Subject: RE: NDA 206544 - Label

Dear Debra,

One additional item to fix in the label

The change (b) (4) to 12 hours didn't make it into the highlights. Please add to the highlights.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Hilfiger, Christopher
Sent: Tuesday, September 01, 2015 12:27 PM
To: 'Webster, Debra'
Subject: NDA 206544 - Label

Dear Debra,

Attached is your label. Please review the edits and return in track changes with comments as needed. If possible, return to me by 9/4/2015.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Tuesday, September 08, 2015 8:51 AM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: NDA 206544 (Morphabond) t-com with Division TODAY

Dear Debra,

The Division wants to have a t-con with you and your colleagues today. We want to discuss the non-clinical portion of your application. I am going to look at schedules and will get back to you with proposed times.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Tuesday, September 08, 2015 9:10 AM
To: 'Webster, Debra'
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

I have scheduled time for 11:30 AM EST. I think that is 10:30 CT.

Please provide a call-in number. We want to discuss the studies provided as non-clinical support for Morphabond.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Tuesday, September 08, 2015 8:57 AM
To: Hilfiger, Christopher
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

Hi Chris,
Thank you for the update. I am available from 10:30 to 11:30 CT or any time after 12:30 CT.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Tuesday, September 08, 2015 7:51 AM
To: Webster, Debra
Subject: NDA 206544 (Morphabond) t-com with Division TODAY

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Sincerely,
Christopher Hilfiger
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Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Tuesday, September 08, 2015 9:24 AM
To: 'Webster, Debra'
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

Yes.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Tuesday, September 08, 2015 9:18 AM
To: Hilfiger, Christopher
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

Hi Chris,
Is this in regard to the excipients?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Tuesday, September 08, 2015 8:10 AM
To: Webster, Debra
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

I have scheduled time for 11:30 AM EST. I think that is 10:30 CT.

Please provide a call-in number. We want to discuss the studies provided as non-clinical support for Morphabond.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Tuesday, September 08, 2015 8:57 AM
To: Hilfiger, Christopher
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

Hi Chris,
Thank you for the update. I am available from 10:30 to 11:30 CT or any time after 12:30 CT.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Tuesday, September 08, 2015 7:51 AM
To: Webster, Debra
Subject: NDA 206544 (Morphabond) t-com with Division TODAY

Dear Debra,

The Division wants to have a t-con with you and your colleagues today. We want to discuss the non-clinical portion of your application. I am going to look at schedules and will get back to you with proposed times.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

APPEARS THIS WAY ON ORIGINAL

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, September 09, 2015 9:13 AM
To: 'Webster, Debra'
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

The study is a 2-generational rat study with (b) (4) from (b) (4) that was presented in a review paper (Talmage, 1994). Here is the reference to the Talmage paper:

Talmage SS (1994) *Environmental and Human Safety of Major Surfactants*: (b) (4)
(b) (4)

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
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10903 New Hampshire Avenue
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Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Tuesday, September 08, 2015 3:55 PM
To: Hilfiger, Christopher
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY
Importance: High

Hi Chris,
Can you please clarify exactly which multigenerational reproductive toxicity study the reviewer was referring to in our call today?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Tuesday, September 08, 2015 8:24 AM

To: Webster, Debra
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

Yes.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Tuesday, September 08, 2015 9:18 AM
To: Hilfiger, Christopher
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

Hi Chris,
Is this in regard to the excipients?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
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debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Tuesday, September 08, 2015 8:10 AM
To: Webster, Debra
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

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Sincerely,
Christopher Hilfiger
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From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Tuesday, September 08, 2015 8:57 AM
To: Hilfiger, Christopher
Subject: RE: NDA 206544 (Morphabond) t-com with Division TODAY

Hi Chris,
Thank you for the update. I am available from 10:30 to 11:30 CT or any time after 12:30 CT.

