CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206544Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	206544
Applicant Name	Inspirion Delivery Technologies LLC
Date of Submission	November 21, 2014
PDUFA Goal Date	September 21, 2015
Proprietary Name / Established (USAN) Name	Morphabond (morphine sulfate) Extended-Release Tablets
Dosage Forms / Strength	15, 30, 60, and 100 mg tablets
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
Action/Recommended Action for NME:	Approval

Material Reviewed, OND package including:	**Review Team**
Cross-Discipline Team Leader Review	John Feeney, MD
Primary Medical Officer Review	Timothy Jiang, MD, PhD
Pharmacology Toxicology Review	Carlic Huynh, PhD, Newton Woo, PhD, Dan Mellon, PhD, Karen Davis-Bruno, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD, Yun Xu, PhD
Audit of Bioanalytical Portions of Bioavailability Study	Young Moon Choi, PhD, Himanshu Gupta, PhD
Biopharmaceutics Review	Tien-Mien Chen, PhD, John Duan, PhD
Chemistry Review	Xiaobin Shen, PhD, Yong Wang, PhD, Ubrani Venkataram, PhD, Julia Pinto, PhD
Product Quality Microbiology Review	Erika Pfeiler, PhD, Stephen Langille, PhD
Clinical Inspection Summary	John Lee, MD, Janice Pohlman, MD, MPH, Kassa Ayalew, MD, MPH
Proprietary Name Review	James Schlick, RPh, MBA, Vicky Borders-Hemphill, PharmD, Irene Chan, PharmD, BCPS
DMEPA Label and Labeling Review	James Schlick, RPh, Vicky Borders-Hemphill, PharmD
Controlled Substances Staff Review	James Tolliver, PhD, Silvia Calderon, PhD, Michael Klein, PhD
Statistical Review (Abuse Potential Study)	Wei Liu, PhD, Qianyu Dang, PhD, Yi Tsong, PhD

OND=Office of New Drugs
DMEPA=Division of Medication Errors Prevention
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives
OSE= Office of Surveillance and Epidemiology
DSI=Division of Scientific Investigations
DCDP=Division of Consumer Drug Promotion
DMPP=Division of Medical Policy Programs

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Signatory Authority Review Template

1. Introduction

The Sponsor has submitted a 505(b)(2) NDA for Morphabond (morphine sulfate) Extended-Release Tablets relying in part on the Agency's previous findings of efficacy and safety for NDA 019516, MS Contin (morphine sulfate extended-release tablets) and on literature. Morphabond was developed with properties intended to deter abuse by the nasal and intravenous routes of administration, and with the proposed indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The Morphabond tablet (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) intended to contribute to the abuse-deterrent (AD) characteristics, (b) (4)

Morphabond will be the first single-entity extended-release morphine product with abuse-deterrent (AD) properties on the US market. This is in distinction to Embeda, NDA 022321, approved in 2009, the first extended-release morphine product with abuse-deterrent properties, but which is a combination drug product consisting of morphine sulfate and naltrexone hydrochloride. At the time of initial approval of Embeda, there was little experience with abuse-deterrent opioid analgesics and the labeling was approached in a very cautious manner. In 2014, in response to a supplement, the abuse-deterrent language in the Embeda label was amended to be consistent with the recommendations in the Guidance for Industry, Abuse-Deterrent Opioid Analgesics – Evaluation and Labeling. Morphabond will fall under the Extended-release and Long-acting Opioid Risk Evaluation and Mitigation Strategy (ERLA REMS), along with all of the other extended-release and long-acting opioid drug products.

As described in the Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling[1], the development of abuse-deterrent formulations of opioid analgesics is recognized by FDA as an important approach to reducing abuse of prescription opioids. Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

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In general, the primary route of abuse of opioid analgesics is oral, followed by different frequencies of intranasal and intravenous abuse depending on the specific product. This is true for both immediate-release and extended-release products. When extended-release products are manipulated to defeat the extended-release characteristics resulting in an earlier peak drug level, the risk for overdose increases. The approach to making Morphabond product abuse-deterrent is to make manipulation to defeat the extended-release characteristics and to prepare material for nasal or intravenous administration more difficult. It is important to remember that even when a product has abuse-deterrent properties that may reduce abuse through manipulation, it does not mean that there is no risk of abuse or addiction. It means, rather, that the risk of abuse is lower than it would be without such properties.

2. Background

Morphabond was developed under IND 115822 and the regulatory history can be found in the review by Dr. Jiang.

The Applicant has submitted this NDA as a 505(b)(2) application. The Applicant has provided the product-specific chemistry, manufacturing, and controls (CMC) information required for review of the NDA. Nonclinical support for morphine sulfate is based on based on reliance on the Agency's previous findings for the referenced drug, MS Contin. Support for the formulation, and in particular, novel excipients and excipients that exceed the amount present in the Inactive Ingredients Guide have been provided, primarily through the submission of supporting information as described in the Nonclinical Pharmacology and Toxicology section of this review. The support for clinical efficacy and safety is based on reliance on the Agency's previous findings for the referenced drug, MS Contin, using relative bioavailability as the scientific bridge for doing so. The Applicant planned on demonstrating that Morphabond is bioequivalent to MS Contin to form the scientific bridge for relying on the Agency's findings for MS Contin and a number of pharmacokinetic studies were conducted. There were some challenges with the demonstration of bioequivalence that are discussed in the Clinical Pharmacology section of this review. As part of the safety assessment, the Applicant provided information necessary to address whether the formulation was likely to stick to the mucosal surface of the gastrointestinal tract.

