

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206544Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

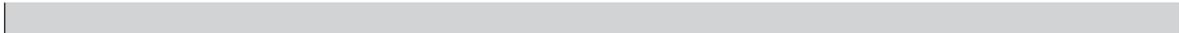
Application Information		
NDA # 206544	NDA Supplement #:	Efficacy Supplement Type SE-
Proprietary Name: MorphaBond Established/Proper Name: morphine sulfate Dosage Form: extended-release tablet Strengths: 15 mg, 30 mg, 60 mg, and 100 mg		
Applicant: Inspirion Delivery Technologies, LLC		
Date of Receipt: 11/21/2014		
PDUFA Goal Date: 9/21/2015		Action Goal Date (if different):
RPM: Christopher Hilfiger		
Proposed Indication(s): management of pain severe enough to require daily, around-the-clock, long-term, opioid treatment and for which alternative treatment options are inadequate		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>published literature</i>	<i>Nonclinical toxicology</i>
<i>NDA 019516 – MS Contin</i>	<i>FDA’s previous finding of safety and effectiveness</i>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The Applicant has evaluated the comparative BA of Morphine ARER versus MS CONTIN following single administration of 100, 30, and 15 mg, and 5-day (steady-state) administration of 100 mg. In these studies, all subjects were naltrexone-blocked to minimize the PD effects of treatment with an opioid in healthy volunteers.

The Applicant is relying on the literature for the safety justification for the (b) (4) as well as their respective (b) (4).

Additionally, the repro and genetox data are from the MS Contin labeling, but in reality, all of that is from the literature as well.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If “NO,” proceed to question #5.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “**NO**”, proceed to question #5.

If “**YES**”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
MS Contin	019516	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Morphabond is a product with abuse-deterrent features.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES X NO
If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES X NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): multiple NDAs and ANDAs, multiple various dosage forms listed in the OB are pharm alternatives

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): no patents are listed in the Orange Book

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

APPEARS THIS WAY ON ORIGINAL

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

PMR/PMC Development Template

NDA 206544

PMR/PMC Description: Conduct a 9-month repeat-dose oral toxicology study in the nonrodent model characterizing the toxicological potential of (b) (4)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	07/2017
	Study/Trial Completion:	07/2018
	Final Report Submission:	12/2018
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Although there are no oral toxicology data for (b) (4), there are several published summaries of reports of studies with comparable compounds suggesting a very large safety margin. Because these data cannot be independently verified, these studies are required to provide definitive data to document the conclusion that there is no safety concern with this novel excipient.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

(b) (4) is used in FDA-approved topical drug products, and it being used in this oral drug product at low levels. The weight-of-evidence suggests an extremely low likelihood of any toxicity associated with this use; however, definitive data are needed to confirm this. This is a general toxicology study that is conducted to support chronic oral use of this excipient. Based on summary data in the published literature with smaller molecular weight compounds similar to (b) (4), there is potential for hepatic toxicity and focal myocarditis at high doses of these compounds.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a general toxicology study to ascertain the potential impact of (b) (4) and its metabolites.
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 206544

PMR/PMC Description: Conduct a 6-month repeat-dose oral toxicology study in the rodent model characterizing the toxicological potential of (b) (4).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	07/2016
	Study/Trial Completion:	05/2017
	Final Report Submission:	10/2017
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4) is used in FDA-approved topical drug products, and it being used in this oral drug product at low levels. The weight-of-evidence suggests an extremely low likelihood of any toxicity associated with this use; however, definitive data are needed to confirm this. This is a general toxicology study that is conducted to support chronic oral use of this excipient.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

(b) (4) is used in FDA-approved topical drug products, but it being used in this oral drug product at low levels. The weight-of-evidence suggests an extremely low likelihood of any toxicity associated with this use; however, definitive data are needed to confirm this. This is a general toxicology study that is conducted to support chronic oral use of this excipient. Based on summary data in the published literature with smaller molecular weight compounds similar to (b) (4), there is potential for hepatic toxicity and focal myocarditis at high doses of these compounds.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a general toxicology study to ascertain the potential impact of (b) (4) and its metabolites.
--

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 206544

PMR/PMC Description: Conduct a fertility and early embryonic development study in both male and female rats with (b) (4).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/2017
	Study/Trial Completion:	05/2018
	Final Report Submission:	10/2018
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4) is present in FDA-approved topical drug products but is considered a new excipient for the oral route of administration. There is a published summary of a multigenerational rat study using a similar compound that reports no adverse effects of fertility and early embryonic development. This study report may be adequate to address the safety of (b) (4); however, this unpublished study is not available for independent review. Based on a weight-of-evidence based argument, the Division has determined that the likelihood of risk is low, but because the compound can be absorbed and the metabolic profile is not clear, there is still a theoretical risk for tissue toxicity. Based on a benefit-risk evaluation, the Division has agreed to allow the studies to be conducted post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a published summary of a multigenerational study for an analogous compound in the literature; however, the results cannot be independently verified. This study is being requested to provide definitive data to support the conclusion that the weight of evidence suggests minimal to no risk. Based on published summaries of similar molecules, there is a potential for decreased body weight of the mother and adverse impact on pup growth and development at high doses.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– Which regulation?

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is a fertility and early embryonic development study that examines the effects of a drug on male and female fertility and early embryonic development up to the point of implantation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 206544

PMR/PMC Description: Conduct an embryofetal development study for (b) (4) in the rat model.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/2017</u>
	Study/Trial Completion:	<u>10/2017</u>
	Final Report Submission:	<u>04/2018</u>
	Other:	<u>N/A</u>

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4) is present in FDA-approved topical drug products but is considered a new excipient for the oral route of administration. There is a published summary of a multigenerational rat study using a similar compound that reports no adverse effects of pre- and postnatal development. This study report may be adequate to address the safety of (b) (4); however, this unpublished study is not available for independent review. Based on a weight-of-evidence based argument, the Division has determined that the likelihood of risk is low, but because the compound can be absorbed and the metabolic profile is not clear, there is still a theoretical risk for tissue toxicity. Based on a benefit-risk evaluation, the Division has agreed to allow the studies to be conducted post-marketing.

7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a published summary of a multigenerational rat study using a similar compound that reports no adverse effects of pre- and postnatal development. This study report may be adequate to address the safety of (b) (4); however, this unpublished study is not available for independent review. Based on a weight-of-evidence based argument, the Division has determined that the likelihood of risk is low, but because the compound can be absorbed and the metabolic profile is not clear, there is still a theoretical risk for tissue toxicity. Based on a benefit-risk evaluation, the Division has agreed to allow the studies to be conducted post-marketing. Based on published summaries of similar molecules, there is a potential for decreased body weight of the mother and adverse impact on pup growth and development at high doses.

8. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an embryo-fetal development study in the rat model to assess the potential for teratogenicity.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

10. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 206544

PMR/PMC Description: Conduct an embryofetal development study for (b) (4) in the rabbit model.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	07/2017
	Study/Trial Completion:	10/2017
	Final Report Submission:	04/2018
	Other:	N/A

11. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4) is present in FDA-approved topical drug products but is considered a new excipient for the oral route of administration. There is a published summary of a multigenerational rat study using a similar compound that reports no adverse effects of embryofetal development. This study report may be adequate to address the safety of (b) (4); however, this unpublished study is not available for independent review. Based on a weight-of-evidence based argument, the Division has determined that the likelihood of risk is low, but because the compound can be absorbed and the metabolic profile is not clear, there is still a theoretical risk for tissue toxicity. Based on a benefit-risk evaluation, the Division has agreed to allow the studies to be conducted post-marketing..

12. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Novel excipients are required to conduct teratogenicity studies in two species. Although there is a published summary of a study suggesting a lack of adverse effects of a similar compound in the rat model, there are no data in the rabbit. The weight-of-evidence suggests low risk, therefore, the definitive studies may be completed post-marketing. Based on published summaries of similar molecules, there is a potential for decreased body weight of the mother and adverse impact on pup growth and development at high doses.

13. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

14. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is a embryo-fetal development study in the rabbit model to assess the potential for teratogenicity.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

15. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 206544

PMR/PMC Description: Conduct a pre- and post-natal development study for (b) (4) in the rat model.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/2017
	Study/Trial Completion:	07/2018
	Final Report Submission:	12/2018
	Other:	N/A

16. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4) is present in FDA-approved topical drug products but is considered a new excipient for the oral route of administration. There is a published summary of a multigenerational rat study using a similar compound that reports no adverse effects of pre- and postnatal development. This study report may be adequate to address the safety of (b) (4); however, this unpublished study is not available for independent review. Based on a weight-of-evidence based argument, the Division has determined that the likelihood of risk is low, but because the compound can be absorbed and the metabolic profile is not clear, there is still a theoretical risk for tissue toxicity. Based on a benefit-risk evaluation, the Division has agreed to allow the studies to be conducted post-marketing..

17. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A pre- and postnatal development study assesses the impact of a compound following administration to the mother during the last period of pregnancy and through weaning. This results in *in utero* exposure and likely exposures via the breast milk. The endpoints evaluate the early growth, survival, and development of the offspring. Based on published summaries of similar molecules, there is a potential for decreased body weight of the mother and adverse impact on pup growth and development at high doses.

18. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

19. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is a pre- and post-natal developmental toxicology study in the rat model.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

20. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 206544

PMR/PMC Description: Conduct a 2-year rodent oral carcinogenicity assessment of (b) (4)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2017</u>
	Study/Trial Completion:	<u>04/2020</u>
	Final Report Submission:	<u>09/2020</u>
	Other:	<u>N/A</u>

21. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Although carcinogenicity studies for chronically administered drugs are generally required prior to approval, since (b) (4) has been used in FDA approved chronic use topical drug products, and there are published oral carcinogenicity studies with a similar compound suggesting no carcinogenic risk, the definitive carcinogenicity study is being allowed to be submitted as a post-marketing requirement. However, since we cannot independently verify the conclusions of the studies based on the summary data, and the studies are not published, definitive studies are recommended as a PMR.

22. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Long-term animal studies in two species to evaluate the carcinogenic potential of a new excipient are standard requirements for drug products with a chronic indication. Based on published summary information, there would appear to be minimal, if any risk of carcinogenicity of this compound. As there are FDA-approved chronic use dermal drug products that contain (b) (4), a single species oral carcinogenicity study should be completed for a chronic use oral drug product. The study would address the potential carcinogenic impact of any (b) (4) of (b) (4) (b) (4) in the chemical composition.

23. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

24. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is a 2-year repeat-dose toxicology study in the mouse model designed specifically to evaluate the carcinogenic potential of a compound.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

25. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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
09/21/2015

JUDITH A RACOOSIN
09/21/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 206544
Product Name: MORPHABOND (morphine sulfate extended release tablets)

PMR/PMC Description: Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of MORPHABOND (morphine sulfate extended release tablets) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of MORPHABOND. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance, *Abuse-Deterrent Opioids—Evaluation and Labeling* (January 2013) and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/2016
	Study/Trial Completion:	08/2020
	Final Report Submission:	02/2021
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of MORPHABOND actually deter abuse of the product in “real world” use.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

FDA has determined that the sponsor must conduct individual post-marketing studies of MORPHABOND ER (morphine sulfate extended release tablets) to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the opioid antagonist properties of MORPHABOND that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The design of the post-marketing study program for MORPHABOND must incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013) and must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of MORPHABOND. In particular, post-marketing studies for MORPHABOND must include individual assessments of all possible routes of abuse and must employ multiple appropriate comparators, including but not limited to 1) immediate and extended release formulations of morphine sulfate and other opioid analgesics and 2) both products with and without properties intended to deter abuse. The study program must include geographically diverse populations that include both opioid-dependent and non-dependent individuals and must address all the abuse-related outcomes of interest: misuse, abuse, addiction, overdose, and death.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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
09/21/2015

JUDITH A RACOOSIN
09/21/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #
Product Name: ER/LA opioid analgesics, with the addition now of NDA 206544 for MORPHABOND

PMR/PMC Description: Conduct one or more studies to provide quantitative estimates of the risks of misuse, abuse, addiction, overdose and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

(b)
(4) Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

(b)
(4) Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/2014
	Study/Trial Completion:	01/2018
	Final Report Submission:	06/2018
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval

- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In order to estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The initial type of study that would be anticipated would be an epidemiological study in large databases to measure the incidences of the adverse outcomes listed above. However, the codes for these outcomes have not been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #
Product Name: ER/LA opioid analgesics, with the addition now of NDA 206544 for MORPHABOND

PMR/PMC Description: Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition) , which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2014</u>
	Study/Trial Completion:	<u>08/2015</u>
	Final Report Submission:	<u>11/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data needed to validate measures of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the outcomes need to be validated, including measures of opioid-related adverse events.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients who fulfill a measure of the opioid-related adverse event, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the case definition.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #
Product Name: ER/LA opioid analgesics, with the addition now of NDA 206544 for MORPHABOND

PMR/PMC Description: Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2014</u>
	Study/Trial Completion:	<u>08/2015</u>
	Final Report Submission:	<u>11/2015</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data needed to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the opioid-related adverse events: misuse, abuse, addiction, overdose, and death would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify opioid-related adverse events: misuse, abuse, addiction, overdose, and death need to be validated.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for opioid-related adverse events: misuse, abuse, addiction, overdose, and death, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the clinical definition.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #
Product Name: ER/LA opioid analgesics, with the addition now of NDA 206544 for MORPHABOND

PMR/PMC Description: Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/2014
	Study/Trial Completion:	08/2015
	Final Report Submission:	11/2015
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the outcomes need to be validated, including measures of “doctor/pharmacy shopping” which are suggestive of misuse, abuse, and/or addiction.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients who fulfill a measure of “doctor/pharmacy shopping”, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the case definition.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #
Product Name: ER/LA opioid analgesics, with the addition now of NDA 206544 for MORPHABOND

PMR/PMC Description: Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/2014
	Study/Trial Completion:	08/2016
	Final Report Submission:	02/2017
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In order to estimate the risk for the development of hyperalgesia following use of opioid analgesics for at least one year, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of serious adverse effects of opioids, including hyperalgesia. The goal of the trial is to determine the risk of developing hyperalgesia.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial is needed to determine the risk of hyperalgesia following long-term treatment with opioids because this condition can be distinguished most easily with a randomized withdrawal design.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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
09/21/2015

JUDITH A RACOOSIN
09/21/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 15, 2015
Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 206544
Product Name and Strength: Morphabond (morphine sulfate) Extended-release Tablets
15 mg, 30 mg, 60 mg, 100 mg
Submission Date: September 14, 2015
Applicant/Sponsor Name: Inspirion Delivery Technologies
OSE RCM #: 2014-2441-1
DMEPA Primary Reviewer: James Schlick, RPh, MBA
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels for Morphabond (Appendix A) submitted on September 14, 2015, to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container labels for Morphabond are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Schlick J. Label and Labeling Review for Morphabond (NDA 206544). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015-MAR-17. 7 p. OSE RCM No.: 2014--2441.

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/s/

JAMES H SCHLICK
09/15/2015

BRENDA V BORDERS-HEMPHILL
09/15/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 11, 2015

To: Christopher Hilfiger, Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Kounq Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP
Sam Skariah, Team Leader – OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 206544
MORPHABOND (morphine sulfate) Extended-release Tablets
Professional Labeling Review

As requested in DAAAP's consult dated February 25, 2015, OPDP has reviewed the substantially complete prescribing information for MORPHABOND (morphine sulfate) Extended-release Tablet. The substantially complete prescribing information was provided to OPDP on September 2, 2015, via email by Christopher Hilfiger with the file name "\\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 206544 (MorphBond Inspirion)\Labeling\FOR OUTSIDE DIVISION draft-labeling-text8.31.15.docx".

OPDP has provided comments on the substantially complete prescribing information in the attached document below. Specifically, we made comments on pages 18, 19 and 21.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Kounq.Lee@fda.hhs.gov.

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/s/

KOUNG U LEE
09/11/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 4, 2015

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Samuel M. Skariah, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): MORPHABOND (morphine sulfate)

Dosage Form and Route: extended-release tablets, for oral use, CII

Application Type/Number: NDA 206544

Applicant: Inspirion Delivery Technologies, LLC

1 INTRODUCTION

On November 21, 2014 Inspirin Delivery Technologies, LLC submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 206544 for MORPHABOND (morphine sulfate) extended-release tablets. The proposed indication is 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. This application relies on FDA's previous findings of safety and effectiveness for the Reference Listed Drug (RLD) MS CONTIN (morphine sulfate extended-release tablets), NDA 019516 (Purdue Pharma L.P.).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on September 2, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for MORPHABOND (morphine sulfate) extended-release tablets.

2 MATERIAL REVIEWED

- Draft MORPHABOND (morphine sulfate) extended-release tablets MG received on November 21, 2014, and received by DMPP on September 2, 2015.
- Draft MORPHABOND (morphine sulfate) extended-release tablets MG received on November 21, 2014, and received by OPDP on September 2, 2015.
- Draft MORPHABOND (morphine sulfate) extended-release tablets Prescribing Information (PI) received on November 21, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on September 2, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
09/04/2015

SAMUEL M SKARIAH
09/04/2015

SHARON R MILLS
09/04/2015

LASHAWN M GRIFFITHS
09/04/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: July 28, 2015

TO: Christopher Hilfiger, Regulatory Project Manager
Timothy Jiang, M.D., Medical Officer
John Feeney, M.D., Team Leader
Division of Analgesia, Anesthesia, and Addiction Products

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATIONS: NDA 206544

APPLICANT: Inspirion Delivery Technologies, LLC

DRUG: Morphine sulfate (trade name pending)

NME: No

INDICATION: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment, for which alternative treatment options are inadequate

REVIEW CLASSIFICATION: Standard

APPLICATION SUBMISSION DATE: November 21, 2014

DARRTS CONSULTATION DATE: March 16, 2015

INSPECTION SUMMARY GOAL DATE: August 1, 2015

REGULATORY ACTION GOAL DATE: September 19, 2015

PDUFA DUE DATE: September 21, 2015

I. BACKGROUND

Inspiration Delivery Technologies, LLC (**IDT**) submitted this 505(b)(2) NDA 206544 for an abuse-resistant and extended-release formulation of morphine (**Morphine ARER**) for the management of pain severe enough to require daily, around-the-clock (**ATC**) long-term opioid treatment for which alternative treatment options are inadequate. This 505(b)(2) application relies on the findings of safety and effectiveness of MS Contin[®] as the reference listed drug, another formulation of extended-release morphine sulfate tablets but without abuse-deterrent features (Purdue Pharma, LP) previously approved under NDA 19516.

In the United States (**US**), the therapeutic use of opioids appears to have increased since 1997, as indicated by the nearly ten-fold increase in the sales of hydrocodone and oxycodone, presumably for the management of chronic pain. With the increasing sales of opioids, their illicit use (drug abuse and/or diversion) appears to have also increased: according to a 2009 US survey, over two million users of prescription pain relievers in 2008 were new opioid abusers, an estimate similar to the number of new marijuana and/or cigarette users for that year.

Of the original studies sponsored by IDT, the human abuse liability (**HAL**) Study M-ARER-002 was identified for on-site audit at good clinical practice (**GCP**) inspection of the only clinical investigator (**CI**) site for this study. This HAL study is described below from an inspectional viewpoint, with comments as applicable to the GCP audit. In the following study description (as in IDT's original study protocol), the study medication Morphine ARER is referred to by its product development name, IDT-001.

Study M-ARER-002

A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Single-Dose, Four-Way Crossover Study to Determine the Relative Bioavailability, Abuse Potential and Safety of Equivalent Doses of Crushed and Intact IDT-001 compared with Crushed MS Contin[®] and Placebo in Opioid Experienced, Non-Dependent Subjects Following Intranasal Administration

This randomized, placebo-controlled, double-blind, four-way crossover study was conducted between October 2012 and January 2013 in 48 healthy recreational opioid users at a single US CI site. The primary study objective was to determine the abuse potential of crushed and intact IDT-001 relative to crushed MS Contin[®] after administering these medications by intranasal (**IN**) and oral (**PO**) routes.

The study consisted of four periods: (1) subject screening; (2) double-blinded qualification testing, naloxone challenge and drug discrimination, three nights in-house followed by 48-hour washout; (3) double-blinded crossover treatments, four two-night in-house sessions, washout of \geq seven days between treatments (discharged between treatments); and (4) safety follow up, 7-10 days after last treatment.

Of the initial 48 subjects enrolled, all passed naloxone challenge testing, 21 failed discrimination testing, 27 proceeded to blinded treatment, and 25 completed the study. The pharmacist was the only unblinded study personnel, whose duties were limited to study drug preparation and assisting the quality control staff in maintaining the integrity of the study blind.

Subject Screening

Inclusion Criteria

- Adult (age 18-55 years) recreational, non-dependent and non-tolerant opioid user in good general health, with overall frequency of opioid use \geq 10 times within last year and at least once within last 12 weeks, including IN use \geq thrice within last year and \geq once in last 12 weeks
- Not opioid dependent or tolerant according to criteria specified in *Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision (DSM-IV-TR)*; negative urine drug screen (**UDS**) at screening and periodically throughout study; for women (and men, as applicable), negative pregnancy testing, acceptable contraception, and child-bearing potential as detailed in the protocol

Exclusion Criteria

- Any clinically significant condition (all organ systems), including any condition that may interfere with drug PK; drug and/or alcohol dependence (except caffeine and nicotine) per DSM-IV-TR criteria
- Any contraindication to opioid use (respiratory depression, asthma, hypercarbia, paralytic ileus); pregnant or nursing women; hypersensitivity to any of the test products or their ingredients

Subject Qualification

Following screening, subjects were tested for lack of potential for opioid withdrawal and for drug responsiveness and tolerance. Subjects proceeded to blinded crossover treatment upon a showing of acceptable testing results and study medication tolerance, including no emesis within two hours of dosing, and as judged by the CI, the ability to adequately insufflate crushed medications and otherwise successfully complete the study.