Regards,
Debra



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debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [<mailto:Christopher.Hilfiger@fda.hhs.gov>]
Sent: Tuesday, September 08, 2015 7:51 AM
To: Webster, Debra
Subject: NDA 206544 (Morphabond) t-com with Division TODAY

Dear Debra,

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Sincerely,
Christopher Hilfiger
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10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, September 09, 2015 2:19 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: NDA 206544 (MorphaBond) Med Guide

Dear Debra,

See the attached MedGuide for changes requested



Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, September 09, 2015 2:34 PM
To: 'Webster, Debra'
Cc: Matthew Iverson
Subject: RE: IDT NDA 206544

Dear Debra,

The Division can have a t-con with you on Friday at 9 AM EST. Please provide some talking points and a call in number.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Wednesday, September 09, 2015 2:13 PM
To: Hilfiger, Christopher
Cc: Matthew Iverson
Subject: IDT NDA 206544

Hi Chris,

We are actively working on the recent requests and would like to schedule a teleconference for this Friday September 11th at 9 AM ET for as a follow-up discussion with the reviewers.

Could you please confirm and I will follow up with the dial-in information.

Thank you.

Regards,

Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
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913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Friday, September 11, 2015 1:25 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: NDA 206544 - MorphaBond REMS

Dear Debra,

The Agency has reviewed your proposed ER/LA Opioid Analgesics REMS (ER/LA REMS) submission from July 31, 2015. We agree with your proposed addition to the FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics (Blueprint). However, a revised version of the ER/LA REMS was approved by the Agency on August 13, 2015 to include the pediatric indication for OxyContin. Attached is a clean PDF which includes the current ER/LA REMS (with the pediatric indication for OxyContin) revised to include MorphaBond information in the Blueprint. Please submit the attached PDF of the ER/LA REMS document and appended materials via the gateway as an amendment to your NDA by Monday (September 14, 2015) for review by the Agency. In addition, submit a clean, word version of the ER/LA REMS Supporting Document.



Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, September 16, 2015 2:52 PM
To: 'Matthew Iverson'; Webster, Debra
Subject: RE: IDT NDA 206544
Attachments: TO_SPONSOR non-clinical PMRs.doc

Dear Matt and Debra,

Attached are the non-clinical PMRs. The Division will need dates that milestones will be met. These are highlighted in yellow. We will also need to discuss these tomorrow at 11:30 AM EST. Provide a call-in number.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Matthew Iverson [mailto:matt.iverson@inspirionrx.com]
Sent: Wednesday, September 16, 2015 9:23 AM
To: Webster, Debra
Cc: Hilfiger, Christopher
Subject: Re: IDT NDA 206544

Chris,

If you need to get a hold of us today the best way for me is either email or my cell phone

(b) (6)

Thanks,

Matt

On Sep 16, 2015, at 07:16, Webster, Debra <debra.webster@cardinalhealth.com> wrote:

Hi Chris,
Just following up on my phone call and email of yesterday and to let you know that I am out of the office today. If the Division needs to have a discussion with IDT today regarding the label please contact Matt Iverson directly and copy me.
I would be available anytime tomorrow except for 845 to 945 AM ET and anytime on Friday.
Thanks!

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile
debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, September 17, 2015 10:36 AM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: NDA 206544 (MorphaBond) - Labelling with separate Medguide

Dear Debra,

Attached is your updated PI. We have attempted to explain our thinking via the comments. Additionally there is a separate document that is a marked up Medguide. Please incorporate that with changes into your PI.

Once finalized, these will need to be submitted via the Gateway.



Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, September 17, 2015 11:23 AM
To: 'Webster, Debra'
Subject: RE: NDA 206544 (MorphaBond) - Labelling with separate Medguide

Yes. But let me do it from my office after the call

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Thursday, September 17, 2015 11:21 AM
To: Hilfiger, Christopher
Subject: RE: NDA 206544 (MorphaBond) - Labelling with separate Medguide

Thanks Chris,
Would you have time for me to call you after the conference call to discuss exactly what is to be submitted and timing?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile
debra.webster@Cardinalhealth.com

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Thursday, September 17, 2015 9:36 AM
To: Webster, Debra
Subject: NDA 206544 (MorphaBond) - Labelling with separate Medguide

Dear Debra,

Attached is your updated PI. We have attempted to explain our thinking via the comments. Additionally there is a separate document that is a marked up Medguide. Please incorporate that with changes into your PI.