Because Morphabond relies on physicochemical properties of excipients in the formulation for both its abuse-deterrent properties and extended-release profile, and because this particular formulation has not been used previously in an approved morphine product, the Applicant was required to conduct in vitro and in vivo studies with the to-be-marketed product to support all of the proposed abuse-deterrent labeling. As described in the section discussing the studies of abuse-deterrent properties in this review, the abuse-deterrent effects appear to be due to the formulation's ability to (b) (4)

(b) (4)

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Therefore, the Applicant could not rely on the findings of the abuse-deterrent properties of Embeda.

3. CMC/Device

The Morphabond tablet consists a [redacted] (b) (4), color coating, and the printing. The different tablet strengths only differ [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) in their color coating layer for strength differentiation in color.

The following has been taken verbatim from CMC review:

> Morphine sulfate is an opioid agonist. It exists as a white [redacted] (b) (4) crystalline powder. [redacted] (b) (4).
>
> The morphine sulfate drug substance is manufactured by Noramco in Wilmington, DE per DMF 6967. The DMF has been last reviewed by this reviewer on 30-Jun-2015 and deemed adequate. The drug substance manufacturer site EES status is acceptable.
>
> Specifications for morphine sulfate drug substance include both USP and ICH requirements. Collectively they include appearance, identification, assay, acidity, chloride, ammonium salts, impurities, limit of foreign alkaloids, residue on ignition, residual solvents, and particle size distribution. The drug substance is packaged in [redacted] (b) (4). The drug substance stability data was referenced to DMF 6967, which is adequate to support its use in the NDA. The drug product is available as 15, 30, 60 and 100 mg strength tablets packaged with a [redacted] (b) (4) packet in 100-cc round [redacted] (b) (4) HDPE bottle [redacted] (b) (4) and closed with child-resistant closure. The tablet excipients include hypromellose, xanthan gum, microcrystalline cellulose, sodium alginate, alginic acid, mannitol, colloidal silicon dioxide, magnesium stearate, two ethyl acrylate and methyl methacrylate copolymer dispersions [redacted] (b) (4) lactose monohydrate, polysorbate 80, [redacted] (b) (4). All excipients are of compendial or equivalent grades. The drug product is manufactured by Cerovene Inc. at Valley Cottage, New York. The drug product manufacturing and testing sites all have acceptable EES status.
>
> The drug product specifications include appearance, identification, assay, content uniformity, dissolution, degradation products, [redacted] (b) (4) [redacted] (b) (4) and [redacted] (b) (4). The drug product primary stability studies were conducted on 3 production scale batches for each strength. 12 to 24 months of stability data is provided for the products stored under long term (25ₒC/60% RH) storage conditions and 6 months of stability data is provided for products stored under accelerated conditions (40ₒC/75% RH). For the tested quality attributes, except the degradant [redacted] (b) (4) [redacted] (b) (4) all others remained relatively unchanged when analytical variations are considered. The maximum of [redacted] (b) (4)% after 12 months. Nevertheless, the projected [redacted] (b) (4) level clearly supports a product

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expiry of 24 months. Overall, the provided stability data supports the applicant's proposed 24 month product expiry.

The CMC concludes that the NDA may be approved based on:

- The drug substance and product specifications provide adequate controls;
- The drug product excipients are of USP/NF or equivalent grade;
- The drug product container closure systems are acceptable for pharmaceutical use.
- Both drug substance and drug product are stable in the studied stability period and support the currently proposed expiry of 24 months for the drug product.

The product quality microbiology assessment of the product found that the microbial limits testing was performed using acceptable methods and the acceptance criteria are consistent with appropriate USP criteria. Although release testing of (b) (4) has been proposed by the Applicant, the Applicant's request for waiver of microbial limits testing for product release was found acceptable in the context of the total proposed microbial control strategies.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

The following has been reproduced from Dr. Huynh's review:

> No nonclinical studies were required to be submitted for morphine sulfate. There were no nonclinical safety concerns with the drug substance and drug product specifications as well as the container closure system as the proposed drug product is formulated as solid oral tablets. With the exception of (b) (4), all excipients in the composition of the proposed drug formulation were determined to be qualified for safety up to the maximum theoretical daily dose (MTDD) of 2 g/day of morphine. Additional data were required to justify the levels of these excipients.

The Applicant's evaluation of the toxicological risk of (b) (4), which exceeds the amount present in previously approved products, and (b) (4), which has not been used in an approved product previously, relies on studies conducted by the Applicant and by a weight of evidence argument to address the aspects not covered by nonclinical studies. Details of the studies conducted can be found in Dr. Huynh's review. As summarized in Dr. Mellon's secondary review:

> (b) (4) are ethylacrylate and methylmethacrylate copolymers. Members of this class of polymers are used in a variety of oral drug products in order to obtain the desired (b) (4) (b) (4) profile. The ethylacrylate and methylmethacrylate copolymer backbone of both

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(b) (4) are sufficiently large to preclude systemic absorption following oral administration (the mean molecular weight of (b) (4) is 750,000 Daltons and (b) (4) is 600,000 Daltons) and the Applicant has provided adequate data to support the conclusion that there are no detectable lower molecular weight entities in the polymeric material, that there is no apparent systemic absorption of the polymers and that (b) (4) are adequately controlled. Therefore there are no safety concerns with the polymeric backbone of either (b) (4).

