

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206544Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 15, 2015
From	John Feeney, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	206544
Supplement#	
Applicant	Inspirion Delivery Technologies LLC
Date of Submission	November 21, 2014
PDUFA Goal Date	September 21, 2015
Proprietary Name / Established (USAN) names	Morphabond (morphine sulfate) Extended-Release Tablets
Dosage forms / Strength	100, 60, 30, and 15 mg strength 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
Recommended:	Complete Response

Material Reviewed	Review Team
Primary Medical Officer Review	Timothy Jiang, MD, PhD
Pharmacology Toxicology Review	Carlic Huynh, PhD, Newton Woo, PhD, Dan Mellon, 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

The Sponsor of this NDA is Inspirion Delivery Technologies (IDT, Inspirion). Throughout all the reviews, Morphabond is sometimes referred to as IDT-001 or Morphine ARER.

(b) (4)



Source: Chemistry Review, page 29.

2. Background

Morphabond was developed under IND 115822. There were several meetings between the Sponsor and DAAAP during the development of Morphabond. These are outlined in Dr. Jiang's Clinical Review.

The early goals of the development program for Morphabond were to: 1) demonstrate BE of the planned highest and lowest strengths of the to-be-marketed formulation (100 mg and 15 mg) to MS Contin, 2) obtain a biowaiver for the intermediate strengths (60 mg and 30 mg), 3) perform the other necessary clinical pharmacology studies, 4) characterize the safety of the formulation, and 5) perform Category 1,2, and 3 AD studies to support labeling.

The Sponsor was made aware that a particular focus for the safety review was to be any propensity of the tablets to cause obstruction of the gastrointestinal (GI) tract. This propensity has been observed with some other products being developed with AD properties, in large part because of the stickiness of tablets imparted by excipients added to provide AD properties. During development, there was agreement that it did not appear that the excipients in this product would predispose to choking, sticking, or GI obstruction and no such events were seen during development.

Initially, single-dose BE was demonstrated for the 100 mg strength, but the BE study of the lowest strength narrowly missed demonstrating BE because of the observed C_{max}. Therefore, the Sponsor conducted a BE study of the 30 mg strength. Again, BE was narrowly missed based on the C_{max}. The Sponsor discussed all these results with DAAAP, with the discussion centering on the chronic use of these drugs and the likely BE under chronic conditions.

The Sponsor has submitted the current application seeking approval for all four tablet strengths.

The need for Morphabond to be part of the ER/LA REMS was discussed with the Sponsor and the Sponsor has submitted REMS documents with their application. REMS elements include a MedGuide, prescriber training/certification, and a communication plan.

Morphabond does not trigger PREA.

There were a number of information requests (IRs) from multiple disciplines to obtain clarifications and additional information during the review cycle. The Sponsor supplied the requested information in a timely manner.

3. Chemistry

The primary Chemistry Review was performed by Xiaobin Shen, PhD and Yong Wang, PhD. The review concludes, “From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.” The recommendation for approval is based on the following:

- Overall facility inspection status (EES) acceptable
- Drug substance drug master file (Noramco, DMF 6967) reviewed and found acceptable
- Drug product specifications acceptable
- Drug product stability data support the proposed 24-month expiration dating
- Carton and container labeling were revised and found acceptable

The drug product is manufactured by Cerovene Inc. at Valley Cottage, New York. The CMC review includes Dr. Wang’s evaluation of the drug product process.

Additionally, the Category 1 AD studies were evaluated as part of the Chemistry Review (pages 54-60). These included physical manipulation studies, small-volume extraction studies (with injectability and syringeability), and large-volume extraction studies comparing Morphabond to MS Contin. (b) (4) smokeability was also assessed. These Category 1 results are also discussed in Dr. Tolliver’s Controlled Substance Staff Review and I will defer summarizing the results to that part of my review.

The stickiness properties were also addressed in the Chemistry Review and pertain to any possible propensity to cause GI obstruction (pages 56-61). Regarding stickiness, the Chemistry Review concludes that the tablets “...effectively do not swell or become sticky (b) (4)

Excipients

The Maximum Theoretic Daily Dose for oral morphine is 2000 mg. Based on that dose, the Chemistry Review highlights the excipients (highlighted in the table on the next page) that will exceed their respective exposures in the IID (inactive ingredients database). The Chemistry (b) (4)

Table 39 IIG Limit for the Morphine ARER Excipients

Excipients in Morphine ARER 100-mg Tablet					
Excipient ^a	Quantity in a Single 100-mg Tablet, mg	Quantity in Twenty 100-mg Tablets, mg	IID		UNII
			Maximum Potency, mg	Formulation	
Hypromellose, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	3NXW29V3WO
Xanthan gum, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	TTV12P4NEE
Microcrystalline cellulose, (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	OP1R32D61U
Sodium alginate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	C269C4G2ZQ
Alginic acid, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	8C3Z4148WZ
Mannitol, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	3OWL53L36A256.4
Colloidal silicon dioxide, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	ETJ7Z6XBU4
Magnesium stearate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	70097M6I30
(ethyl acrylate and methyl methacrylate copolymer (b) (4) dispersion [2:1; 750000 M _w])	(b) (4)	(b) (4)	(b) (4)	(b) (4)	P2OM2Q86BI
(ethyl acrylate and methyl methacrylate copolymer (b) (4) dispersion (2:1; 600000 M _w))	(b) (4)	(b) (4)	(b) (4)	(b) (4)	XRK36F13ZZ
Lactose monohydrate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	EWQ57Q815X
Polysorbate 80, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	6OZP39ZG8H
IID = Inactive Ingredients Database; M _w = weight average molar mass; NF = National Formulary; UNII = Unique Ingredient Identifier; USP = United States Pharmacopoeia.					
^a =	(b) (4)				
^b =	(b) (4)				
^c =	(b) (4)				
^d =	(b) (4)				
^e =	(b) (4)				

Source: Chemistry Review, page 27.