Once finalized, these will need to be submitted via the Gateway.

Sincerely,
Christopher Hilfiger
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Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, September 17, 2015 2:06 PM
To: 'Webster, Debra'
Cc: Matthew Iverson
Subject: RE: IDT NDA 206544 PMR dates

Thanks. I will probably have some more to send as well that deal with the ERLA REMS PMRs. As discussed previously, those are not negotiable and the dates will seem not possible. However, it is part of the REMS and they cannot be changed.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Thursday, September 17, 2015 1:59 PM
To: Hilfiger, Christopher
Cc: Matthew Iverson
Subject: IDT NDA 206544 PMR dates

Hi Chris,

See attached the PMR with the dates added.

As requested by the reviewer our justification for the timing of the studies is based on steps that will be needed prior to initiating any toxicology program, for example development and validation of an analytical method for measuring (b) (4) conducting a pharmacokinetic/toxicokinetic study to support dose selection and investigate metabolism and accumulation, investigation of in vitro metabolism, and conduct a full body radiolabeled study to guide target tissue identification. In addition, it is anticipated that a dose-ranging study may also be needed to support dose selection for the first chronic study and the reproduction toxicity study in rabbits. We feel that this will take 6 to 9 months to complete all of the initial work. The timing of other reports relative to completion of the 6-month chronic toxicity study is designed to provide for sequential conduct of the studies to allow for use of data from one study to guide another. If the Division has any modification to the dates please adjust accordingly and we will submit to the NDA.

Regards,
Debra

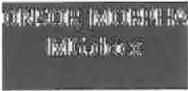


Debra Aub Webster, PhD
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debra.webster@Cardinalhealth.com

APPEARS THIS WAY ON ORIGINAL

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, September 17, 2015 3:01 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: Updated MedGuide



Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, September 17, 2015 3:04 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: ER/LA PMRS and EPI Study PMRs

Dear Debra,

Attached are the required ER/LA PMRs along with the PMR for epi studies.

These are not negotiable based on the ER/LA REMs. Please update the highlighted section and return to me via email.



Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, September 17, 2015 4:02 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: RE: Updated MedGuide

I should have added that this should be the final MedGuide that is submitted to your NDA.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Hilfiger, Christopher
Sent: Thursday, September 17, 2015 3:01 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: Updated MedGuide

<< File: TO_SPONSOR_MORPHABOND MG.docx >>

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Monday, September 21, 2015 7:49 AM
To: 'Webster, Debra'
Subject: RE: IDT NDA 206544 revised PI

It will be possible. I will schedule this soon. Please provide a call-in number

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Saturday, September 19, 2015 3:21 PM
To: Hilfiger, Christopher
Subject: IDT NDA 206544 revised PI
Importance: High

Hi Chris,
IST would like to know if it would be possible to have a quick teleconference on Monday morning with the Division regarding the latest changes. We would like to wrap this up on Monday with email submission of the PI. Would this be possible?

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
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7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Monday, September 21, 2015 10:28 AM
To: 'Webster, Debra'
Subject: RE: telcon?

Yes. Sorry

11 am

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
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10903 New Hampshire Avenue
Building 22, Room 3240
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(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Monday, September 21, 2015 10:17 AM
To: Hilfiger, Christopher
Subject: telcon?

Hi Chris,
Any word on scheduling the call – we don't want to interfere with the PDUFA date and are ready to submit the PI today.