However, there is one question of toxicological risk that has not been fully characterized. This is described in the following taken from Dr. Mellon's review:

> However, in addition to differences in molecular weight, these two (b) (4) also differ by the presence of the (b) (4) in the product. In the case of (b) (4), the (b) (4); whereas, (b) (4) employs the (b) (4) (b) (4). As the backbone polymethacrylate polymer is not absorbed systemically, and there are older data that have been historically used to support these polymers, the backbone is not believed to present any novel risk to the patients. In contrast, there are considerably less data for the (b) (4) and there are no distribution data for these compounds to directly demonstrate if the (b) (4) are or are not absorbed systemically. Therefore, the NDA review has focused on the safety of the (b) (4) (b) (4) and the (b) (4) when the product is used up to the maximum theoretical daily dose (MTDD) of morphine (2 grams/day). The Applicant has not conducted toxicology studies for these two compounds. Rather they justify the safety of the (b) (4) in the drug product formulation as this (b) (4) was present in the toxicology studies for (b) (4) This alone is inadequate as there are no fertility and early embryonic development study, pre- and post-natal development study, or carcinogenicity studies with these (b) (4). To address these issues, the Applicant and Dr. Huynh have conducted a weight-of-evidence review based on literature and data on analogous compounds.

(b) (4)

As described by Drs. Huynh and Mellon, the Applicant's weight-of-evidence arguments were sufficient to support the safety of (b) (4), (b) (4) They recommend a complete response and that the following studies be conducted prior to approval:

- Chronic toxicology studies with (b) (4) in two species (6-month rodent and 9-month nonrodent) are required for a chronic indication.
- Reproductive and developmental toxicology battery with (b) (4): fertility and early embryonic development (rat), embryofetal development (rat and rabbit), and pre- and postnatal development studies (rat).

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- A carcinogenicity assessment of (b) (4) in mice. As per the guidance for industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf

(b) (4)

(b) (4)

In a tertiary review, Dr. Bruno-Davis discusses that requiring additional pre-approval testing of the low level of exposure to (b) (4) which is below the qualification threshold for impurities

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is a very conservative position, and together with the history of exposure in in Europe, and likely metabolites which are of no toxicological concern, she believes that it would be appropriate to obtain this additional safety information post-approval through PMRs. The following is from her review:

> The Pharmacology/Toxicology reviews for NDA 206544, recommend additional toxicology studies with [redacted] (b) (4) to address the concern for [redacted] (b) (4). These studies include: chronic toxicology in two species, a complete reproductive toxicology battery (fertility, embryo-fetal development (EFD; in rat and rabbit) and rat pre- and post-natal development) as well as a 2-year carcinogenicity study. While this is consistent with current guidelines for excipients it represents a conservative approach. For instance, a 6-month transgenic mouse carcinogenicity study could be substituted for the recommended 2-year carcinogenicity study. While chronic and reproductive toxicity studies may not be available with [redacted] (b) (4), their utility seems limited if this compound doesn't achieve appreciable systemic distribution from Morphabond administration. If the goal is to confirm summary information available in published literature a single species chronic toxicity study (6-month rat) would probably suffice.

[redacted] (b) (4)

There are adequate data to support the safety of the components of the proposed formulation. In [redacted] (b) (4) more information is needed in the post-approval context to further assess the potential risk. My conclusion is consistent with the assessments of Drs. Mellon and Davis-Bruno that [redacted] (b) (4) is unlikely to represent a safety concern. The Guidance for Industry - Nonclinical Studies for the

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Safety Evaluation of Pharmaceutical Excipients describes the recommended testing for novel excipients but also that it is acceptable to evaluate the excipients in the context of use on a case-by-case basis and that there may be a basis for exceptions from the standard approach regarding permitting completion of the evaluation conducted post-marketing. While Morphabond does not represent a lifesaving therapy, it is indicated for a serious medical condition, and as a novel abuse-deterrent formulation, offers additional benefit from a public health perspective.

To complete the safety assessment of (b) (4) the following studies will be issued as post-marketing requirements. If the Applicant is able to obtain additional information about the safety of (b) (4), its metabolic pathway, or the data underlying the safety of (b) (4), some or all of the studies may not be necessary.

1. Conduct a 9-month repeat-dose oral toxicology study in the nonrodent model characterizing the toxicological potential of (b) (4).

2. Conduct a 6-month repeat-dose oral toxicology study in the rodent model characterizing the toxicological potential of (b) (4)

3. Conduct a fertility and early embryonic development study in both male and female rats with (b) (4)

- Conduct an embryofetal development study for (b) (4) in the rat model.
- Conduct an embryofetal development study for (b) (4) in the rabbit model.
- Conduct a pre- and post-natal development study for (b) (4) in the rat model.
- Conduct a 2-year oral rodent carcinogenicity assessment of (b) (4).