BE in vivo and similar in vitro dissolution profile comparison (f_2 value >50) between Morphine ARER ER tablets (Test) and the MS Contin tablets (RLD) for both the 100 mg and 15 mg strengths.” I discussed this with Drs. Chen and Duan and they agree that, since the Clinical Review has concluded that the 15 mg, 30 mg, and 100 mg strengths of Morphabond and MS Contin will perform similarly under the chronic conditions of use, a biowaiver for the 60 mg strength is supported.

4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology Review was performed by Carlic Huynh, PhD with Newton Woo, PhD as the Acting Team Leader. Dan Mellon, PhD wrote a secondary review. All recommend a Complete Response.

The nonclinical development program for this 505(b)(2) NDA application relies on the Agency’s previous finding of safety for MS Contin. However, several excipients in Morphabond are considered new excipients and the Sponsor provided justifications, including several nonclinical studies, to support these new excipients.

According to the Pharmacology/Toxicology Review, “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 are qualified for safety up to the maximum theoretical daily dose (MTDD) of 2 g/day of morphine.”

I will discuss (b)(4) first because it seems the most problematic for the approval of Morphabond.

(b)(4) is not present in any FDA-approved oral drug product. Two components of (b)(4) can be discussed, the polymeric backbone and an added (b)(4). The safety of the (b)(4) polymeric backbone, which consists of ethyl acrylate and methyl methacrylate copolymer, was addressed in the NDA submission and Drs. Huynh, Woo, and Mellon agree that the safety of the backbone has been reasonably established. (b)(4)

However, based on the weight-of-evidence argument, Dr. Mellon’s secondary review states, “I believe that the likelihood of any adverse effects occurring via use of Morphabond is extremely small.” He recommends a Complete Response (b)(4)

(b)(4)

(b)(4)

With the added information, I believe a stronger weight-of-evidence argument could support approval, with postmarketing requirements (PMRs) for the additional studies described in Dr. Mellon's secondary review:

- Conduct a 9-month repeat-dose oral toxicology study in the nonrodent model characterizing the toxicological potential of (b) (4)
- Conduct a 6-month repeat-dose oral toxicology study in the rodent model characterizing the toxicological potential of (b) (4)
- 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).

(b) (4): As with (b) (4), there are two components of (b) (4) for discussion, the polymeric backbone and an added (b) (4). The (b) (4) in (b) (4)

(b) (4) As with the other (b) (4) the safety of the (b) (4) polymeric backbone was addressed in the NDA submission and Drs. Huynh, Woo, and Mellon agree that the safety of the backbone has been reasonably established. They also agree that the safety of (b) (4) has been reasonably established based on a weight-of-evidence argument. The argument relies in part on the safety profile of an analogous molecule (b) (4)

5. Clinical Pharmacology

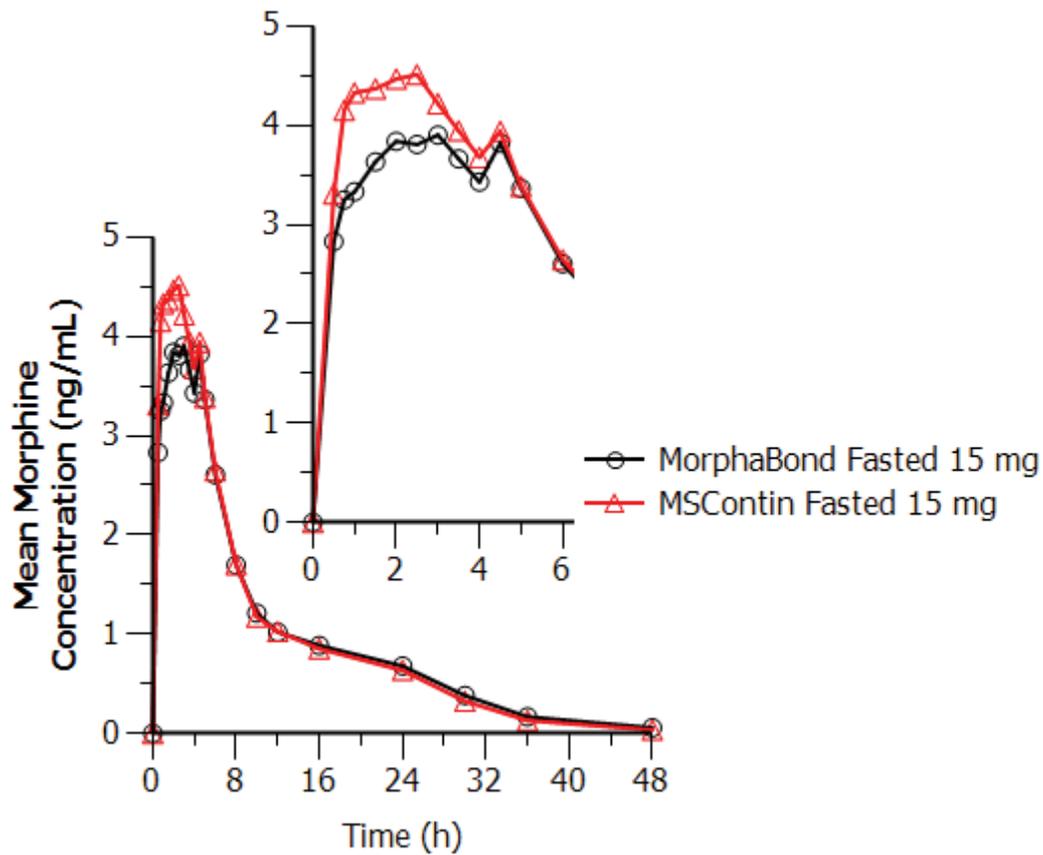
The Clinical Pharmacology Review was completed by Srikanth Nallani, PhD with concurrence from Yun Xu, PhD. They have no outstanding clinical pharmacology issues and labeling recommendations have been made.