- **Naloxone Challenge:** This screening test was to minimize the potential for opioid withdrawal during blinded crossover treatment. All subjects initially received 0.2 mg of intravenous (**IV**) naloxone. If no withdrawal signs were seen (COWS), an additional 0.6 mg was given. If again no withdrawal signs were seen, the subject proceeded to be evaluated for drug discrimination.
- **Drug Discrimination:** This screening test was to confirm the subject's ability to distinguish crushed IN morphine sulfate IR (30 mg tablet) from placebo for pharmacodynamic (**PD**) effects indicative of abuse potential. While remaining in-house, a limited randomized, double-blind, two-way crossover (1:1 ratio) study was conducted as a screening study in which subjects received single IN doses of morphine and placebo (≥ 24 hours between doses). Acceptable results were as follows:

Drug Liking, bipolar (negative to positive) 0-100 mm VAS scores within two hours of dosing: (1) with morphine IR, minimum peak score ≥ 65 mm; (2) with morphine and placebo, ≥ 15 mm higher peak with morphine relative to placebo; and (3) with placebo, 40-60 mm (inclusive)

Drug High, unipolar (none to maximum) 0-100 mm VAS scores within two hours of dosing: (1) ≥ 30 mm difference between scores for active and placebo treatments; and (2) placebo response between 0-10 mm (inclusive)

Blinded Crossover Treatments

Subjects remained in-house (two-nights) for each of the four crossover treatments. Between treatments, subjects were discharged for a minimum of seven-days to washout the previous treatment. Subjects returned to the clinic to complete the one-day safety follow up, at 7-10 days after the last treatment. The four crossover treatment groups were:

- Treatment A (IN/PO placebo): crushed IN placebo and intact PO placebo
- Treatment B (IN MS Contin[®]): crushed IN MS Contin[®] (60 mg) and intact PO placebo
- Treatment C (IN IDT-001): crushed IN IDT-001 (60 mg) and intact PO placebo
- Treatment D (PO IDT-001): crushed IN placebo and intact PO IDT-001 (60 mg)

Major Endpoints and Analyses

Subjects rated their perception of euphoric effect at workstations using Scheduled Measurement System (SMS), a proprietary software for measuring perceived euphoric (PD) effects. The SMS screens presented various VAS questionnaires, and the VAS data were plotted to determine PD endpoints indicative of abuse potential.

Pupillometry served as the only objective, sensitive, and reliable measure of opioid action. The pupil diameter was measured using NeurOptic[®] VIP-200 pupillometer, consistently on the same eye under similar controlled conditions. The major study endpoints and analyses are summarized below.

- Measured subjective PD endpoints indicative of abuse potential
 - *Drug Liking* (primary endpoint)
 - *Any Drug Effects, Good Effects, Drug High, Bad Effects, Sick, Nausea, Sleepy, Dizzy*
 - *Snorting Experience, Overall Drug Liking, and Take Drug Again*
 - Addiction Research Center Inventory (**ARCI**) and Morphine-Benzedrine Group (**MBG**) scale
 - Price Value Assessment Questionnaire (**PVAQ**)
- Calculated PD endpoints: *Drug Liking*, other drug effects questionnaires (**DEQs**), pupillometry
 - Peak effect (**E_{max}**) and time to peak effect (**TE_{max}**)
 - Area under effect curve (**AUE**) at 1 hour (**AUE_{0-1h}**)
 - AUE at two, eight, 12, and 24 hours (**AUE_{0-2h}**, **AUE_{0-8h}**, **AUE_{0-12h}**, **AUE_{0-24h}**)
 - AUE at maximum morphine concentration (**AUE_{0-Tmax}**)
- Pharmacokinetic (**PK**) endpoints
 - Assays for morphine and its metabolite morphine 6-glucuronide (**M6G**)
 - PK parameters calculated using non-compartmental methods
- Safety endpoints
 - Adverse events (**AEs**), physical examination findings, vital signs
 - Clinical laboratory test results, 12-lead electrocardiogram (**ECG**) findings
- Analyses (treatment comparisons)
 - Primary comparison: Treatment B (IN MS Contin[®]) and Treatment C (IN IDT-001)
 - Secondary comparisons: all other treatment pairs (B/D, C/A, D/A, D/C, and B/A)
 - Validation comparison: Treatment B (IN MS Contin[®]) and Treatment A (IN/PO placebo)

OSI Comments:

For the efficacy data audit, measured data relevant to the primary efficacy analysis were to be verified against the source records for at least 15 representative subjects, randomly selected among those randomized, to confidently exclude unacceptable data management. The audit included: initial measurement and documentation, data transcription, database entry, electronic data transfer, internal data audit and data compilation.

For the safety audit, all SAEs and all AEs leading to study discontinuation were to be verified for all enrolled subjects. Other AEs observed during blinded crossover treatments were to be verified against the source records for 15 representative subjects, randomly selected among those enrolled and different from the 15 selected for the efficacy audit.

Major Sponsor-Reported Outcomes

- *Drug Liking* scores were lower for crushed IN IDT-001 than for crushed IN MS Contin, suggestive of less abuse potential for IDT-001 (relative to MS Contin) by IN route. For IDT-001, no significant differences were observed between crushed IN and intact PO.
- PK and PD results were consistent, with substantially higher peak plasma concentrations (**C_{max}**) for crushed IN MS Contin. IDT-001 given crushed IN showed an extended-release PK profile similar to that for intact PO.
- IDT-001 was well tolerated by subjects. Nasal congestion and rhinorrhea occurred frequently with IN administration, for crushed IDT-001 and placebo. The safety profile (AEs) of IN IDT-001 was consistent with the known profile for opioid-containing drugs.

II. INSPECTION OUTCOME

Study M-ARER-002 was the only study that supported abuse deterrence of Morphine ARER, and the single CI site at which this study was (entirely) conducted was identified for GCP inspection. No special review concerns were identified at NDA review regarding CI conflict of interest or study conduct.

Clinical Investigator	Study and Subjects	Inspection Outcome
Lynn R. Webster, M.D. CRI Lifetree, Inc. 3838 South 700 East, Suite 202 Salt Lake City, Utah	Study M-ARER-002 48 enrolled, 27 randomized	July 13 - 21, 2015 Pending, preliminary NAI

NAI = no action indicated (no significant violations)

Pending = preliminary results based on communication with field investigator

Lynn R. Webster, M.D

a. What was inspected:

Records review: institutional review board oversight, sponsor's study monitoring, CI financial disclosure, drug accountability and disposition, and subject records

Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification (randomization, efficacy, AEs, protocol deviations, and subject discontinuations)

b. General observations and comments:

Seventy subjects were screened, 48 were enrolled (qualification phase), 27 were randomized, and 25 completed the study. Records were reviewed for all enrolled subjects, including detailed review for 30 subjects (15 randomized for efficacy, 15 others enrolled for safety).

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, drug accountability, AE monitoring, and reporting of AEs and protocol deviations. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, case report forms (CRFs), and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The findings noted above are based on preliminary communication with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

To support the review of this 505 (b)(2) NDA for Morphine ARER, the HAL study M-ARER-002 was audited at GCP inspection of the only site at which this study was entirely conducted. Subject case records were reviewed for all enrolled subjects, including detailed review for 30 subjects: 15 of 27 randomized (56%) for the efficacy audit, and 15 others of 48 enrolled (31%) for the safety audit.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including IRB oversight and sponsor monitoring of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from this HAL study appear reliable as reported in the NDA.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Janice K. Pohlman, M.D., M.P.H.
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/s/

JONG HOON LEE

07/28/2015

CIS goal date: August 1, 2015

JANICE K POHLMAN

07/28/2015

KASSA AYALEW

07/28/2015



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 17, 2015

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Silvia Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Morphabond¹ (Morphine Extended-Release Tablets), NDA 206-544
Trade Name, dosages, formulations, routes: Extended Release Formulation for oral administration with dosage strengths of 15 mg, 30 mg, 60 mg, and 100 mg morphine sulfate.
IND Number: 115,822
Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Sponsor: Inspirion Delivery Technologies, LLC
PDUFA Goal Date: September 21, 2015

Materials Reviewed:

Abuse-related preclinical and clinical data in NDA submission, (eCTD number, submission date)
Additional materials

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¹ “Morphabond” is the approved proprietary name for morphine ARER tablets (DARRTS, NDA 206-544, 04-02-2015, Author: Vaishali Jarrel). In this review the name “Morphabond” is used in place of “morphine ARER” or “IDT-001.”

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I. Summary

1. Background

This memorandum responds to a consult request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) dated December 8, 2014, to evaluate from a CSS perspective materials submitted by Inspirion Delivery Technologies, LLC in NDA 206-544 for Morphabond (morphine sulfate extended-release) Tablets. According to Sponsor the product is formulated to have abuse deterrent properties. The drug product is indicated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Morphabond Tablets was developed under IND 115,822 as an extended release formulation containing 15 mg, 30 mg, 60 mg, and 100 mg morphine sulfate per tablet. Proposed dosage regime is 15 mg to 100 mg orally every ^{(b) (4)} 12 hours. The product has not been marketed in the United States or other countries. Morphabond is in Schedule II of the federal Controlled Substances Act (CSA)

2. Conclusions

1. The overall findings of the in vitro studies and the intranasal human abuse potential study suggest a possible intranasal abuse deterrent effect of Morphabond tablets relative to MS Contin. The studies demonstrate that Morphabond tablets retain the extended release properties upon crushing and extraction. Thus, Morphabond tablets resist manipulation for purposes of intravenous abuse.
2. Study M-ARER-002 provides evidence that the insufflation of crushed Morphabond 60 mg compared to crushed MS Contin 60 mg is associated with less subjective effects of drug liking (measured on the 0-100 point bipolar Drug Liking VAS) and high (measured on the 0-100 point unipolar High VAS), compared to MS Contin.
3. With respect to Drug Liking, insufflated Morphabond 60 mg compared to MS Contin produced significantly ($p < 0.0001$) lower levels of maximum Drug Liking (E_{max}) (LS means of 71.13 mm versus 84.79 mm, respectively) and overall experience of drug liking over first two hours post-dose (AUE_{0-2hrs}) (117.95 h·mm versus 142.6 h·mm, respectively). Likewise, insufflation of crushed Morphabond 60 mg compared to insufflated crushed MS Contin produced significantly lower levels

($p < 0.0001$) of E_{max} for High (LS means of 43.0 mm versus 67.7 mm, respectively) and AUE_{0-2hrs} (36.65 h·mm versus 91.63 h·mm, respectively).

4. Intranasal crushed Morphabond 60 mg and intact oral Morphabond 60 produced similar E_{max} s of Drug Liking (LS means of 71.13 mm versus 67.03 mm, respectively) and High (LS means of 43.0 mm versus 34.2 mm) that was significantly ($p < 0.0001$) greater than the E_{max} produced by intranasal placebo for either Drug Liking or High, indicating that both treatments were associated with abuse potential. At the same time, both the manipulation by crushing followed by the alternative route of administration (insufflation) of Morphabond tablets did not cause a significant increase in subjective measures such as Drug Liking or High compared to that produced by intact oral Morphabond.
5. Using the 0-100 point bipolar Take Drug Again VAS, individuals were more willing ($p = 0.0341$) if given the opportunity again to insufflate MS Contin 60 mg (LS mean E_{max} of 76.5 mm) than Morphabond 60 mg (LS mean E_{max} of 66.6 mm). Whereas study subjects expressed no interest in insufflating placebo (LS mean E_{max} of 49.48 mm) again if given the opportunity, they showed some interest in taking again either intranasal crushed Morphabond 60 mg (LS means of E_{max} of 66.56 mm versus 49.48 mm, $p = 0.0004$) or oral intact Morphabond 60 mg (LS means of E_{max} of 64.33 mm versus 49.48 mm, $p = 0.0019$).
6. All subjects were able to insufflate the entire amount of crushed Morphabond 60 mg, crushed MS Contin 60 mg, and placebo, all of which consisted of matching weights. In addition, based on the 0-100 point bipolar Snorting Experience VAS, subjects recorded a similar overall experience for insufflation of the three treatments. This suggests that the insufflation of crushed Morphabond was not associated with aversive intranasal effects.
7. Morphabond tablets, but not MS Contin tablets, demonstrated resistance to physical manipulation. using household tools (b) (4)

(b) (4)

(b) (4) This procedure, being the most effective to reduce particle size, was used to prepare the treatment of crushed Morphabond used in the intranasal human abuse potential study (M-ARER-002).