If the results of these studies or if additional information demonstrate that there is a safety concern associated with (b) (4), several options are available including adding information to the labeling and limiting the dose range. In the event that a serious safety concern arises, the overall risk and benefit of the product will be re-evaluated and additional actions taken if warranted.

5. Clinical Pharmacology/Biopharmaceutics

The required clinical pharmacology studies and the approach for bridging all of the proposed strengths of Morphabond to MS Contin were discussed with the Applicant throughout the development program. The Applicant submitted pharmacokinetic studies comparing Morphabond and MS Contin at each of the 15 mg, 30 mg, and 100 mg strengths and requested a biowaiver for the 60 mg strength. In addition, data from a food-effect study and a multiple-dose PK study were also submitted.

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Bioequivalence was demonstrated for the 100 mg strength of Morphabond and MS Contin in a fasted, single-dose study and in a five-day multiple-dose study. In separate fasted, single-dose studies, compared with the 15 mg and 30 mg strengths of MS Contin, the total exposure to morphine from the 15 mg and 30 mg strengths of Morphabond met bioequivalence criteria. However, the Cmax was lower with the ratios of 87.4 and 80.7, for the 15 mg and 30 mg of Morphabond compared to MS Contin, respectively, with lower limits of the confidence interval of 79.08%, and 76.24%, respectively, missing the minimum criterion of 80%.

In a food-effect study of Morphabond 100 mg tablets administered after a high-fat breakfast in naltrexone-blocked subjects, the Cmax was approximately 33% higher and the median Tmax was 0.5 hours longer when compared with the fasted state. There was no change in overall extent of morphine bioavailability, with the geometric 90% CI for both morphine AUC0-t and AUC0-∞ falling within the range of 80% to 125%. Therefore, Morphabond can be dosed without regard to food.

The effect of alcohol on the release of morphine from Morphabond was evaluated in an in vitro alcohol interaction study. As noted in the biopharmaceutics review, there was no evidence of dose-dumping in the presence of alcohol, and no in vivo alcohol interaction study was conducted or required.

The pharmacokinetic profiles of Morphabond and MS Contin were evaluated in a human abuse liability study following crushing and intranasal administration as part of the evaluation of the abuse-deterrent properties. This study is described and discussed in the section on abuse-deterrent properties below.

As noted in Dr. Jiang's clinical review, the basis for a biowaiver for the 60 mg strength was discussed with the Applicant at a type C meeting on April 10, 2014. The following reasons formed the basis for agreement that the biowaiver request would be reasonable:

1. The 60 mg strength and 100 mg strength product have the same dosage form.

2. There appear to be acceptable bioavailability and bioequivalence data for the 100 mg strength.

3. The 60 mg strength product is (b) (4) (b) (4) (b) (4) to the 100 mg strength product.

4. Dissolution profile comparisons between the 60 and 100 mg strengths in three different media meet the f2 similarity requirements.

The following is taken directly from the biopharmaceutics review by Dr. Chen:

> The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution method development report, comparative dissolution profile data, proposed dissolution method and acceptance criteria, biowaiver request, and the *in vitro* alcohol dose-dumping study results.

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Granting the biowaiver for 60 mg strength is pending successful demonstration of BE in vivo and similar in vitro dissolution profile comparison (f2 value >50) between Morphine ARER ER tablets (Test) and the MS Contin tablets (RLD) for both the 100 mg and 15 mg strengths.

Reviewer's Comments:

1. The dissolution method development in accompany with the formulation development and the in vitro alcohol dose-dumping study were reviewed and found acceptable.

2. The Applicant accepted the Agency's 04/29/15 recommendation for dissolution acceptance criteria and submitted the updated Specification (M32P51) and other related sections to the Agency.

3. Per discussions with the Clinpharm reviewer, based on the Agency's BE acceptance criteria, the highest strength 100 mg did demonstrate BE between the Morphine ARER and MS Contin, however, the lowest strength 15 mg missed slightly the lower boundary of BE assessment when compared to MS Contin 15 mg. Additional BE analysis by Clinpharm reviewer is needed and/or Medical Division will make final decision on the acceptance of both BE studies. Therefore, granting the biowaiver for the 60 mg tablet strength is therefore pending the Clinpharm and/or Medical Division's final decision.

RECOMMENDATION

From the Biopharmaceutics perspectives, the recommendation for this NDA is pending final decision on the acceptance of the two BE studies by Clinpharm and/or Medical Division.

The pharmacokinetic profile of Morphabond is sufficiently similar to MS Contin to rely on the clinical safety and efficacy findings from MS Contin for the proposed indication. Morphabond met bioequivalence criteria when compared to MS Contin for the 100 mg strength, and met bioequivalence criteria for the total exposure of the 15 mg and 30 mg strengths, with a small difference in Tmax. The Cmax for the 15 and 30 mg strengths of Morphabond was slightly below the 80% lower limit of the confidence interval when compared to MS Contin. The slightly lower Cmax with the 15 and 30 mg strengths is not expected to have an effect on efficacy as Morphabond is dosed on an around-the-clock basis resulting in steady-state morphine levels. One of the benefits of extended-release opioid analgesics over immediate-release opioid analgesics is that the former typically have a lower Cmax and a higher Cmin, representing less variability in morphine exposure over time, which may reduce adverse effects associated with the peak level and avoid a reduction in efficacy at the trough level. As the dissolution method and data appear acceptable, the 60 mg strength and 100 mg strength are (b) (4) (b) (4), and based on the relative bioavailability studies for the 15, 30 and 100 mg strengths, there is no need for any addition pharmacokinetic studies to support the 60 mg strength. I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

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7. Clinical/Statistical-Efficacy

No new efficacy studies were conducted in support of the application. The exposure to morphine following dosing with Morphabond is comparable to MS Contin based on relative bioavailability studies and the proposed indication is the same. Therefore, there is an adequate scientific bridge to rely in the agency's previous finding of efficacy for MS Contin to support the efficacy of Morphabond.