In support of the 505(b)(2) application, the Sponsor performed a comparative bioavailability program, including Morphabond 15 mg, 30 mg, and 100 mg tablets as well as the listed drug MS Contin. A biowaiver was requested for the 60 mg strength and this was discussed in the biopharmaceutics section of this review.

The Sponsor performed both single- and multiple-dose PK studies of Morphabond, including a food-effect study.

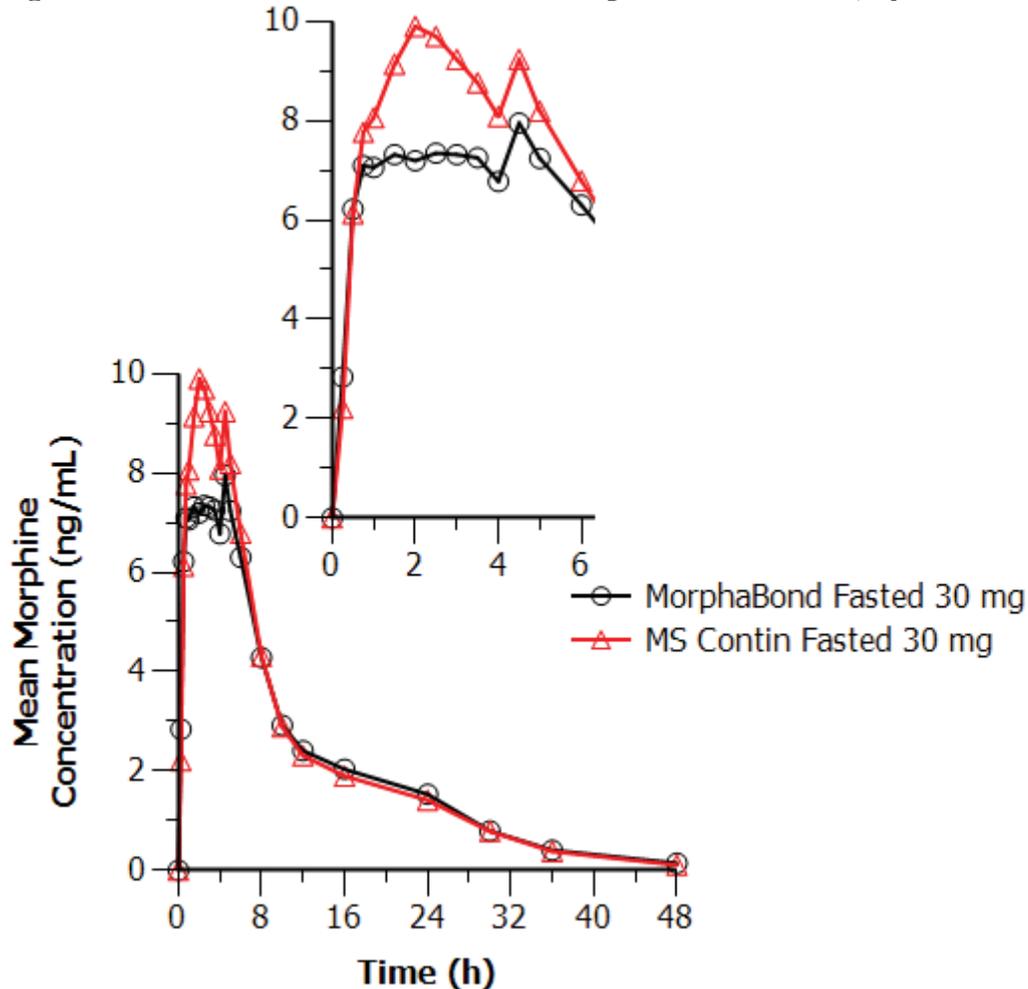
The Sponsor concluded that Morphabond 100 mg was bioequivalent to MS Contin 100 mg, based on both C_{max} and AUC values. Dr. Nallani agrees. For both the 15 mg and 30 mg tablet strengths of Morphabond, BE was demonstrated for AUC but was slightly missed for C_{max}. The 90% confidence interval (CI) for C_{max} for the 15 mg Morphabond tablet was 79.1% to 96.6%, just missing the lower bound of 80% for BE. The 90% CI for C_{max} for the 30 mg Morphabond tablet was 76.2% to 85.3%, also missing the lower bound for BE. The concentration-time profiles for morphine are shown in the following figures from Dr. Nallani's review (page 53).