Regards,
Debra



Debra Aub Webster, PhD
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913.661.3881 dir | 913.451.3846 fax | (b)(6) mobile
debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Wednesday, September 30, 2015 2:38 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: Labelling update

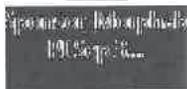
Dear Debra,

Please update the following 2 attached items

1. MEDGUIDE – there was a statement left out. add “that could lead to death.” See the note in the PDF



2. There is one minor change the PI section 2.2 (See tracked changes of the PI)



The Medguide must be submitted to your NDA. If possible, submit the labelling as well.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, October 01, 2015 8:21 AM
To: 'Webster, Debra'
Subject: RE: Labelling update

Can we talk later today?

Maybe around 11 am EST? If yes, I can call you

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Wednesday, September 30, 2015 4:32 PM
To: Hilfiger, Christopher
Subject: Labelling update

Hi Chris,
Please find attached the word files (clean and redlined) and the pdfs of the Medication Guide and the PI.
I will submit the pdf of these via the ESG on Friday, October 2nd.
Please let me know if anything other than the pdfs need to be submitted.
Thank you!

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
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debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, October 01, 2015 8:55 AM
To: 'Webster, Debra'
Cc: matt.iverson@inspirionrx.com
Subject: RE: Labelling update

Dear Debra and Matt,

Here is what Lisa Basham has forwarded for changes. It includes the MedGuide and PI (I told Debra only MedGuide by mistake). I will be available after 11 am today if you need to talk.

• HL – Change (b) (4)
(b) (4)

To: Nursing Mothers: Nursing is not recommended. (8.3)

8.3 Nursing Mothers – Change

(b) (4)

To:

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with MORPHABOND.

Medication Guide – change

(b) (4)

To:

Breastfeeding: Not recommended; may harm your baby.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
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10903 New Hampshire Avenue
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To: Hilfiger, Christopher
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Thank you!

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Debra



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debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, October 01, 2015 9:50 AM
To: 'Matthew Iverson'; 'Webster, Debra'
Subject: RE: Labelling update

received

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Matthew Iverson [mailto:matt.iverson@inspirationrx.com]
Sent: Thursday, October 01, 2015 9:42 AM
To: Hilfiger, Christopher; 'Webster, Debra'
Subject: RE: Labelling update

Chris,

Here are the updated PDFs along with redline word documents to make your review easier. Please feel free to call me directly if there are any additional items that you need. The best way to reach me is on my cell (b) (6). The updated PDFs will be submitted via the ESG on Friday, October 2nd. Please confirm the receipt of the files.

Best regards,

Matt



Matthew Iverson, MPH | Vice President, Clinical Development | Inspirion Delivery Technologies, LLC
612 Corporate Way, Suite 10 | Valley Cottage, NY 10989 | Office 801.931.4745 Cell: (b) (6) | ✉:matt.iverson@inspirationrx.com

Mailing address: 233 Mt. Airy Road, Suite 100 | Basking Ridge, NJ 07920

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Thursday, October 1, 2015 06:54
To: Webster, Debra <debra.webster@cardinalhealth.com>

Cc: matt.iverson@inspirionrx.com

Subject: RE: Labelling update

Dear Debra and Matt,

Here is what Lisa Basham has forwarded for changes. It includes the MedGuide and PI (I told Debra only MedGuide by mistake). I will be available after 11 am today if you need to talk.

• HL – Change (b) (4)
(b) (4)

To: Nursing Mothers: Nursing is not recommended. (8.3)

8.3 Nursing Mothers – Change

(b) (4)

To:

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with MORPHABOND.

Medication Guide – change

(b) (4)

To:

Breastfeeding: Not recommended; may harm your baby.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]

Sent: Wednesday, September 30, 2015 4:32 PM

To: Hilfiger, Christopher

Subject: Labelling update

Hi Chris,

Please find attached the word files (clean and redlined) and the pdfs of the Medication Guide and the PI.

I will submit the pdf of these via the ESG on Friday, October 2nd.
Please let me know if anything other than the pdfs need to be submitted.
Thank you!