8. Safety

Most of the pharmacokinetic studies were conducted with healthy volunteers who had been given naltrexone to block the mu-agonist effects of morphine. Therefore, the safety data from these studies are useful only from the perspective of not demonstrating any problems with swallowing the formulation. The human abuse potential study evaluating the pharmacokinetic and pharmacodynamic profile of Morphabond did not reveal any adverse events that would be unexpected for an opioid agonist. The most common treatment emergent adverse events were nausea, vomiting, abdominal pain, somnolence, and headache, which may have been a result of expsoure to morphine, and nasal congestion in subjects participating in the intranasal human abuse liability study.

Some of the excipients used to impart abuse-deterrent properties to opioid analgesic tablet formulations have resulted in the tablet becoming tacky and swelling when wet and sticking to the gastrointestinal mucosa. Through a series of in vitro tests, the Applicant demonstrated that the Morphabond tablet (b) (4). This may represent the design of the formulation in which the (b) (4) (b) (4)

The limited safety database from this development program is acceptable because the basis for the safety of Morphabond for the intended patient population is based on reliance of the Agency's prior finding of safety for MS Contin. As with efficacy, an appropriate scientific bridge for relying on MS Contin was created through the demonstration of similar pharmacokinetic profiles in relative bioavailability studies and the same intended patient population.

9. Advisory Committee Meeting

No advisory committee was convened to review this application. The data presented to support the efficacy and safety of Morphabond in a 505(b)(2) application relying the Agency's previous findings of safety and efficacy for MS Contin, and the additional literature referenced, did not raise any scientific questions requiring the advice of an advisory committee. The results of the in vitro and in vitro studies evaluating the abuse-deterrent properties were readily interpretable and did not raise any scientific questions requiring the advice of an advisory committee.

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10. Pediatrics

This application does not trigger any of the requirements for pediatric studies under the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

Abuse Deterrence
The Applicant assessed the abuse-deterrent characteristics of Morphabond using a variety of physical and chemical approaches. The highest strength Morphabond, 100 mg, was used for the in vitro testing and was compared to the 100 mg strength MS Contin.

(b) (4)

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(b) (4)

Study M-ARER-002 was a single-center, randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover study. The qualification phase required subjects to be able to distinguish the effects of a 30 mg test dose of morphine sulfate.

The four treatments were prepared and administered as indicated below:

- Treatment A: crushed intranasal IDT-00l placebo plus intact oral IDT-001 placebo.
- Treatment B: crushed intranasal MS Contin 60 mg (with crushed placebo tablet for added for volume) plus intact oral IDT-001 placebo.
- Treatment C: crushed intranasal IDT-001 60 mg plus intact oral IDT-001 placebo.
- Treatment D: crushed intranasal IDT-001 placebo plus intact oral IDT-001 60 mg.

Of the 48 subjects enrolled, 21 failed the drug discrimination phase. Of the remaining 27, two did not complete all treatment periods. The majority of subjects were male and white nonhispanic. Ages ranged from 19 to 53 years for the safety/PK populations and from 19 to 31 years for the PD population.

The Cmax of morphine was 49% lower for crushed intranasal Morphabond (also referred to as Morphine ARER) than for crushed intranasal MS Contin. The value for area under the time curve (AUC)0-0.5h was 75% lower for morphine from Morphabond than for crushed intranasal MS Contin. These results demonstrate that there is less systemic absorption following insufflation of (b) (4) Morphabond compared to MS Contin. The pharmacokinetic results are presented in the next figure and table, taken from Dr. Nallani's review.

Figure: Pharmacokinetic Profile of Morphine Following Intranasal Abuse of 60 mg Morphabond or MS Contin Compared to Intact Morphabond Taken Orally.