Figure: Mean Plasma Concentration of Morphine versus Time, by Treatment, 15 mg



Note: N = 28 Subjects in Fasted State
Inset shows expansion of the profile over first six hours.
Source: Clinical Pharmacology Review, page 53.

Figure: Mean Plasma Concentration of Morphine versus Time, by Treatment, 30 mg



Note: N = 41 Subjects in Fasted State

Inset shows expansion of the profile over first six hours.

Source: Clinical Pharmacology Review, page 59.

Dr. Nallani addresses this as follows: “For both 15 mg and 30 mg MorphaBond tablets, C_{max} slightly missed the 80% lower bound. For such extended release products, T_{max} and C_{max} values will highly depend on PK sampling time, and the observed T_{max} and C_{max} values may not reflect the real T_{max} and C_{max} values. Considering the fact that C_{max} missed the 80% lower bound slightly and this product will be titrated to effect, this observation may not be clinically significant.”

Supporting the small magnitude of the difference seen for formal C_{max} BE for the 30 mg tablet strength, in a smaller earlier bioavailability study, n=15, that also compared Morphabond 30 mg and MS Contin 30 mg, the CI for the difference in C_{max} was 86.5% to 105.8% which would meet the targeted CI in larger formal BE studies. Given this C_{max} data and the demonstrated BE for AUC, the 15 mg and 30 mg Morphabond strengths are expected to be BE to the similar strengths of MS Contin under the intended chronic use conditions for Morphabond; the Sponsor performed simulations of multiple dosing with 15 mg and 30 mg Morphabond tablets to support this.

The Sponsor conducted two multiple-dose PK studies comparing Morphabond 100 mg and MS Contin 100 mg. The first study, M-ARER-006 was complicated by the irregular PK profiles observed for eight of the 28 completers. Because of the possibility of poor compliance in that study, the Sponsor conducted a second multiple-dose study, M-ARER-008. M-ARER-008 was a single-center, open-label, multiple-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover study designed to compare the bioavailability of Morphabond 100 mg tablets to MS CONTIN 100 mg tablets in healthy adult subjects. Patients were dosed twice daily for five days. BE was demonstrated for both C_{max} and AUC in this study.

Regarding the food effect for Morphabond, Dr. Nallani states, “Taking MorphaBond with FDA high-fat meal increases C_{max} of morphine by 33% without any effect on AUC.”

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The primary clinical review was performed by Timothy Jiang, MD, PhD. He notes that the Sponsor is relying on previous findings of efficacy and safety for MS Contin to support the Morphabond NDA. Therefore, no formal efficacy studies were conducted with Morphabond.

The indication sought by the sponsor for Morphabond is management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The proposed dosing guidelines are identical to those for MS Contin.

Dr. Jiang notes that while the 100 mg Morphabond tablet was shown to be BE to the 100 mg MS Contin tablet for both C_{max} and AUC, the two lowest-strength tablets of Morphabond were BE only for AUC. The 90% confidence interval (CI) for C_{max} for the 15 mg Morphabond tablet was 79.1% to 96.6%, just missing the lower bound for BE. The 90% CI for C_{max} for the 30 mg Morphabond tablet was 76.2% to 85.3%, also missing the lower bound for BE.

Dr. Jiang concludes in his Clinical Review, “Although C_{max} is lower for both two lower strength Morphine ARER tablets (15 mg with ratio 87.4%, 90% CI, 79.1% to 96.6% and 30

mg with ratio 80.7%, 90% CI, 76.2% to 85.3%), the reviewer agrees that not meeting the BE criteria will not affect the efficacy and safety for the following reasons:

- For chronic therapy, BE at steady-state is more relevant to demonstration of similar efficacy...
- Two lower strengths are mostly used as initiation and titration doses
- Lower C_{max} would not pose a safety concern.”

I agree with Dr. Jiang. Morphabond and other ER/LA opioids have been developed specifically to facilitate dosing in the chronic-use setting. In the chronic-use setting, Morphabond, dosed with the 15 mg and 30 mg tablets, is expected to provide morphine plasma levels that are BE to the levels achieved with MS Contin 15 mg and 30 mg respectively.

8. Safety

The primary review of the safety data was performed by Timothy Jiang, MD, PhD.

The safety database submitted in the NDA contains safety data from six clinical pharmacology studies and a single intranasal human-abuse-liability (HAL) study. The clinical pharmacology studies were all conducted in normal volunteers who were naltrexone-blocked. The HAL study was performed in healthy volunteers who were experienced opioid users but were not opioid dependent.

A total of 241 volunteers were exposed to at least one dose of Morphabond across all studies. Of these, 152 received a single dose and 89 received between two and nine doses. In three studies, patients received a single dose of Morphabond. In one study, the food-effect study, patients received two doses of Morphabond (in the fed and fasted states). In the HAL study, patients received two doses of Morphabond (one oral dose and one intranasal dose). In the two multiple-dose studies (M-ARER-006 and M-ARER-008), 64 patients were dosed twice daily for 4.5 days, for a total of nine doses of 100 mg.