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, October 01, 2015 12:07 PM
To: 'Matthew Iverson'
Subject: RE: Labelling update

received

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Matthew Iverson [mailto:matt.iverson@inspirionrx.com]
Sent: Thursday, October 01, 2015 11:54 AM
To: Hilfiger, Christopher; 'Debra Webster'
Subject: FW: Labelling update

Chris,

I received a noticed that this was not delivered. Please let me know if you received this updated email with the correct files. It should contain the PDF of the medication guide and PI and redlines for both documents.

Thanks,

Matt



Matthew Iverson, MPH | Vice President, Clinical Development | Inspirion Delivery Technologies, LLC
612 Corporate Way, Suite 10 | Valley Cottage, NY 10989 | Office 801.931.4745 Cell: (b) (6) | ✉:matt.iverson@inspirionrx.com

Mailing address: 233 Mt. Airy Road, Suite 100 | Basking Ridge, NJ 07920

From: Matthew Iverson [mailto:matt.iverson@inspirionrx.com]
Sent: Thursday, October 1, 2015 09:15
To: 'Hilfiger, Christopher' <Christopher.Hilfiger@fda.hhs.gov>; 'Webster, Debra' <debra.webster@cardinalhealth.com>
Subject: RE: Labelling update

Chris,

I just noticed that the PDF for the PI was not attached. Here are the correct files again.

Thanks,

Matt

From: Matthew Iverson [mailto:matt.iverson@inspirionrx.com]

Sent: Thursday, October 1, 2015 07:42

To: 'Hilfiger, Christopher' <Christopher.Hilfiger@fda.hhs.gov>; 'Webster, Debra' <debra.webster@cardinalhealth.com>

Subject: RE: Labelling update

Chris,

Here are the updated PDFs along with redline word documents to make your review easier. Please feel free to call me directly if there are any additional items that you need. The best way to reach me is on my cell (b) (6). The updated PDFs will be submitted via the ESG on Friday, October 2nd. Please confirm the receipt of the files.

Best regards,

Matt



Matthew Iverson, MPH | Vice President, Clinical Development | Inspirion Delivery Technologies, LLC
612 Corporate Way, Suite 10 | Valley Cottage, NY 10989 | Office 801.931.4745 Cell: (b) (6) ✉:matt.iverson@inspirionrx.com

Mailing address: 233 Mt. Airy Road, Suite 100 | Basking Ridge, NJ 07920

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]

Sent: Thursday, October 1, 2015 06:54

To: Webster, Debra <debra.webster@cardinalhealth.com>

Cc: matt.iverson@inspirionrx.com

Subject: RE: Labelling update

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To:

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Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

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Thank you!

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
Specialty Solutions
7400 W 110th St, Suite 300, Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax | (b) (6) mobile
debra.webster@Cardinalhealth.com

APPEARS THIS WAY ON ORIGINAL

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Thursday, October 01, 2015 2:07 PM
To: 'Matthew Iverson'
Subject: RE: Labelling update

I have received it via the Gateway. If needed, I will update any date September dates to the month approved.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Matthew Iverson [mailto:matt.iverson@inspirionrx.com]
Sent: Thursday, October 01, 2015 1:29 PM
To: Hilfiger, Christopher; 'Webster, Debra'
Subject: RE: Labelling update

Chris,

I just wanted to let you know that the medication guide and PI have been submitted via the ESG. I have attached the receipt acknowledgement from the system. Please let me know if there is anything else that is needed.