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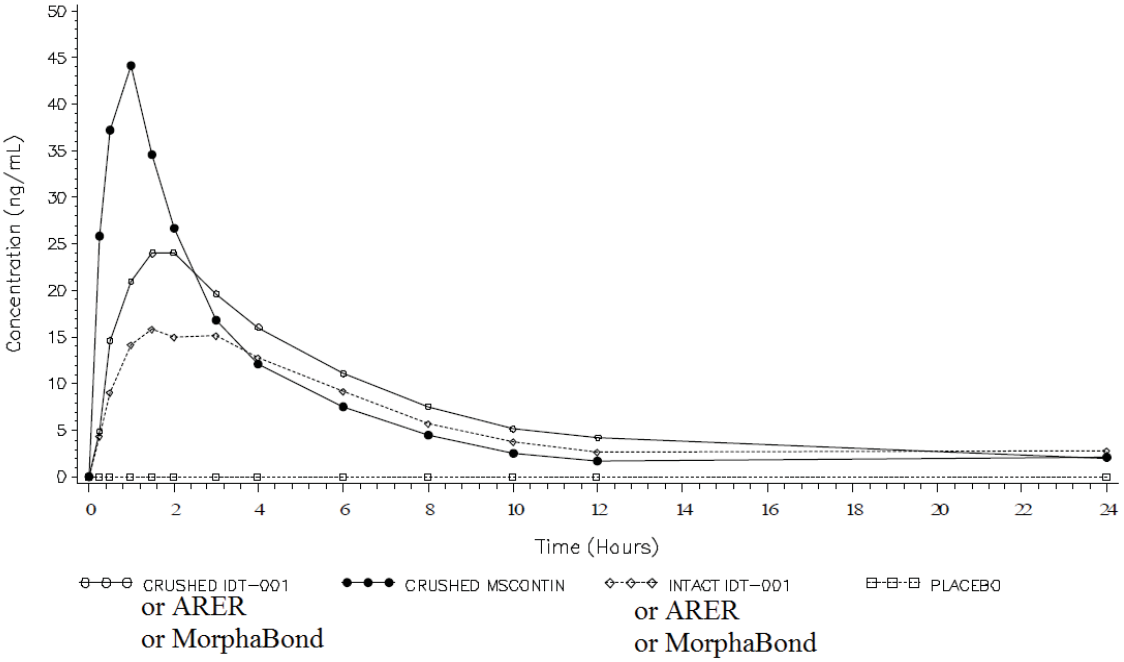
Concentration (ng/mL)
50
45
40
35
30
25
20
15
10
5
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hours)
CRUSHED IDT-001
or ARER
or MorphaBond
CRUSHED MSCONTIN
INTACT IDT-001
or ARER
or MorphaBond
PLACEBO

Table : Pharmacokinetic Parameters for Morphine after Administration of Crushed Intranasal IDT-001, Crushed Intranasal MS Contin, and Intact Oral IDT-001 (PK Population, N = 27)

Parameter	Analyte	Crushed Intranasal IDT-001 Mean ± SD	Crushed Intranasal MS Contin Mean ± SD	Intact Oral IDT-001 Mean ± SD
C_{max}	Morphine	26.2 ± 11.2	49.5 ± 17.3	18.6 ± 5.7
(ng/mL)	M6G	58.2 ± 30.7	169.0 ± 55.0	108.2 ± 18.2
T_{max}	Morphine	1.6 (1.0-3.1)	1.1 (0.2-1.6)	1.6 (0.5-3.1)
(hr)	M6G	3.1 (2.1-10.0)	1.6 (1.1-10.1)	2.1 (1.6-4.1)
$AUC_{0-0.5h}$	Morphine	2.8 ± 1.2	10.9 ± 5.2	2.1 ± 1.3
(ng•hr/mL)	M6G	0.4 ± 0.5	1.9 ± 1.3	2.2 ± 1.3
AUC_{0-t}	Morphine	178.5 ± 77.7	171.6 ± 55.2	139.4 ± 40.1
(ng•hr/mL)	M6G	441.8 ± 202.0	777.9 ± 156.9	844.4 ± 146.5
$AUC_{0-\infty}$	Morphine	219.8 ± 97.4[a]	188.0 ± 51.5[b]	158.0 ± 21.9[c]
(ng•hr/mL)	M6G	575.1 ± 263.5[d]	907.7 ± 158.6[e]	1,054.7 ± 154.5[f]
k_e	Morphine	0.0997 ± 0.0649[g]	0.0684 ± 0.0583[c]	0.0688 ± 0.0399[h]
(hr^{-1})	M6G	0.0768 ± 0.0448[a]	0.0761 ± 0.0384[e]	0.0720 ± 0.0365[i]
$t_{1/2}$	Morphine	10.8 ± 8.3[g]	21.0 ± 20.9[c]	18.4 ± 20.0[h]
(hr)	M6G	11.9 ± 6.1[a]	11.5 ± 6.2[e]	14.0 ± 11.4[i]
AUC_{0-1}	Morphine	11.2 ± 4.8	30.8 ± 12.1	7.5 ± 3.2
(ng•hr/mL)	M6G	4.8 ± 3.1	26.9 ± 13.3	18.3 ± 6.5
AUC_{0-2h}	Morphine	34.2 ± 13.7	67.0 ± 22.9	22.6 ± 7.5
(ng•hr/mL)	M6G	35.8 ± 18.9	161.4 ± 68.5	96.6 ± 20.3
AUC_{0-8h}	Morphine	120.9 ± 48.2	136.5 ± 43.4	89.3 ± 25.4
(ng•hr/mL)	M6G	266.6 ± 124.2	588.3 ± 151.5	545.2 ± 90.1
AUC_{0-12h}	Morphine	143.2 ± 57.8	148.1 ± 47.4	105.6 ± 29.5
(ng•hr/mL)	M6G	331.8 ± 149.8	660.3 ± 145.7	659.7 ± 116.5
AUC_{0-24h}	Morphine	181.1 ± 75.9	171.6 ± 55.2	139.4 ± 40.1
(ng•hr/mL)	M6G	446.8 ± 196.5	777.9 ± 156.9	844.4 ± 146.5

Values for T_{max} are medians and ranges.
n = 27 for Crushed intranasal MS Contin and n = 26 for both IDT-001 treatments, except as noted.
[a] n = 19 [b] n = 4 [c] n = 5 [d] n = 14 [e] n = 6 [f] n = 11
[g] n = 22 [h] n = 7 [i] n = 13
Source: Table 14.2.9-1, Table 14.2.9-2, Table 14.2.9-3, Table 14.2.9-4, Table 14.2.11-3, and Table 14.2.11-4.