Serious Adverse Events

Dr. Jiang describes one patient who went to the emergency room and was observed for 12 hours before being discharged. Per the Sponsor:

“About 5.5 hours after dosing in period 1 with the test product, Subject 20 (b) (6) developed acute onset of abdominal pain, associated with nausea, vomiting, and diarrhea. As the abdominal cramping worsened, the subject became incontinent and soiled his clothing due to diarrhea. While being attended to by clinical staff, the subject independently contacted 911. EMS staff arrived and, simultaneously with the investigator, evaluated the subject. The subject desired further evaluation at the emergency room, and the subject was transported to the local emergency room.”

The patient was evaluated and treated symptomatically. The symptoms resolved. Dr. Jiang’s comments about that patient follow below:

“This is a young man who developed GI symptoms and headache shortly after taking a 15 mg study product, and was treated in hospital’s emergency room, but not admitted to hospital. While the GI symptoms such as abdominal cramps, nausea, vomiting, and diarrhea may be related to study product, the totality of the presentation and imaging in emergency room don’t suggest GI obstruction.”

As discussed in the Chemistry section of my review, some AD products have shown a propensity to stickiness once exposed to fluids. The lack of such evidence with Morphabond is described in the Chemistry section and Dr. Jiang does not believe this clinical case, or any other case in the NDA, is explained by such a phenomenon.

Discontinuations

A total of 15 volunteers withdrew from treatment with Morphabond prematurely across all studies, 6 from the single-dose studies and 9 from the multiple-dose studies. Reasons for withdrawal were:

- Adverse event, n=7
- Withdrew consent, n=4
- Lost-to-follow-up, n=3
- Protocol violation, n=1 (positive drug screen)

The AEs that led to discontinuation for the seven Morphabond-treated subjects are listed in Table 21 of the Clinical Review and included:

- Vomiting and abdominal pain
- Vomiting, abdominal pain, nausea, diarrhea, and headache
- Nausea and headache
- Nausea and headache
- Nausea and vomiting
- Herpes zoster
- Nausea and vomiting

All were rated mild-moderate except for the case of severe abdominal pain that was discussed as the serious AE case above.

Adverse Events of Special Interest

Dr. Jiang’s review summarizes the GI AEs during the development program. Across all studies, there were 40 GI-related events with Morphabond, representing 16.6% of all subjects exposed. This is not surprising for an opioid and a similar percentage of volunteers exposed to MS Contin experienced GI-related AEs.

Dr. Jiang also summarizes a number of search criteria that were used by the Sponsor to query their AE data investigating GI AEs that may have been related to tablet stickiness. The particular queries undertaken may not have been optimal because of the difficulties in discriminating groups of AE terms specific for obstruction versus more general opioid-related

GI AEs. However the GI terms were grouped, the incidence of events was comparable for Morphabond and MS Contin (Table 12 of the Clinical Review) providing reassurance that the AD properties of the Morphabond tablet did not confer any additional GI risk over MS Contin. The two products are similarly tolerated.

Common Adverse Events

Given the different study designs and the fact that not all studies utilized naltrexone blockade (the HAL study did not), the presentation of the AE data for the single-dose studies in Table 16 of Dr. Jiang's review is not very informative. The multiple-dose study AE data presented in Table 17 of the Clinical Review allow for a side-by-side comparison of the AEs experienced by patients randomized to multiple doses of MS Contin 100 mg versus Morphabond 100 mg (in the presence of naltrexone blockade). The AEs observed are all those expected with an opioid and no significant differences are observed between the two treatments.

Dr. Jiang also describes a number of transient laboratory abnormalities that were observed during the trials. None of these raised additional concern. Some vital sign abnormalities were observed consistent with the AE profile for opioids.

Discussion

Dr. Jiang concludes, "Overall, I agree with the Applicant's review of the safety findings that the AEs seen in the safety population, albeit not in target pain population, were generally consistent with those of the known safety profile of the opioid." I agree with this assessment.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not deemed necessary for this application because the types of studies needed to characterize AD properties of opioid products have already been extensively discussed, to include the performance and the evaluation of those studies. The current thinking on this topic is expressed in the FDA guidance for industry: *Abuse-Deterrent Opioids – Evaluation and Labeling*.

10. Pediatrics

The application does not trigger the requirements of PREA.

11. Other Relevant Regulatory Issues

Clinical Site Inspection

The Clinical Inspection Summary was prepared by John Lee, MD with concurrence from Janice Pohlman, MD, MPH and Kassa Ayalew, MD, MPH.

An inspection was performed at the single site involved in the human abuse liability study (HAL) Study M-ARER-002. The inspection was performed July 13-21, 2015.

Name	Number Randomized	Final Classification
Lynn Webster, MD CRI Lifetree, Inc. Salt Lake City, Utah	48 enrolled; 27 randomized	Preliminary NAI

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable

Preliminary results based on communication with field investigator

No significant deficiencies were observed and a Form 483 was not issued. The review states, "The data from this HAL study appear reliable as reported in the NDA."

OSIS Inspections

The Office of Study Integrity and Surveillance (OSIS) recommended that an on-site inspection of the site of the clinical pharmacology studies, Novum Pharmaceutical Research Services in Las Vegas, Nevada, not be conducted. The rationale was that the site was inspected within the last four years with the results classified as NAI.