8. (b) (4)

9.

10

11

12

13

(b) (4)

14. Under the conditions used by the Sponsor, abuse of Morphabond tablets by smoking is not likely. The temperatures used produced extensive degradation and little vaporization of the morphine sulfate.

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. Consideration should be given to allow the Sponsor to insert language into Section 9 of the label briefly describing the results from the in vitro studies on Morphabond tablets compared to MS Contin. Inclusion of this information is appropriate considering that Morphabond tablets, compared to MS Contin, are more difficult to manipulate with (b) (4) and more resistant to

dose-dumping in various solvents including (b) (4) compared to MS Contin. In addition, both the formation of a viscous liquid upon exposure to (b) (4), as well as the limited extraction of morphine sulfate, (b) (4) Morphabond tablets to form a solution suitable for abuse by intravenous injection. This data is relevant because the injectable route is considered a major route of abuse of morphine containing products.

- Sponsor is proposing to place into Section 9.2 of the label language describing the results of intranasal human abuse potential study M-ARER-002. Such language with possible modifications appear to be acceptable since the results of this study provide evidence suggesting that Morphabond tablets may provide resistance to intranasal abuse, compared to MS Contin.

II. Discussion

1. Chemistry

1.1 Substance information

The drug substance, morphine sulfate, USP, is the active ingredient in Morphabond tablets. Morphine sulfate is a pentahydrate with a theoretical content of (b) (4)% water.

The composition for all strengths of Morphabond tablets is provided in Table 1. The Morphabond tablet comprises a (b) (4) color coating, and ink printing. According to Sponsor, (b) (4) impart the proprietary abuse-deterrent characteristics (b) (4)

Table 1. Quantitative Composition for All Strengths (15 mg, 30 mg, 60 mg, and 100 mg) of Morphabond Tablets. (Source: Table 2.3.P-1 found on pages 12-14 of the Drug Product Summary Module 2.3.P)

Component	Function	Quantitative Composition of Morphabond Tablets							
		15 mg		30 mg		60 mg		100 mg	
		mg/Tab	% w/w	mg/tab	% w/w	mg/Tab	% w/w	mg/Tab	% w/w
Hypomellose (hydroxypropyl methylcellulose (b) (4) (b) (4)									
Xanthan Gum (b) (4)									
Microcrystalline Cellulose (b) (4) (b) (4)									
Sodium alginate									

		(b) (4)			
Alginic acid					
Mannitol	(b) (4)				
Colloidal silicon dioxide	(b) (4)				
Magnesium stearate	(b) (4)				
.....					
Lactose monohydrate	(b) (4)				
Polysorbate 80	(b) (4)				
.....					
Morphine Sulfate	Active	15.0	(b) (4) 30.0	(b) (4) 60.0	(b) (4) 100.0
Ethyl acrylate and methyl methacrylate copolymer dispersion					(b) (4)
					(b) (4)
Ethyl acrylate and methyl methacrylate copolymer dispersion					(b) (4)
.....					

(b) (4)

(b) (4)

As can be seen from Table 1, Morphabond tablets are large, ranging from (b) (4) for the 15 mg strength to (b) (4) for the 100 mg tablets.

1.3 In vitro manipulation and extraction studies for products with Abuse-Deterrent features

In support of NDA 206-544, Sponsor submitted the following documents involving the Category 1 in vitro testing program conducted on Morphabond tablets (100 mg) and using MS Contin as the comparator.

- Inspirion Delivery Technologies In-Vitro Tamper Resistance Testing Protocol M-ARER-001 – Evaluation of the Morphine ARER Tablet (Abuse Resistant Extended Release Morphine) Product Code – IDT-001 vs MS Contin
- Inspirion Delivery Technologies, LLC Morphine ARER Category I Study Summary dated September 25, 2014.
- Specific Category 1 Testing Reports covering physical manipulation, large volume extractability, injectability, syringeability, and small volume extractability as well as smokeability studies.

The in vitro studies were reviewed by OPQ/CMC. A copy of the OPQ review regarding the in vitro studies is attached at the end of this review. The following summary of the in vitro studies is based in part on the review provided by OPQ and on CSS examination of the studies submitted by Sponsor.

Physical Manipulation Studies – Comparison of 100 mg Morphabond to 100 mg MS Contin.



Collectively, the data demonstrate that Morphabond 100 mg tablets were more resistant to crushing and particle size reduction compared to MS Contin 100 mg tablets.

Large Volume (b) (4) Extractability Studies – (b) (4)

The extraction of morphine sulfate, expressed as the percentage label claim (% LC extracted), from intact and (b) (4) Morphabond 100 mg tablets and MS Contin 100 mg tablets in (b) (4) under selected extraction conditions is shown in Table 2.

MS Contin 100 mg Tablets – Intact and (b) (4)



Table 2. Percent Label Claim (%LC) of Morphine Sulfate Extracted in (b) (4) from Intact and (b) (4) Morphabond 100 mg and MS Contin 100 mg Tablets. (Data taken from In Vitro Study Reports ARS-98-22 and ARS-98-23)

Product and Extraction Conditions	% LC of Morphine Sulfate Extracted	
	Intact	(b) (4)
Morphabond 100 mg (b) (4)	(b) (4)	(b) (4)
MS Contin 100 mg (b) (4)	(b) (4)	(b) (4)

Morphabond 100 mg Tablets – Intact and (b) (4)

(b) (4)	(b) (4)
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Large Volume (b) (4) Extractability Studies – Solvents Other than (b) (4)

(b) (4)	(b) (4)
---------	---------

(b) (4)

Injectability, Syringeability, and Small Volume Extractability Studies

(b) (4)

Using a double-blind, within-subject, randomized, placebo-controlled study design, Stoops et al., (2010)² examined the subjective effects of intravenous injection of morphine sulfate (5 mg, 10 mg, and 20 mg) on subjective effects, including Drug Liking (visual analog scale), in non-dependent, recreational opioid users with a history of intravenous opioid use. Intravenous injection of 5 mg, 10 mg or 20 mg of morphine sulfate produced levels of drug liking that were significantly above that produced by placebo. These data suggest that a solution suitable for intravenous injection should contain at least (b) (4) of morphine sulfate, which is likely to produce sufficient reinforcing effects such as drug liking.

Morphabond 100 mg Tablets (intact, cut, and (b) (4)) were compared to 100 mg MS Contin tablets (intact and (b) (4)) using (b) (4) for producing solutions suitable for intravenous injection. Morphabond tablets were cut into pieces (approximately (b) (4)). Morphabond was produced by (b) (4).

Intact, cut, and ground tablets were extracted, using (b) (4). The resulting mixture was immediately drawn into (b) (4) needles. The volume of syringeable (b) (4) liquid was recorded and the content analyzed for morphine.

Use of Intact 100 mg MS Contin Tablets

(b) (4)

² Stoops WW, Hatton KW, Lofwall MR, Nuzzo PA, and Walsh SL (2010). Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. *Psychopharmacology*, 212: 193-203

(b) (4)

Use of (b) (4) (b) (4) *MS Contin 100 mg*

(b) (4)

Use of One Intact 100 mg Morphabond Tablet

(b) (4)

Use of Cut (b) (4) or (b) (4) (b) (4) 100 mg Morphabond Tablet

(b) (4)

Smokeability Studies

Smokeability studies are intended to examine the manipulation of Morphabond tablets for purposes of abuse by inhalation. Under the conditions of manipulation used by the Sponsor, Morphabond tablets would not be susceptible to abuse by smoking. Although not examined by Sponsor, it is anticipated that the conditions used by Sponsor, including the high temperatures resulting in degradation of morphine sulfate, would not be suitable for smoking MS Contin.

(b) (4)

4. Clinical Studies

4.1 Human abuse potential studies

In support of NDA 206-544, Sponsor submitted intranasal study M-ARER-002 entitled “A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Single-Dose, Four-Way Crossover Study to Determine the Relative Bioavailability, Abuse Potential, and Safety of Equivalent Doses of Crushed and Intact IDT-001 compared with Crushed MS Contin® and Placebo in Opioid Experienced, Non-Dependent Subjects Following Intranasal Administration.” Study was conducted between October 2012 and January 2013. Final report date is May 6, 2014.

At the request of CSS, the Office of Biostatistics completed a statistical review of study M-ARER-002 (DARRTS, NDA 206-544, April 1, 2015, Author: Wei Liu, Ph.D.). For the purposes of this review, the statistical review conducted by the Office of Biostatistics will be used to assess the data provided in study M-ARER-002.

Methodology – Study Design

Study M-ARER-002 was a single-center, randomized, double-blind, double-dummy, placebo-controlled, single-dose, four-way crossover study. The study consisted of a Screening Phase, Drug Discrimination Phase, Treatment Phase, and Follow-up.

Primary objective was to determine the abuse potential of crushed and intact Morphabond tablets 60 mg relative to crushed intranasal MS Contin® 60 mg when administered intranasally and orally to non-dependent, recreational opioid users.

Secondary objectives included the following:

- To determine the abuse potential of crushed and intact Morphabond 60 mg relative to placebo when administered intranasally to non-dependent, recreational opioid users;
- To determine the relative bioavailability of morphine in plasma from crushed and intact Morphabond 60 mg compared with crushed intranasal MS Contin 60 mg when administered intranasally and orally to non-dependent, recreational opioid users; and
- To determine the safety of crushed and intact Morphabond 60 mg compared with crushed intranasal MS Contin 60 mg and placebo following intranasal and oral administration in non-dependent, recreational opioid users.

Study used 25 subjects in the pharmacodynamic assessment and 27 subjects in the pharmacokinetic assessment. Subjects were non-dependent, recreational opioid users with experience with intranasal

drug administration, defined as intranasal use on at least 3 occasions within the last year prior to the Screening Visit.

Subjects were subjected to naloxone challenge testing to ensure they were not physically dependent to opioids.

Methodology – Drug Discrimination Phase

Drug discrimination test consisted of a two-way crossover, 1:1 ratio, double-blind, randomized design, subjects received a single, intranasal dose each of morphine sulfate IR (30 mg crushed tablet) and placebo (crushed Placebo Tablet for Reference Product). Both treatments were bulked up using crushed PTRP tablets to match the weight of powder (approximately (b) (4)) used in the Treatment Phase. Each dose was separated by at least a 24-hour period. To be eligible for the Treatment Period, subjects were required to meet the following criteria:

- With regard to bipolar Drug Liking VAS: have a minimum E_{max} score of 65 in response to active treatment in the first 2 hours; have a ≥ 15 mm difference between active and placebo treatments in the first 2 hours post-dosing; and have a placebo response ≥ 40 and ≤ 60 mm during the first two hours post-dosing
- With regard to unipolar High VAS: display a ≥ 30 mm difference between active and placebo treatments during the first 2 hours following dosing; and have a placebo response \geq and ≤ 10 mm during the first two hours post-dosing.
- Have ability to tolerate crushed 30 mg morphine sulfate IR administered intranasally as assessed by no emesis within 2 hours following dosing, ability to insufflate the entire volume of crushed treatments, or as otherwise as judged by the Investigator
- Acceptable response to other study assessments, as determined by the Investigator.
- Ability to successfully complete the study as judged by the Investigator.

Methodology – Treatment Phase

During the Treatment Period, subjects received each of 4 treatments in a randomized, four-way crossover, double-blind, double-dummy, 1:1:1:1 ratio design. Each Treatment Period encompassed a 2-night stay for dosing, followed by a minimum 7-day outpatient washout period. Specific treatments administered are provided in Table 3.