The following information about the pharmacodynamic assessment are from Dr. Tolliver's review:

> 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

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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

Figure: Mean Drug Liking Scores versus Time, by Treatment

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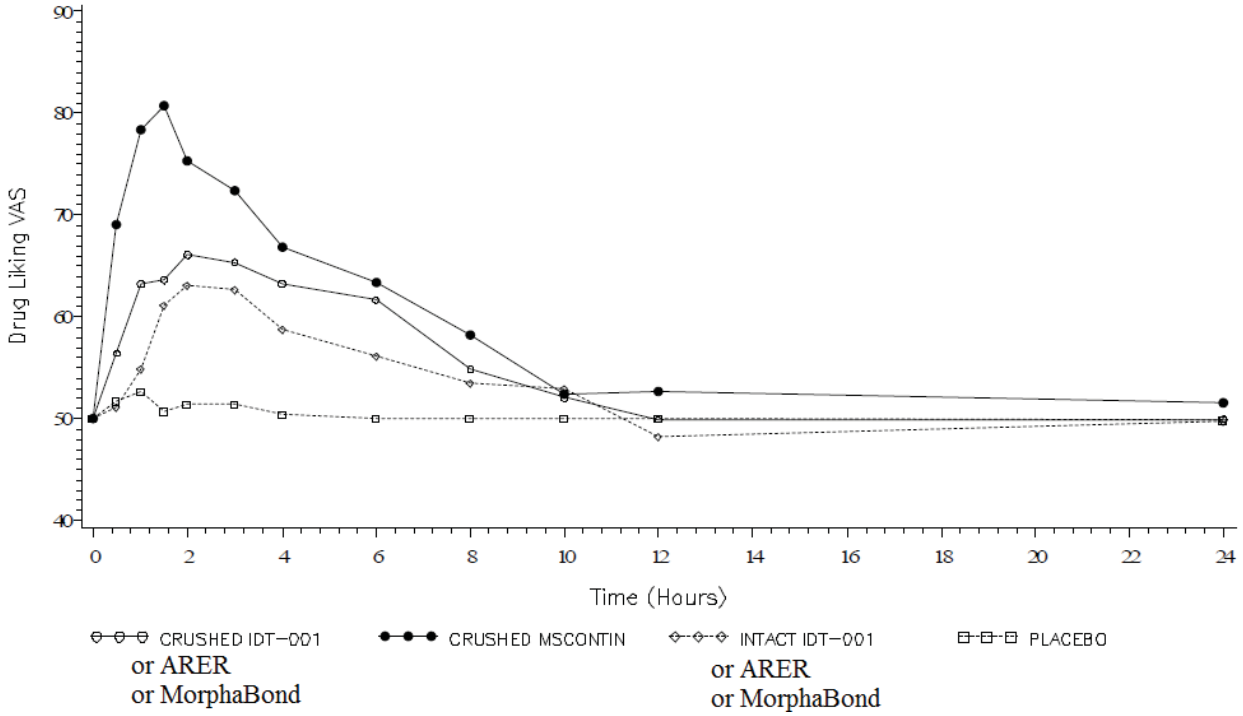

The following is also from Dr. Tolliver's review:

> 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}, $AUE_{0\text{-}1hr}$, and $AUE_{0\text{-}2hrs}$) on the Unipolar High VAS following the four treatments are shown in Table 7.

Table 7. Statistical Parameters for E_{max}, TE_{max}, $AUE_{0\text{-}1hr}$, and $AUE_{0\text{-}2hrs}$ 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)
$AUE_{0\text{-}1hrs}$ (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

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$AUE_{0\text{-}2hrs}$ (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

As shown in the previous tables and confirmed by statistical analysis, the intranasal administration of crushed Morphabond resulted in a substantially lower response to Drug Liking, High, and Take Drug Again, compared to crushed MS Contin. The responses to crushed and intact oral Morphabond were very similar.

Taken together, the results of the in vitro assessments of syringeability and low volume extraction, and the results of the intranasal human abuse liability study demonstrate that Morphabond has characteristics that are likely to deter intravenous and intranasal abuse as compared to MS Contin.

Inspections

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The site where the human abuse liability study was conducted was inspected. No significant deficiencies were observed and a Form 483 was not issued. OSI concluded that the data from this HAL study appear reliable as reported in the NDA.

An inspection of the site of the clinical pharmacology studies was requested, but OSI recommended that inspection of the site, (b) (4) not be conducted because the site had been inspected within the last four years with the results classified as NAI.