OSIS did conduct an inspection for the bioanalytical portions of BE studies conducted by (b) (4). 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."

Controlled Substances Staff (CSS)

The review of the AD data submitted in the NDA was reviewed as part of both the Chemistry and CSS Reviews. James Tolliver, PhD and Silvia Calderon, PhD provided the CSS review with concurrence from Michael Klein, PhD. Multiple Category 1 in vitro studies were performed to investigate the physical-chemical properties of Morphabond. Dr. Tolliver summarized these Category 1 results in his review. The supporting statistical review of Study M-ARER-002, a category 2/3 nasal human abuse liability (HAL) study, was performed by Wei Liu, PhD with concurrence from Qianyu Dang, PhD and Yi Tsong, PhD.

The CSS reviewers concluded that the data provided do support placement of abuse-deterrent language in the label.

In Vitro Studies

The in vitro studies were performed to investigate various methods of defeating the controlled-release properties of Morphabond with the intent to abuse the product by various methods of administration, including intravenous, oral, nasal, and smoking. The active control in these studies was MS Contin. Dr. Tolliver's review provides a comprehensive description of these studies and results.

Morphabond resisted

(b) (4)

(b) (4)

(b) (4)



Source: CSS Review, Table 2, page 9.

Morphabond 100 mg tablets were also compared to MS Contin 100 mg tablets for (b) (4)

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Nasal Abuse Potential Study

Additionally, the Sponsor conducted a category 2/3 nasal HAL study in non-dependent recreational opioid users to investigate the AD properties of Morphabond following nasal administration. The primary objective of the study was to determine the abuse potential of crushed Morphabond 60 mg administered intranasally and intact Morphabond 60 mg administered orally, both relative to crushed intranasal MS Contin 60 mg. A total of 70 subjects were screened with 48 entering the qualification phase. After a Naloxone Challenge Test and a Drug Discrimination Test, there were 27 subjects that were randomized in the Treatment Phase of the study, with 25 completing. There were 25 subjects included in the pharmacodynamics assessment and 27 included in the PK assessment. Two subjects were withdrawn from the study due to positive urine drug screens upon admission to the clinic. The study was a 4-way crossover study with the following treatment groups:

- Treatment A: crushed IN placebo and intact PO placebo
- Treatment B: crushed IN MS Contin 60 mg and intact PO placebo
- Treatment C: crushed IN Morphabond 60 mg and intact PO placebo
- Treatment D: crushed IN placebo and intact PO Morphabond 60 mg

A crushed MS Contin tablet produces a small volume compared to a crushed Morphabond tablet, (b) (4), (b) (4) were presented to the subjects. Morphabond was (b) (4) using a (b) (4), while MS Contin was (b) (4) using a (b) (4). Category 1 studies identified the (b) (4) as an efficient means of grinding Morphabond. All intranasal doses were consumed in eight minutes or less, with a median time of two minutes for all crushed treatments.

PK parameters were determined and the following measures of drug-liking were obtained: Bipolar Drug Liking on a 0-100 point VAS, Unipolar High on a 0-100 point VAS, Bipolar Take Drug Again on a 0-100 point VAS, and Bipolar Snorting Experience on a 0-100 point VAS. Primary parameters for Drug Liking were: maximum drug effect (E_{max}), time to reach maximum drug effect (TE_{max}), area under the time-effect curve from 0 to 1 hour post-dosing (AUE_{0-1hr}) and area under the time-effect curve from 0 to 2 hours post-dosing (AUE_{0-2hrs}).

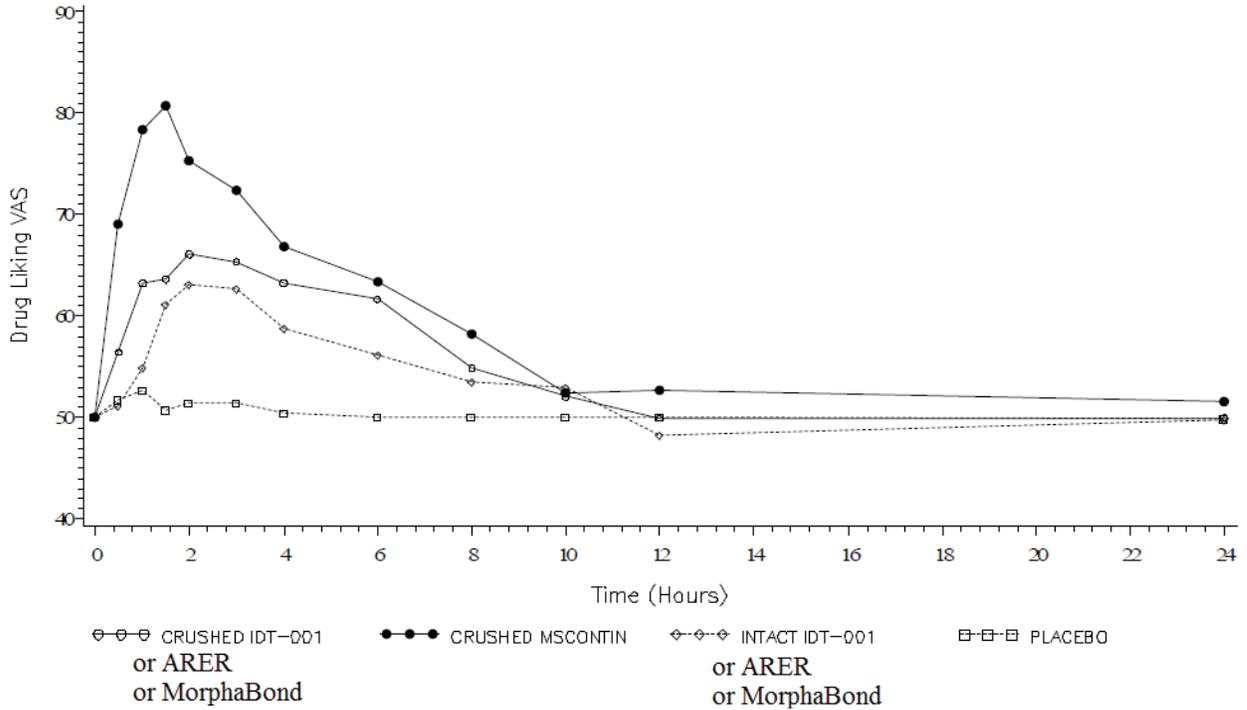
The primary treatment comparison was Treatment B versus Treatment C for Bipolar Drug Liking.