Table 3. Description of treatments Administered During the Treatment Phase. (Source: M-ARER-002 Clinical Study Report)

Treatment	Designation	Description
A	IN/Oral Placebo	Crushed IN IDT-001 Placebo + Intact Oral Morphabond Placebo
B	IN MS Contin 60 mg	Crushed IN MS Contin 60 mg (with crushed Placebo Tablet for Reference Product added for volume) + Intact Oral Morphabond Placebo
C	IN Morphabond 60 mg	Crushed IN Morphabond 60 mg + Intact Oral Morphabond Placebo
D	Intact Oral Morphabond 60 mg	Crushed IN Morphabond Placebo + Intact Oral Morphabond 60 mg

Because crushed MS Contin produces a small volume of material (roughly (b) (4) the volume of an Morphabond tablet), a PTRP tablet, consisting of (b) (4) mannitol and magnesium stearate, was crushed and added to crushed MS Contin for Treatment B; thus, the volume of the crushed MS Contin and crushed PTRP matched the volume of all other crushed treatments (approximately (b) (4) of powder) administered in the Treatment Period.



With crushed PTRP tablet added to the crushed MS CONTIN, the overall particle sizes of the 3 treatments were comparable thereby maintaining treatment blinding.

Methodology – Product Manipulations

Sponsor provided the following reports regarding manipulations of 60 mg Morphabond and 60 mg MS Contin in preparation of treatments for study M-ARER-002:

- ARS-97-01: Particle sized determinations for likability testing studies for Morphine ARER tablets 60 mg.
- ARS-97-02: Drug recoverability study from the sample preparation for likability studies for Morphine ARER tablets 60 mg
- ARS-97-03: Drug recoverability study from the sample preparation for likability studies for Morphine ARER tablets 60 mg
- ARS-97-05: Particle size determination for likability testing studies for Morphine ARER tablets 60 mg, MS Contin Tablets 60 mg, placebo tablets for references product and placebo for Morphine ARER tablets 60 mg.

Morphabond 60 mg tablets and MS Contin 60 mg tablets (b) (4) (b) (4) (b) (4) (b) (4) respectively. This was an appropriate method of manipulation considering that the Category 1 in vitro studies demonstrated that IDT-001 tablets are resistant to crushing (b) (4) (b) (4) (b) (4) (b) (4) IDT-001 tablets. Additional studies showed that (b) (4) Morphabond tablets (b) (4) (b) (4) Morphabond placebo tablets were also (b) (4) (b) (4) (b) (4) a (b) (4) (b) (4) PTRP tablet was crushed using (b) (4)

(b) (4) (b) (4) (b) (4). The powdered PTRP tablet was insufflated just following the insufflation of the crushed MS Contin tablet.

Roughly a similar particle size distribution was observed between crushed 60 mg Morphabond and crushed 60 mg MS Contin + Placebo for Reference Product Tablet.

- Approximately (b) (4) % retained on (b) (4) mesh sieve
- Approximately (b) (4) % retained on (b) (4) mesh sieve
- Approximately (b) (4) % retained on (b) (4) mesh sieve

Methodology – Pharmacokinetic Measures

During each Treatment Period blood samples for PK determination were taken within 1 hour pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose. Pharmacokinetic parameters were calculated for plasma morphine concentration data using non-compartmental methods. The following PK parameters were determined:

- C_{max} = Maximum measured plasma concentration of morphine
- T_{max} = Time to achieve C_{max} for plasma morphine
- $AUC_{0-30min}$ = Area under the morphine plasma concentration vs. time curve from 0 to 30 minutes
- AUC_{0-t} = Area under the plasma morphine concentration vs. time curve from 0 to last measurable concentration
- AUC_{0-inf} = Area under the plasma morphine concentration vs. time curve from 0 to infinity

Relative bioavailability was calculated for Morphabond (crushed) versus MS CONTIN (crushed) using the ratio (and 90% confidence interval) of geometric means for AUC_{0-inf} , AUC_{0-8hr} , and C_{max} . Analyses of C_{max} and AUCs used the natural log-transform ($\ln(C_{max})$ and $\ln(AUC)$). PK parameters were analyzed using a linear mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence will be used. Least-squares geometric means for C_{max} and AUCs along with 90% CIs will be provided for each treatment. The LS mean difference for T_{max} and geometric mean ratios for C_{max} and AUCs along with 90% CI were calculated for all treatment comparisons of interest.

Methodology - Pharmacodynamic Measures

The primary pharmacodynamic measure was bipolar Drug Liking VAS. The primary parameters included:

- E_{max} = peak effect
- TE_{max} = time to E_{max}
- AUE_{0-1hr} = Area under the effect curve to 1 hour
- AUE_{0-2hrs} = Area under the effect curve to 2 hours.

Secondary pharmacodynamic measures examined in this review include:

- Unipolar High VAS
- Bipolar Take Drug Again VAS – mean response determined at 24 hour time point
- Point Snorting Experience VAS

Drug Liking VAS and High VAS were administered at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dosing. Take Drug Again VAS was administered at 12 hours and 24 hours post-dose. The Snorting Experience VAS was completed within 5 minutes after intranasal administration of study drugs.

Results

Disposition of Subjects

Forty-eight (48) subjects entered the study, passed the Naloxone Challenge Test, and underwent the Drug Discrimination test. Of these subjects, 21 failed the Drug Discrimination Test and were withdrawn from the study.

Of the 27 subjects who entered the Treatment Period, 2 subjects did not complete all treatment periods: both of these subjects were withdrawn from the study due to a positive urine drug screens upon admission to the clinic. The pharmacodynamic population consisted of 25 subjects who completed all treatments under the Treatment Phase. The pharmacokinetic population consisted of 27 subjects.

Time to Snort Treatments

All intranasal doses, including Morphabond placebo, MS Contin, and Morphabond 60 mg, were completely consumed in 8 minutes or less. The median amount of time required for intranasal administration of all crushed treatments was 2 minutes suggesting that intranasal administration was not more difficult for any treatment.

Snorting Experience of the Pharmacodynamic Population (N = 25)

Assessment of the snorting experience was conducted at 5 minutes following administration of the intranasal treatments using the bipolar 100-point VAS scale. Subjects respond to the statement “My snorting experience with this drug is:” by marking a single vertical line on the VAS. The question was scored using a 0-100 point bipolar VAS anchored on the left with “very unpleasant to snort (score of 0); “indifferent to the pleasantness of the snorting experience” (score of 50) in the middle; and anchored on the right with “very pleasant to snort” (score of 100).

The least square (LS) mean scores for IN crushed MS Contin, IN Morphabond, and IN Morphabond placebo were 50.42 mm, 50.17 mm and 42.65 mm, respectively. Statistical analysis conducted by Sponsor showed no significant differences in the scores between IN treatments whereby indicating a similar snorting experience following each of the IN treatments.

Pharmacokinetics of Morphine in Plasma

Pharmacokinetic parameters for morphine in plasma following active treatments are found in Table 4. ANOVA based on least square mean differences conducted by Sponsor demonstrated that intranasal (IN) Morphabond 60 mg, compared to IN MS Contin 60 mg, produced significantly ($p < 0.0001$) lower levels of maximum morphine levels (C_{max}) as well as lower morphine exposure (partial AUC curves) over the period of 0.5 to 8.0 hours post-dosing. When compared to oral intact Morphabond 60 mg, IN

Table 4. Pharmacokinetic Parameters for Morphine in Plasma after Administration of Intranasal Morphabond, Intranasal MS Contin, and Intact Oral Morphabond in the Pharmacokinetic Population (N = 27)

Pharmacokinetic Parameter for Plasma Morphine	Statistic	Morphabond 60 mg Crushed Intranasal	MS Contin 60 mg Crushed Intranasal	Morphabond 60 mg Intact Oral
C_{max} (ng/mL)	Mean (SD)	26.2 (11.2)	49.5 (17.3)	18.6 (5.7)
	LS Mean	24.03	46.85	17.72
T_{max} (hrs)	Median	1.6	1.1	1.6
	Range	1.0 – 3.1	0.2 – 1.6	0.5 – 3.1
$AUC_{0-0.5hrs}$ (ng·hr/mL)	Mean (SD)	2.8 (1.2)	10.9 (5.2)	2.1 (1.3)
	LS Mean	2.53	9.87	1.76
AUC_{0-2hrs} (ng·hr/mL)	Mean (SD)	34.2 (13.7)	67.0 (22.9)	22.6 (7.5)
	LS Mean	31.40	63.48	21.50
AUC_{0-8hrs} (ng·hr/mL)	Mean (SD)	120.9 (48.2)	136.5 (43.4)	89.3 (25.4)
	LS Mean	109.96	130.43	85.64
AUC_{0-inf} (ng·hr/mL)	Mean (SD)	219.8 (97.4)	188.0 (51.5)	158.0 (21.9)
	LS Mean	197.56	166.87	217.10

Morphabond 60 mg tended to produce somewhat higher (not statistically significant) C_{max} and partial AUCs (0 to 0.5 hrs, 0 to 2 hrs, and 0 to 8 hrs) for morphine. In terms of total drug exposure as represented by AUC_{0-inf} there was no difference in total morphine exposure between treatments.

Results – Drug Liking VAS

The 0-100 point bipolar Drug Liking VAS was the single primary measure used in study M-ARER-002. This scale assesses “at the moment” perception of Drug Liking. Subjects respond to the statement “Do you like the drug effect you are feeling now?” The question was scored using a 0-100 point bipolar VAS anchored on the left with “strong disliking” (score of 0); “neither like nor dislike” (score of 50) in the middle; and anchored on the right with “strong liking” (score of 100).

Statistical parameters (E_{max} , TE_{max} , AUE_{0-1hr} , and AUE_{0-2hrs}) on the bipolar Drug Liking VAS following the four treatments are shown in Table 5. Statistical analyses of differences in PD parameters between treatments, as provided by CDER Office of Biostatistics are provided in Table 6.

Intranasal MS Contin produced an LS mean E_{max} of drug liking (84.79 mm) and AUE_{0-2hrs} (143.10 h·mm) that was significantly ($p < 0.0001$) higher than that produced by placebo (54.22 mm and 101.04 h·mm) thereby validating study M-ARER-002.