Best regards,

Matt



Matthew Iverson, MPH | Vice President, Clinical Development | Inspirion Delivery Technologies, LLC
612 Corporate Way, Suite 10 | Valley Cottage, NY 10989 | Office 801.931.4745 Cell: (b) (6) ✉:matt.iverson@inspirionrx.com

Mailing address: 233 Mt. Airy Road, Suite 100 | Basking Ridge, NJ 07920

From: Hilfiger, Christopher [mailto:Christopher.Hilfiger@fda.hhs.gov]
Sent: Thursday, October 1, 2015 07:49
To: Matthew Iverson <matt.iverson@inspirionrx.com>; 'Webster, Debra' <debra.webster@cardinalhealth.com>
Subject: RE: Labelling update

received

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
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Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Matthew Iverson [<mailto:matt.iverson@inspirionrx.com>]
Sent: Thursday, October 01, 2015 9:42 AM
To: Hilfiger, Christopher; 'Webster, Debra'
Subject: RE: Labelling update

Chris,

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Matt



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612 Corporate Way, Suite 10 | Valley Cottage, NY 10989 | Office 801.931.4745 Cell: (b) (6) | [✉:matt.iverson@inspirionrx.com](mailto:matt.iverson@inspirionrx.com)

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Subject: Labelling update

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Regards,

Debra



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debra.webster@Cardinalhealth.com

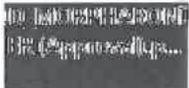
Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Friday, October 02, 2015 3:07 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: NDA 206544 - MorphaBond - Approval Letter

Dear Debra,

See the attached letter for the Approval of NDA 206544 – MorphaBond. Please call me if you have any further questions.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
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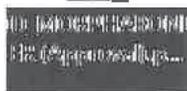


Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Friday, October 02, 2015 4:23 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: RE: NDA 206544 - MorphaBond - Approval Letter

Please do not use the previous Approval letter.

Here is one without my signature.



Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

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Sent: Friday, October 02, 2015 3:07 PM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: NDA 206544 - MorphaBond - Approval Letter

Dear Debra,

See the attached letter for the Approval of NDA 206544 – MorphaBond. Please call me if you have any further questions.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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10903 New Hampshire Avenue
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Silver Spring, MD 20933-0002
(P) 301.796.4131

<< File: DD_MORPHABOND ER (Approval).pdf - Adobe Acrobat Pro.pdf >>

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Tuesday, January 13, 2015 11:02 AM
To: Webster, Debra (debra.webster@cardinalhealth.com)
Subject: NDA 206544 Information request

Dear Dr. Aub Webster,

I have the following information requests for you:

1. We had provided guidance in the past regarding the conduct of oral liking study (M-ARER-003) IDT's Morphine Sulfate ARER tablet. We notice that the results of this study M-ARER-003 were not submitted to the NDA. Provide information on the status of this study (completed, discontinued, etc.).
2. Provide the pharmacy manual from Inspirion for the intranasal HAP study M-ARER-002 under NDA 206544 (b) (4)

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

Hilfiger, Christopher

From: Hilfiger, Christopher
Sent: Monday, November 24, 2014 10:34 AM
To: Webster, Debra
Subject: RE: Inspirin Delivery Technologies, LLC NDA 206544 for Morphine ARER

We received your NDA. I will be the PM for the review process. I am busy with an AC Monday and Tuesday and taking the rest of the week off. Either email or call me next week so we can discuss your submission.

Sincerely,
Christopher Hilfiger
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3240
Silver Spring, MD 20933-0002
(P) 301.796.4131

From: Webster, Debra [<mailto:debra.webster@cardinalhealth.com>]
Sent: Tuesday, November 18, 2014 11:50 AM
To: Hilfiger, Christopher
Cc: 'Matthew Iverson'
Subject: Inspirin Delivery Technologies, LLC NDA 206544 for Morphine ARER

Hi Chris,
Good morning! I hope all is well with you. I just want to drop you a quick note to let you know that we anticipate submitting NDA 206544 for Morphine ARER this November, on the 21st at the earliest and the 25th at the latest. IDT submitted the PDUFA fee on November 14th.

We look forward to working with you and the Division over the next 6 months of review. Please let me know if you have any questions.

On another note, were you ever able to find out anything regarding the status of the proprietary name submission (IND (b) (4))?

Thank you.

Regards,
Debra



Debra Aub Webster, PhD
Director, Executive Consultant
Regulatory Sciences
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APPEARS THIS WAY ON ORIGINAL