Results

Pharmacodynamic

The primary analysis was a comparison of Drug Liking between IN crushed Morphabond and IN crushed MS Contin. The results for that comparison can be viewed in the figure below and the table that follows shows the results of the statistical analyses as provided by CDER Office of Biostatistics.

Figure: Mean Drug Liking Scores versus Time, by Treatment



Source: Clinical Pharmacology Review, page 14.

Table: Statistical Analyses for Bipolar Drug Liking VAS, Unipolar High VAS, and Take Drug Again VAS

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 p=0.0442	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

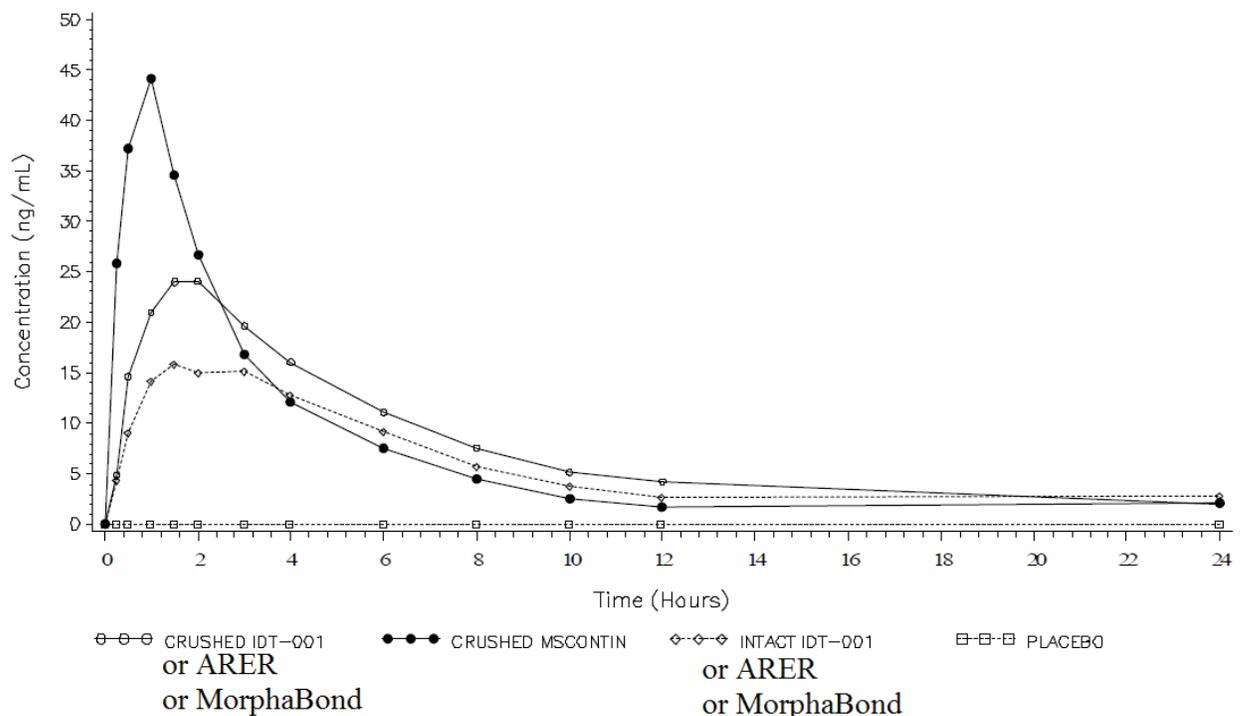
Source: CSS Review, Table 6, page 20. Statistical results provided by CDER Office of Biostatistics.

The results support an AD effect of Morphabond to intranasal abuse compared to MS Contin. At the same time, the significantly higher drug liking with IN Morphabond compared to IN placebo indicates a significant abuse potential.

Pharmacokinetic

The pharmacokinetic results are consistent with the observed pharmacodynamic results. The PK results were supportive of the Drug Liking results, with substantially higher peak plasma concentrations (C_{max}) for IN crushed MS Contin relative to IN crushed Morphabond. The PK profile of morphine after IN crushed Morphabond was similar to that seen after PO intact Morphabond.