Table 5. Statistical Parameters for E_{max} , TE_{max} , AUE_{0-1hr} , and AUE_{0-2hrs} on the Primary Measure of Bipolar Drug Liking VAS in the Pharmacodynamic Population (N=25). (Source: FDA CDER Office of Biostatistics)

Drug Liking VAS	Statistic (N = 25)	Placebo Crushed Intranasal	MS Contin 60 mg Crushed Intranasal	Morphabond 60 mg Crushed Intranasal	Morphabond 60 mg Intact Oral
E_{max} (mm)	Mean (SE)	54.23 (1.63)	85.32 (2.42)	71.72 (2.87)	67.32 (3.13)
	Median (Range)	51.0 (50.0-80.0)	85.0 (56.0-100.0)	72.00 (50.0-100.0)	66.00 (50.0-99.0)
	LS Mean (SEM)	54.22 (2.6)	84.79 (2.6)	71.13 (2.6)	67.03 (2.6)
	95% CI	49.04, 59.40	79.61, 89.97	65/95, 76.31	61.85, 72.21
TE_{max} (h)	Median	1.0	1.5	2.0	2.0
	Range	(0.5-10)	(0.5-6.0)	(0.5-6.0)	(0.5-6.0)
AUE_{0-1hrs} (h·mm)	Mean (SE)	49.60 (0.81)	63.25 (2.94)	54.75 (1.74)	49.88 (0.63)
	Median (Range)	48.33 (41.93 – 61.60)	59.88 (36.53 – 84.52)	52.50 (47.50 – 85.00)	48.58 (47.50 – 62.73)
	LS Mean (SEM)	49.6 (1.8)	63.0 (1.8)	54.4 (1.8)	49.8 (1.8)
	95% CI	45.9, 53.2	59.4, 66.6	50.8, 58.0	46.2, 53.5
AUE_{0-2hrs} (h·mm)	Mean (SE)	101.01 (2.33)	143.10 (5.26)	118.63 (4.37)	110.01 (2.46)
	Median (Range)	98.33 (75.83 – 134.85)	140.88 (88.53 – 183.27)	116.08 (97.50 – 185.00)	111.58 (97.50 – 134.8)
	LS Mean (SEM)	101.04 (3.9)	142.6 (3.9)	117.9 (3.9)	109.9 (3.9)
	95% CI	93.2, 108.9	134.8, 150.4	110.1, 125.8	102.1, 117.7

As evidenced from LS means for E_{max} of drug liking, the positive comparator intranasal MS Contin 60 mg produced a peak drug liking (84.79 mm) that was significantly ($p < 0.0001$) above that produced by intranasal crushed Morphabond 60 mg (71.13 mm) or by oral Morphabond 60 mg (67.03 mm). In addition, the total drug liking experienced up to 2 hours post-dosing was significantly higher ($p < 0.0001$) following crushed MS Contin (67.7 h·mm) compared to either crushed Morphabond or oral Morphabond. In addition, there was no significant difference in the E_{max} of drug liking ($p = 0.0846$) or AUE_{0-2hrs} ($p = 0.1034$) between crushed intranasal Morphabond and oral Morphabond. These observations support an abuse-deterrent effect of Morphabond tablets to intranasal abuse.

It should be noted that compared to intranasal placebo, intranasal Morphabond 60 mg produced a significantly higher LS mean E_{max} of drug liking ($p < 0.0001$) and AUE_{0-2hrs} of drug liking ($p = 0.0005$), thereby indicating a significant abuse potential.

Based on percentage reduction calculations conducted by CDER Office of Biostatistics, the majority of subjects (68% $n = 17$) experienced some reduction in E_{max} of Drug Liking VAS with crushed intranasal Morphabond 60 mg compared with crushed intranasal MS Contin 60 mg. Of the total number of subjects, 48% ($n = 12$) and 36% ($n = 9$) experienced 30% and 40% reductions in E_{max} of drug liking, respectively.

Table 6. Statistical Analyses of LS Mean Parameters (E_{max} , AUE_{0-1hr} , and AUE_{0-2hrs}) for Bipolar Drug Liking VAS, Unipolar High VAS, and Take Drug Again VAS in the Pharmacodynamic (PD) Population (N=25). (Treatment differences in LS means were determined using a mixed model with the PD parameter as the dependent variable and sequence, period, and treatment as fixed effects, and subject nested with sequence as a random effect.) (Statistical Analysis provided by the CDER Office of Biostatistics.)

VAS	Parameter	Statistical Analyses of Treatment Comparisons – LS Means					
		60 mg Crushed MS Contin vs 60 mg Crushed Morphabond	60 mg Intact Morphabond vs 60 mg Crushed Morphabond	60 mg Crushed MS Contin vs 60 mg Intact Morphabond	60 mg Crushed Morphabond vs Placebo	60 mg Intact Morphabond vs Placebo	60 mg Crushed MS Contin vs Placebo
Bipolar Drug Liking	E_{max} (mm)	84.79 v 71.13 p<0.0001	67.03 v 71.13 p=0.1675	84.79 v 67.03 p<0.0001	71.13 v 54.22 p<0.0001	67.03 v 54.22 p<0.0001	84.79 v 54.22 p<0.0001
	AUE_{0-1hr} (h·mm)	63.01 v 54.41 p=0.0005	49.85 v 54.41 p=0.0578	63.01 v 49.85 p<0.0001	54.41 v 49.56 p0.0442	49.85 v 49.56 p=0.9042	63.01 v 49.56 p<0.0001
	AUE_{0-2hrs} (h·mm)	142.6 v 117.95 p<0.0001	109.91 v 117.9 p=0.0846	142.6 v 109.9 p<0.0001	117.9 v 101.0 p=0.0005	109.9 v 101.0 p=0.0567	142.6 v 101.0 p<0.0001
Unipolar High	E_{max} (mm)	67.7 v 43.0 p=0.0001	34.2 v 43.0 p = 0.1499	67.7 v 34.2 p<0.0001	43.01 v 9.54 p<0.0001	34.24 v 9.54 p=0.0001	67.73 v 9.54 p<0.0001
	AUE_{0-1hr} (h·mm)	30.8 v 11.38 p<0.0001	3.71 v 11.38 p=0.0603	30.8 v 3.71 p<0.0001	11.38 v 3.33 p=0.0490	3.71 v 3.33 p=0.9249	30.80 v 3.33 p<0.0001
	AUE_{0-2hrs} (h·mm)	91.63 v 36.65 p<0.0001	22.19 v 36.65 p=0.1034	91.63 v 22.19 p<0.0001	36.65 v 10.52 p=0.0040	22.19 v 10.52 p=0.1859	91.63 v 10.52 p<0.0001
Bipolar Take Drug Again	E_{max} (mm)	76.5 v 66.6, p=0.0341	64.3 v 66.6, p=0.6306	76.5 v 64.3, p=0.0103	66.56 v 49.48 p=0.0004	64.33 v 49.48 P=0.0019	76.52 v 49.48 p<0.0001

Results – Unipolar High VAS

The 0-100 point unipolar High VAS is anchored on the left by ‘none (score of 0)’ and on the right by ‘extremely (score of 100).’ Subjects respond to the question “How High are you now?”

Statistical parameters (E_{max} , TE_{max} , AUE_{0-1hr} , and AUE_{0-2hrs}) on the Unipolar High VAS following the four treatments are shown in Table 7. Statistical analyses of differences in E_{max} between treatments are provided in Table 6. As evidenced from LS means for E_{max} , intranasal MS Contin produced a peak high (67.73 mm) that was significantly ($p \leq 0.0001$) above that produced by intranasal crushed Morphabond or placebo, and by oral Morphabond but with a similar TE_{max} (median of 2 hours for each of the three active treatments). Crushing followed by snorting of Morphabond did not result in a significantly ($p=0.1499$) higher E_{max} of high when compare to oral administration of Morphabond (LS means of 43.0 mm versus 34.2 mm). This observation along with the reduced E_{max} of high produced by crushed Morphabond intranasal compare to crushed MS Contin intranasal, suggest a deterrent effect of Morphabond to intranasal abuse. Nevertheless, crushed intranasal Morphabond and oral Morphabond were associated with some abuse potential as evidence by E_{max} of high significantly ($p \leq 0.0001$) above that produced by placebo (LS means 43.0 mm and 34.2 mm, compared to 9.45 mm produced by placebo).

The degree of high, as represented by LS mean of AUE_{0-2hrs} , experienced in the first 2 hours post-dosing by individuals snorting crushed MS Contin (91.63 h·mm) was significantly higher than that experienced following snorting of crushed Morphabond (36.65 h·mm), oral Morphabond (22.19 h·mm), or placebo (10.52 h·mm). Again, crushing followed by snorting of Morphabond did not result in a larger total high (AUE_{0-2hrs}) compared to oral administration of Morphabond administered to subjects. Crushed intranasal Morphabond ($p=0.040$), but not oral Morphabond ($p=0.1859$), resulted in a significantly higher AUE_{0-2hrs} compared to placebo.

Table 7. Statistical Parameters for E_{max} , TE_{max} , AUE_{0-1hr} , and AUE_{0-2hrs} on the Unipolar High VAS in the Pharmacodynamic Population (N=25). (Source: CDER Office of Biostatistics)

Unipolar High VAS	Statistic N=25	Placebo Crushed Intranasal	MS Contin 60 mg Crushed Intranasal	Morphabond 60 mg Crushed Intranasal	Morphabond 60 mg Intact Oral
E_{max} (mm)	Mean (SE)	9.8 (4.02)	68.8 (4.81)	44.3 (5.97)	34.7 (5.47)
	Median (Range)	2.0 (0.0 – 78.0)	70.0 (8.0 – 100.0)	42.0 (0.0 – 98.0)	38.0 (0.0 – 100.0)
	LS Mean (SEM)	9.54 (5.2)	67.73 (5.2)	43.01 (5.2)	34.24 (5.2)
	95% CI	-0.77, 19.84	57.43, 78.04	32.70, 53.31	23.94, 44.54
TE_{max} (h)	Median	0.5	2.0	2.0	2.0
	(Range)	(0.5 – 2.0)	(0.5 – 6.0)	(1.5 – 3.0)	(1.0 – 4.0)
AUE_{0-1hrs} (h·mm)	Mean (SE)	3.3 (1.51)	31.1 (4.86)	11.9 (3.10)	3.7 (1.08)
	Median (Range)	0.2 (0.0 – 33.5)	26.1 (0.0 – 66.3)	5.4 (0.0 – 54.6)	1.7 (0.0 – 20.7)
	LS Mean (SEM)	3.33 (3.1)	30.80 (3.1)	11.38 (3.1)	3.71 (3.1)
	95% CI	-2.83, 9.49	24.64, 36.96	5.23, 17.54	-2.45, 9.86
AUE_{0-2hrs} (h·mm)	Mean (SE)	10.4 (5.06)	92.4 (10.03)	38.1 (6.99)	22.3 (4.49)
	Median (Range)	1.2 (0.0 – 111.3)	85.4 (2.7 – 164.1)	39.8 (0.0 – 135.8)	19.4 (0.0, 69.5)
	LS Mean (SEM)	10.52 (7.1)	91.63 (7.1)	36.65 (7.1)	22.19 (7.1)
	95% CI	-3.64, 24.68	77.47, 105.79	22.50, 50.81	8.03, 36.35

Results – Take Drug Again VAS

In the 0-100 point bipolar Take Drug Again VAS subjects responded to the statement “Would you want to take the drug you just received again, if given the opportunity?” The question was scored using a 0-100 point bipolar VAS anchored on the left with “definitely would not” (score of 0); “do not care” (score of 50) in the middle; and anchored on the right with “definitely would” (score of 100).

Statistical parameters for E_{max} on the Unipolar Take Drug Again VAS following the four treatments are shown in Table 8. Statistical analyses of differences in E_{max} between treatments are provided in Table 6. Study subjects displayed a willingness to take crushed MS Contin (LS mean of 76.5 mm) intranasally again, but showed indifference to retaking crushed placebo (LS mean 49.5 mm) intranasally. In addition, subjects documented a similar ($p=0.6306$) low level of willingness (LS means of 66.6 mm and 64.3 mm) to retain either crushed Morphabond intranasally or oral Morphabond that was significantly higher ($p=0.0004$, $P=0.0019$) than placebo intranasal but lower than crushed MS-Contin intranasal ($p=0.0341$, $p=0.0103$).