Inspections were conducted for the bioanalytical portions of bioequivalence studies conducted by (b) (4). As noted in Dr. Feeney's review:

> "As part of that study, the analytical component of Inspirion's relative bioavailability study of Morphabond 100 mg and MS Contin 100 mg was reviewed. "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."
>
> The review notes that, during some studies (none directly involving morphine), there was different recovery of analytes and their internal standards. (b) (4) acknowledged the difference and located the root cause for the difference. Repeat results were improved and (b) (4) agreed to modify their SOP (standard procedure) so that a future difference in recovery greater than 15% would result in an investigation to identify the source of the difference.
>
> The review concludes that the observation "…did not impact accuracy and precision of study sample analyses. The study data for audited studies and for other studies conducted during the interval since the last inspection can be accepted by the Agency for further review… 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."

No concerns with the Applicant's financial disclosure were found.

There are no other unresolved relevant regulatory issues

12. Labeling

Consultations from DMEPA were obtained for the proprietary name, package insert, and carton and container labels. While there was initial concern about the lack of use of an ER modifier in the name, it was noted that there are a number of other extended-release opioid analgesics marketed without the ER modifier in the proprietary name. Recommendations for labeling were conveyed to the Applicant.

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13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

The Applicant has provided an adequate assessment of the pharmacokinetic properties of Morphabond, in comparison to MS Contin, to create the scientific bridge needed to rely on the Agency's prior finding of clinical safety and efficacy of MS Contin. There are adequate data describing the chemistry, manufacturing and controls to support marketing Morphabond with a 24-month expiry. There are adequate data to support the safety of the proposed formulation. In [redacted] (b) (4) I conclude that the additional nonclinical studies may be conducted as post-marketing requirements.

There are adequate data to support the Applicant's request to include the results of the assessment of the abuse-deterrent properties of Morphabond and to conclude that Morphabond is likely to deter abuse by the intranasal and intravenous routes of administration, [redacted] (b) (4)

- Recommendation for Postmarketing Risk Management Activities

Morphabond will be part of the Extended-release and Long-acting Opioid Analgesic REMS.

- Recommendation for Postmarketing Study Requirements

An analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Assess the known serious risks of misuse, abuse, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which Morphabond (morphine sulfate) is a member;

- Identify an unexpected risk of serious adverse outcome of cancer due to chronic exposure to the excipient [redacted] (b) (4) in Morphabond;

- Identify an unexpected risk of serious adverse outcomes such as focal myocarditis and hepatotoxicity due to chronic exposure to the excipient [redacted] (b) (4) in Morphabond; and

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- Identify an unexpected risk of teratogenicity, serious embryo-fetal developmental, and/or post-natal developmental adverse events due to chronic exposure to the excipient (b) (4) in Morphabond.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2065-1 Conduct one or more studies to provide quantitative estimates of the serious 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:

a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with 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. 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.

2065-2 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.

2065-3 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. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

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2065-4 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.

Additionally, the following individual postmarketing studies of MORPHABOND (morphine sulfate) extended-release tablets are required:

2961-1 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.

The following timetable proposes the schedule by which this study will be conducted:

Final Protocol Submission:	8/2016
Study Completion:	8/2020
Final Report Submission:	02/2021

2961-2 Conduct a 9-month repeat-dose oral toxicology study in the nonrodent model characterizing the toxicological potential of (b) (4).

The following timetable proposes the schedule by which this study will be conducted:

Final Protocol Submission:	07/2017
Study Completion:	07/2018
Final Report Submission:	12/2018

2961-3 Conduct a 6-month repeat-dose oral toxicology study in the rodent model characterizing the toxicological potential of (b) (4).

The following timetable proposes the schedule by which this study will be conducted:

Final Protocol Submission:	07/2016
Study Completion:	05/2017
Final Report Submission:	10/2017

2961-4 Conduct a fertility and early embryonic development study in both male and female rats with (b) (4).

The following timetable proposes the schedule by which this study will be conducted:

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Final Protocol Submission: 12/2017
Study Completion: 05/2018
Final Report Submission: 10/2018

2961-5 Conduct an embryofetal development study for (b) (4) in the rat model.

The following timetable proposes the schedule by which this study will be conducted:

Final Protocol Submission: 07/2017
Study Completion: 10/2017
Final Report Submission: 04/2018

2961-6 Conduct an embryofetal development study for (b) (4) in the rabbit model.

The following timetable proposes the schedule by which this study will be conducted:

Final Protocol Submission: 07/2017
Study Completion: 10/2017
Final Report Submission: 04/2018

2961-7 Conduct a pre- and post-natal development study for (b) (4) in the rat model.

The following timetable proposes the schedule by which this study will be conducted:

Final Protocol Submission: 12/2017
Study Completion: 07/2018
Final Report Submission: 12/2018

2961-8 Conduct a 2-year rodent oral carcinogenicity assessment of (b) (4)

The following timetable proposes the schedule by which this study will be conducted:

Final Protocol Submission: 08/2017
Study Completion: 04/2020
Final Report Submission: 09/2020

have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioid analgesics, of which MORPHABOND (morphine sulfate) is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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2065-5 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.

The following timetable proposes the schedule by which this study will be conducted:

Final Protocol Submission:	08/2014
Trial Completion:	08/2016
Final Report Submission:	02/2017

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

/s/

SHARON H HERTZ
10/02/2015