Figure: Mean Plasma Concentrations of Morphine versus Time, by Treatment



Source: Clinical Pharmacology Review, page 12.

Conclusions from Study M-ARER-002

1. First, the CSS review notes that “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.”

2. Second, Drug Liking scores were lower for IN crushed Morphabond than for IN crushed MS Contin, suggestive of less abuse potential for Morphabond relative to MS Contin by the IN route. The CSS review notes that “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.”
3. For Morphabond, no significant differences for Drug Liking were observed between IN crushed Morphabond and PO intact Morphabond.

Recommendations from the CSS Review

The CSS Review includes the detailed conclusions of Dr. Tolliver and Calderon after review of the Category 1-3 data. Based on those conclusions, they recommend:

- “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 [REDACTED] (b) (4) [REDACTED] and more resistant to dose-dumping in various solvents including water compared to MS Contin. In addition, both the formation of a viscous liquid upon exposure to water, as well as the limited extraction of morphine sulfate, precludes the need to crush 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.
2. 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 appears 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.”

Schedule

Morphabond tablets will be in Schedule II of the Controlled Substances Act.

Financial Disclosures

According to Dr. Jiang’s clinical review, the Sponsor has not identified any financial arrangements that would affect the approvability of this application. The Clinical Review states, “The Applicant’s submission included the completed Certification: Financial Interests and Arrangements of Clinical Investigators in compliance with 21CFR part 54. This certified that the Applicant had not entered into any financial arrangements with the listed clinical investigators, that each clinical investigator had no financial interests to disclose and that no investigator was the recipient of any other sorts of payments from the Applicant for studies.”

REMS

Morphabond will be part of the ER/LA REMS.

12. Labeling

Proprietary Name

The proposed proprietary name, Morphabond, was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found acceptable from both a promotional and a safety perspective (reviews dated November 13, 2014 and March 16, 2015). The Sponsor was notified that the name was acceptable in a letter dated April 2, 2015.

One issue addressed in the DMEPA review was the lack of a modifier in the name to emphasize the ER nature of the product. “While we still have a concern about the potential for confusion between immediate and extended-release formulations resulting in wrong frequency errors, we looked at other currently marketed morphine extended-release oral dosage forms marketed without a modifier in the proprietary name, and we did not identify any wrong frequency error or wrong technique error cases for these products in the FDA Adverse Event Reporting System (FAERS).” DMEPA plans to monitor for any errors through postmarketing surveillance and will consider additional regulatory action if any confusion arises related to the lack of such a modifier.

Carton and Container Labeling

The DMEPA reviewer for Morphabond was James Schlick, RPh, MBA with concurrence from Vicky Borders-Hemphill, PharmD. The review dated March 17, 2015 evaluated the carton and container labels for Morphabond to assess risk for medication errors. The review identified several items to improve readability and increase prominence of important information. I agree with their proposals for the container labels. The proposals have only recently been shared with the Sponsor.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

At this time, I recommend a Complete Response for the Morphabond application. Prior to Approval, the weight-of-evidence argument to support the new excipient (b) (4) should be strengthened. The Sponsor should 1) make further attempts to obtain the final study reports for the two 2-year rat dietary studies and the multi-generation rodent study, and 2) seek any further available evidence supportive of (b) (4).

With that added information, I believe a stronger weight-of-evidence argument can support approval, with postmarketing requirements (PMRs) for the more definitive studies outlined by Dr. Mellon.

Risk Benefit Assessment

Morphabond has physicochemical properties that are expected to reduce, but not totally prevent, abuse of the drug. In particular, the properties of Morphabond are expected to reduce the risks of intranasal and intravenous abuse. The development of opioids with AD properties is a valuable component of the broader approach to reducing abuse and misuse, while still making appropriate treatments available for patients. Currently, Embeda (morphine sulfate and naltrexone hydrochloride) ER capsules represent the only AD ER formulation of morphine marketed in the U.S. Embeda was approved in 2009.

The Morphabond application relies on the previous findings of efficacy and safety for MS Contin. The Sponsor has demonstrated BE between the 100 mg strength tablets of Morphabond and MS Contin in single- and multiple-dose studies. BE between the 15 mg strength tablets and between the 30 mg strength tablets is expected under the conditions of use, chronic therapy, and a biowaiver can be granted for the 60 mg strength Morphabond tablet based on similarity in dissolution profiles. Dosing recommendations will be identical to MS Contin. The data across the Category 1, 2, and 3 AD studies supports AD labeling for the product.

Recommendation for Postmarketing Risk Management Activity

Morphabond will be part of the ER/LA REMS.

Recommendation for Postmarketing Study Requirements

Once the weight-of-evidence argument for (b) (4) is bolstered with the information described above, potentially supporting an Approval action, the pharmacology/toxicology PMRs described above will remain.

Postmarketing studies of Morphabond will eventually be needed to assess the effects of the AD features on the risk for abuse of Morphabond and the consequences of that abuse in the community.

In addition, Morphabond is part of the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS), which requires companies to make available to health care professionals educational programs on how to safely prescribe ER/LA opioid analgesics and to provide Medication Guides and patient counseling documents containing information on the

safe use, storage, and disposal of ER/LA opioids. The postmarketing study requirements under the ER/LA REMS will apply for Morphabond.

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

/s/

JOHN J FEENEY
09/15/2015