Table 8. Statistical Parameters for E_{max} , on the Unipolar Take Drug Again VAS in the Pharmacodynamic Population (N=25). (Source: CDER Office of Biostatistics)

Bipolar Take Drug Again VAS	Statistic (N=25)	Placebo Crushed Intranasal	MS Contin 60 mg Crushed Intranasal	IDT-001 60 mg Crushed Intranasal	IDT-001 60 mg Intact Oral
Emax	Mean (SE)	49.1 (2.21)	76.4 (4.17)	66.4 (3.76)	64.0 (4.58)
	Median (Range)	50.0 (0.0 – 64.0)	75.0 (17.0 – 100.0)	64.0 (38.0 – 100.0)	60.0 (0.0 – 100.0)
	LS Mean (SEM)	49.5 (3.9)	76.5 (3.9)	66.6 (3.9)	64.3 (3.9)
	95% CI	41.7, 57.2	68.8, 84.3	58.8, 74.3	56.6, 72.1

Discussion

Study M-ARER-002 provides evidence that the insufflation of crushed Morphabond 60 mg compared to crushed MS Contin 60 mg is associated with less subjective effects of drug liking (measured on the 0-100 point bipolar Drug Liking VAS) and high (measured on the 0-100 point unipolar High VAS) thereby suggesting a possible abuse deterrent effect of Morphabond tablets to intranasal abuse, compared to MS Contin. With respect to Drug Liking, insufflated Morphabond 60 mg compared to MS Contin produced significantly ($p < 0.0001$) lower levels of maximum drug liking (E_{max}) (LS means of 71.13 mm versus 84.79 mm, respectively) and overall experience of drug liking over first two hours post-dose (AUE_{0-2hrs}) (117.95 h·mm versus 142.6 h·mm, respectively). Likewise, insufflation of crushed Morphabond 60 mg compared to insufflated MS Contin produced significantly lower levels ($p < 0.0001$) of E_{max} for high (LS means of 43.0 mm versus 67.7 mm, respectively) and AUE_{0-2hrs} (36.65 h·mm versus 91.63 h·mm, respectively)

Intranasal crushed Morphabond 60 mg and intact oral Morphabond 60 produced similar E_{max} s of drug liking (LS means of 71.13 mm versus 67.03 mm, respectively) and high (LS means of 43.0 mm versus 34.2 mm) that was significantly ($p < 0.0001$) above the E_{max} produced by intranasal placebo for either drug liking or high, indicating that both treatments were associated with an abuse potential. At the same time, both the manipulation by crushing followed by the alternative route of administration (insufflation) of Morphabond tablets did not cause a significant increase in subjective measures such as drug liking or high compared to that produced by intact oral Morphabond.

Using the 0-100 point bipolar Take Drug Again VAS, individuals were more willing ($p = 0.0341$) to take again, if given the opportunity, insufflated MS contin 60 mg (LS mean E_{max} of 76.5 mm) than insufflated Morphabond 60 mg (LS mean E_{max} of 66.6 mm). Whereas study subjects expressed no interest to insufflating placebo again if given the opportunity, they showed some interest in taking again either intranasal crushed Morphabond 60 mg (LS means of E_{max} of 66.56 mm versus 49.48 mm, $p = 0.0004$) or oral intact Morphabond 60 mg (LS means of E_{max} of 64.33 mm versus 49.48 mm, $p = 0.0019$). All subjects were able to insufflate the entire amount of crushed Morphabond 60 mg, crushed MS Contin 60 mg, or placebo. In addition based on the 0-100 point bipolar Snorting Experience VAS, subjects recorded a similar overall experience in insufflation of the three treatments. This suggests that the insufflation of crushed Morphabond was not associated with aversive intranasal effects.

4.4 Evidence of abuse, misuse and diversion in clinical trials

Sponsor provided an integrated summary of safety report for Morphabond tablets detailing the adverse events documented in the clinical development program comprised 7 studies, including 6 studies conducted in healthy naltrexone-blocked subjects and 1 human abuse potential study conducted in healthy subjects who were opioid-experienced, recreational drug users. The clinical program was designed to compare the bioavailability of Morphine ARER to MS CONTIN, the RLD, and assess the effect of food on bioavailability. MedDRA was used to code all AEs in the safety population of the individual clinical study reports and the integrated summary of safety (ISS) analyses. The most current version of MedDRA was used for the clinical study reports at the time they were being written and version 17.0 was used for the integrated database. For the ISS, the safety population was defined as all enrolled and randomized subjects who received at least 1 dose of Morphine ARER or MS CONTIN.

The following seven studies constituted the clinical development program for the to-be-marketed formulation of Morphabond tablets.

1. Study M-ARER-004 – single-center, randomized, open-label, single-dose, 2-period crossover study of bioavailability of Morphabond 100 mg with comparison to MS Contin 100 mg in 54 healthy, naltrexone volunteers.
2. Study M-ARER-004 – single-center, randomized, open-label, single-dose, 2 treatment crossover study to assess food effect on bioavailability of Morphabond 100 mg tablets in 28 healthy, naltrexone blocked volunteers.
3. Study M-ARER-007 – single-center, randomized, open-label, single-dose, 2 treatment crossover study evaluating the bioavailability of Morphabond 15 mg tablets compared to MS Contin 15 mg under fasted conditions in 32 healthy, naltrexone-blocked volunteers.
4. Study M-ARER-012 – single-center, randomized, single-dose, open-label, 2 treatment crossover study evaluating the bioavailability of Morphabond 30 mg tablets compared to MS Contin tablets in 42 healthy, naltrexone-blocked volunteers.
5. Study M-ARER-002 – Intranasal abuse potential study
6. Study M-ARER-006 – Single-center, randomized, multiple-dose, open-label, 2 treatment crossover study examining the bioequivalence of Morphabond 100 mg tablets and MS Contin 100 mg tablets at steady-state in 45 healthy, naltrexone-blocked volunteers.
7. Study M-ARER-008 – single-centered, randomized, multiple-dose, open-label, 2-treatment crossover study evaluating bioequivalence of Morphabond 100 mg tablets and MS Contin 100 mg tablets at steady-state in 37 healthy, naltrexone-blocked volunteers.

There were only two instances in which “euphoric feeling” was documented as an adverse event. Both cases occurred in the single dose bioavailability Study M-ARER-004 in the same subject (No. 43) following treatment with 100 mg Morphabond and 100 mg MS Contin. These two adverse events were designated as “mild” and considered to be treatment related with complete recovery.

There were three adverse events designated a “lightheadedness.” Two of these events occurred in multiple dose bioavailability Study M-ARER-008 following treatment with 100 mg MS Contin. The third event was documented in Study M-ARER-012 following administration of 30 mg Morphabond. All were rated as “mild” and considered treatment-related.

There were no other adverse events associated with abuse. There was no mention of withdrawal.

5. Regulatory issues and assessment

Morphabond Tablets, containing the Schedule II substance, morphine sulfate, will be in Schedule II of the federal Controlled Substances Act (CSA) and so designated in Section 9.1 of the label.

In Vitro Studies Under Section 9 of the Proposed Label

Sponsor is proposing to insert language into Section 9 of the label briefly describing the results from the in vitro studies on Morphabond tablets compared to MS Contin. Inclusion of this information is appropriate considering that Morphabond tablets, compared to MS Contin, are more difficult to manipulate with common household tools and is more resistance to dose-dumping in various solvents. In addition, both the formation of a viscous liquid upon exposure to (b) (4), as well as the limited extraction of morphine sulfate, precludes the used of crushed Morphabond tablets to form a solution suitable for abuse by intravenous inject.

Sponsor should remove from the proposed wording under the description of in vitro studies the phrase “therefore an intravenous human abuse potential trial was not necessary.”

Clinical Abuse Potential Study M-ARER-002 Under Section 9 of the Proposed Label

Sponsor is proposing to place into Section 9.2 of the label language describing the results of intranasal human abuse potential study M-ARER-002. Such language with possible modifications is acceptable since the results of this study do provide evidence suggesting that Morphabond tablets may provide resistance to intranasal abuse, compared to MS Contin. The following comments are provided regarding the language proposed by Sponsor:

- Table (b) (4) under Section 9.2 contains E_{max} (b) (4) for Drug Liking VAS. Considering that E_{max} for active treatments is achieved with a median of 2 hours, Sponsor should consider deleting the (b) (4) data.
- According to the Office of Biostatistics, for generation of (b) (4) under Section 9.2 of the label, the (b) (4), as recommended in the 2015 Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling document. By email dated June 25, 2015, DAAAP requested that Sponsor modify (b) (4) using the recommended mathematical formula for calculating percentage reduction in Drug Liking VAS. Sponsor, via submission to the NDA on July 9, 2015 (SN 0006) subsequently agreed to use the recommended mathematical formula for calculating percentage reduction and provided a revised (b) (4)

6. Other relevant information

Morphabond Tablets developed by Inspirion Delivery Technologies LLC has not been previously marketed in the United States or other countries. No information concerning Morphabond Tablets is available in the scientific and medical literature. There are currently no Periodic Safety Update Reports regarding Morphabond Tablets.

ATTACHMENT

OPQ Review of the Category 1 In Vitro Studies Provided by Email April 14, 2015.

Abuse Deterrence Studies

Category 1 abuse deterrence studies are provided and evaluated in this CMC review. The studies assessed physical manipulation and extractability of morphine from the drug product in comparison with the RLD MS Contin tablets. In addition to direct observation and simple laboratory techniques used such as sieving analysis and volume measurements, sample quantification was completed using a HPLC method that is also used in drug product content uniformity analysis, the method has been validated as suitable for its use.

The drug products are available in strengths of 15, 30, 60, and 100 mg. Since the ratio of morphine to the tablet matrix materials is the highest for the 100 mg strength, for the abuse deterrence study perspective, the applicant chose to conduct the studies using this strength only as it represents the most “vulnerable” scenario for abuse deterrence.

1. Physical Manipulation

Because abusers often reduce tablets to small particles to induce “dose dumping” and increase the bioavailability of the API, this study explored how time consuming and difficult it is to manipulate the 100 mg Morphine ARER tablet, via different common tools and approaches, to small particles, as compared to the RLD MS Contin 100 mg.

The studied methods of manipulation included the use of a (b) (4), (b) (4).

The studies found out that the RLD MS Contin 100 mg tablets were easily and quickly (within (b) (4) (b) (4)) reduced into consistently small particles using any of the included approaches. The Morphine ARER tablets were difficult to impossible to be (b) (4) within (b) (4) using all included methods except the (u) (4), (b) (4) (u) (4).

Pretreatment by (b) (4) did not substantially alter particle size distribution with any of the (b) (4) tested to manipulate the Morphine ARER tablets. The (b) (4) (b) (4) was the only (b) (4) that yielded a crushed powder with reproducible (b) (4), obtaining not more than (u) (4) of particles less than (b) (4).

Evaluation: Noted. Comparatively speaking, when manipulated for (b) (4) using the commonly available (b) (4) the Morphine ARER tablets are generally more resistant to crushing and (b) (4) than the RLD MS Contin.

2. Large Volume Extractability

The extraction volumes of (b) (4) (large) and (b) (4) (very large) were studied. Similarly, MS Contin 100 mg tablets are used as the reference product.

Upon crushing the MS Contin 100 mg tablets with a (b) (4) of the API can be recovered with (b) (4), this drastically contrasts with the less than (b) (4) recovered from the intact MS Contin tablets and supports the suitability of the API recovery and quantification methods.

(b) (4)

Evaluation: Noted. Compared to MS Contin 100 mg tablets, it is more difficult and time consuming to recover the API from the crushed Morphine ARER 100 mg tablets, despite the use of pre-treatment, (b) (4). Using saline, ethanol and a group of common organic solvents do not increase the API recoveries from the crushed Morphine ARER tablets. Even after crushing, most of the extended release characteristics of the original tablets are retained. This helps to deter the potential abuse of the Morphine ARER tablets after crushing with (b) (4) (b) (4) via snorting and API recovery with solvent extraction.

3. Injectability, Syringeability, and Small Volume Extractability

The applicant cited literature to say that morphine extended release product is misused or abused via injection approximately 48% of time. Therefore they conducted a significant amount of in vitro syringeability and Injectability testing to evaluate the difficulty and time required to syringe the Morphine ARER as compared to the RLD MS Contin.

Using a literature reported maximum of 16 minutes as the time an abuser is willing to spend tampering with another crush-resistant tablet, the applicant selected (b) (4) as the stopping point for maximum time for the studies.

Intact, cut, and crushed tablets were extracted, using (b) (4) (b) (4) (b) (4). The volume of syringeable liquid was recorded and the content analyzed for morphine content.

Manipulated MS Contin was easily drawn into a (b) (4) (b) (4). In contrast, manipulated Morphine ARER tablets immediately formed a non-syringeable material in each condition. There was no syringeable liquid from tablets that were cut with a (b) (4) or crushed in a (b) (4) (b) (4) in any volume, condition, or timeframe through (b) (4) (b) (4) (b) (4). Furthermore, there was no liquid that was syringeable through (b) (4) (b) (4) (b) (4) manipulated tablets could not be syringed through the (b) (4) (b) (4) (b) (4) needles; only through (b) (4) (b) (4) needles could a (b) (4) amount of the mixture be syringed.

Intact tablets released incrementally higher amounts of morphine in larger volumes, (b) (4) (b) (4) to a maximum mean of about (b) (4) % for the cut tablets extracted at (b) (4). This contrasts with the intact MS Contin tablets which released (b) (4) % of morphine within (b) (4) and (b) (4) % within (b) (4) under these facilitated conditions. Crushed MS Contin tablets released (b) (4) % and (b) (4) % of their morphine within (b) (4) respectively.

Evaluation: Noted. Compared to MS Contin 100 mg tablets, it is more difficult and time consuming to tamper and prepare the Morphine ARER 100 mg tablets into injection in general. At certain tested conditions, (b) (4) (up to (b) (4) %) of the API can be prepared and drawn into the syringe.

4. Smokeability

The ability and extent to (b) (4) intact and manipulated (crushed) Morphine ARER tablets was evaluated to assess its potential for abuse via the smoking route of administration.

The study essentially (b) (4) the intact and crushed Morphine ARER tablets, collected and quantified the morphine (b) (4)

(b) (4)

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/s/

JAMES M TOLLIVER
07/17/2015

SILVIA N CALDERON
07/17/2015

MICHAEL KLEIN
07/17/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 26, 2015

TO: John Peters, M.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

Sharon Hertz, M.D.
Director (Acting)
Division of Anesthetics, Analgesia and Addiction
Products (DAAAP)
Office of Drug Evaluation II (ODEII)

FROM: Young Moon Choi, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
Office of Scientific Integrity & Surveillance

Himanshu Gupta, Ph.D.
Staff Fellow
Division of Generic Drug Bioequivalence Evaluation
Office of Scientific Integrity & Surveillance

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Acting Director, Division of Generic Drug
Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of (b) (4)
(b) (4)

At the request of the Division of Anesthetics, Analgesia and Addiction Products (DAAAP) and Office of Bioequivalence, Office of Generic Drugs (OGD), the Office of Study Integrity & Surveillance (OSIS) conducted an inspection of bioanalytical portions of bioequivalence studies conducted by (b) (4)
(b) (4)

NDA 206544 (Morphine ARER tablets)

Study #: (b) (4) 1206133

Study Title: "A Study to Evaluate the Relative Bioavailability of a Formulation of Morphine ARER Tablets 100 mg (Morphine Sulfate Pentahydrate Extended-Release Tablets) (Inspirion Delivery Technologies LLC) compared to MS CONTIN® (morphine sulfate controlled-release) 100 mg Tablets CII (Purdue Pharma L.P.) in Healthy Volunteers under Fasted Conditions"

Analysis dates: (b) (4)

NON-RESPONSIVE

(b) (4)

NON-RESPONSIVE

Analytical

The analytical portions of the above studies were audited at (b) (4) by Young Moon Choi, Ph.D. (Lead Pharmacologist, DGDBE) and Himanshu Gupta Ph.D. (Staff Fellow, DGDBE) during (b) (4). The audits included a thorough examination of facilities and equipment, review of study records including correspondence, and interviews and discussions with (b) (4) management and staff. As global assessment of the firm's bioanalytical operations, several key study components were selected for audit, to represent the firm's bioanalytical operations since the previous inspection.

During the inspection, objectionable conditions were observed, and Form FDA 483 was issued at the conclusion of the inspection. Responses to the inspectional observations were received from (b) (4) on (b) (4) (**Attachment 1 - 3**).

DGDBE evaluations of the observations and the firm's responses are discussed below:

(b) (4)

Conclusion:

Following review of the inspectional findings, Form FDA 483 observations, and (b) (4) responses to the observations, these reviewers conclude that data from the audited studies were reliable. Therefore, we recommend that data from the studies below be accepted for Agency review:

NDA 206544 Study # (b) (4)-1206133

NON-RESPONSIVE

(b) (4)

OSIS recommends the next surveillance inspection at (b) (4) in approximately two years, and that the inspection should confirm that the corrective actions have been implemented.

Young Moon Choi, Ph.D.
Division of Generic Drug Bioequivalence
Evaluation
Office of Scientific Integrity &
Surveillance

Himanshu Gupta, Ph.D.
Division of Generic Drug Bioequivalence
Evaluation
Office of Scientific Integrity &
Surveillance

Attachment 1

Attachment 2

Attachment 3

(b) (4)

Final Classification:

Analytical

VAI: (b) (4)

CC:

OSI/DBGLPC/Taylor/Bonapace/Haidar/Skelly/Choi/Dasgupta/Gupta

OSI/DBGLPC/Fenty-Stewart/Nkah/Dejernett/Johnson

CDER/OND/DAAAP/Hilfiger/Hertz

CDER/OGD/DB2/Stier/Vehovic/Mahadevan/Nhu, Duong

ORA/CE-FO/ (b) (4)

(b) (4)

Draft: HG 6/11/2015

Edit: YMC 6/24/2015

Edit: MFS 6/26/2015

File # BE6821 (NDA 206544); FACTS: (b) (4)

NON-RESPONSIVE

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ (b) (4) /Inspection May 2015 (b) (4)

Himanshu Gupta -S

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DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Himanshu Gupta -S,
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Date: 2015.06.26 15:29:06 -04'00'

Himanshu Gupta Ph.D., Staff Fellow

Young M. Choi -A

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ou=FDA, ou=People, cn=Young M. Choi -A,
0.9.2342.19200300.100.1.1=1300119993
Date: 2015.06.26 15:42:37 -04'00'

Young Moon Choi Ph.D., Lead Pharmacologist

Michael F. Skelly -S

c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300099113, cn=Michael F. Skelly -S
2015.06.26 15:32:57 -04'00'

[Skelly signing on behalf of Dr. Haidar]

Sam H Haidar, Ph.D., R.Ph., Director (Acting), DGDBE

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/s/

HIMANSHU GUPTA
06/29/2015

YOUNG M CHOI
06/29/2015
sing on behalf of Dr. Sam Haidar

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 7, 2015

TO: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 206544

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting the data without an on-site inspection. The rationale for this decision is noted below.

The site listed below was inspected within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	Novum Pharmaceutical Research Services	3760 Pecos McLeod Las Vegas, NV 89121

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/s/

SHILA S NKAH
04/07/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 17, 2015

Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 206544

Product Name and Strength: Morphabond (morphine sulfate) Extended-release Tablets
15 mg, 30 mg, 60 mg, 100 mg

Product Type: Single Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Inspirion Delivery Technologies

Submission Date: November 21, 2014

OSE RCM #: 2014-2441

DMEPA Primary Reviewer: James Schlick, RPh, MBA

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

As part of the approval process for Morphabond, DAAAP requested that we review the proposed container labels and package insert labeling for areas that may lead to medication errors. Morphabond (morphine sulfate) is an opioid product with abuse deterrent properties, and Inspirion uses MS Contin as their reference listed drug (RLD) in their 505(b)(2) NDA application.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A B
Human Factors Study	N/A C
ISMP Newsletters	N/A D
FDA Adverse Event Reporting System (FAERS)*	N/A E
Other	N/A F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we have identified medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Inspirion proposes to introduce an extended release morphine sulfate tablet containing four strengths (15 mg, 30 mg, 60 mg, and 100 mg). (b) (4)

(b) (4)

(b) (4)

(b) (4) we find the proposed strengths acceptable.

We performed a risk assessment of the proposed container labels and prescribing information to identify deficiencies that may lead to medication errors and other areas for improvement.

Container Labels

After our review of the container labels, we recommend that the presentation of the dosage form be made more prominent. Increased prominence may mitigate confusion between this morphine extended-release oral tablet product and other morphine immediate release oral

tablet products. To increase the prominence of the dosage form statement (extended release tablets), we recommend locating it outside of the parentheses of the established name in title case to mitigate potential confusion. For example:

Morphabond
(morphine sulfate) Extended-release Tablets

We contacted ONDQA to determine if this presentation of the established name and dosage form is acceptable, and they concurred with this presentation in an email dated March 12, 2015. Thus we provide a recommendation in Section 4.1 and 4.2 to address this concern.

We also identified other areas of the container labels that can be improved to mitigate the risk of confusion that can lead to medication error. These areas are listed as follows:

-  (b) (4)
- The statement on the side of the container labels that instructs patients to swallow the tablets whole is not prominent enough and should be moved to the principal display panel to improve the prominence of this important information.

We provide recommendations in Section 4.2 to address these additional concerns.

Prescribing Information

Our review of the *Dosage and Administration* section in the Highlights section of the Prescribing Information identified areas of improvement to increase clarity of important information. We identified that this section did not include important administration information “Swallow tablets whole. Do not break, crush, dissolve or chew”. Thus, we provide recommendations to mitigate the risk of wrong technique errors and to promote safe use of this product in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

We recommend that Inspirion increase the readability and prominence of important information in the proposed container labels and package insert labeling to promote the safe use of the product. We provide recommendations to DAAAP in Section 4.1 and Inspirion in Section 4.2 to address these concerns.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. We provide a recommendation to add important administration information to mitigate the risk of wrong technique errors in Appendix G.3 for the Highlights of Prescribing Information Section of the Package Insert Labeling.

4.2 RECOMMENDATIONS FOR INSPIRION

We recommend the following be implemented prior to approval of this NDA:

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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Morphabond that Inspirion submitted on November 21, 2014, and the reference listed drug, MS Contin.

Table 2. Relevant Product Information for Morphabond and Reference Listed Drug		
Product Name	Morphabond	MS Contin
Initial Approval Date	N/A	May 29, 1987
Active Ingredient	Morphine sulfate	Same as Morphabond
Indication	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Same as Morphabond
Route of Administration	Oral	Same as Morphabond
Dosage Form	Extended-release Tablets	Same as Morphabond
Strength	15 mg, 30 mg, 60 mg, and 100 mg	15 mg, 30 mg, 60 mg, and 100 mg, and 200 mg
Dose and Frequency	Every (b) (4) 12 hours	Same as (b) (4)
How Supplied/ Container Closure	Plastic bottles containing 100 tablets	Plastic bottles containing 100 and 500 tablets
Storage	Room temperature	Same as Morphabond

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

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

/s/

JAMES H SCHLICK
03/17/2015

BRENDA V BORDERS-HEMPHILL
03/17/2015