CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202515Orig1s000

MEDICAL REVIEW(S)

Clinical Review

Date	October 6, 2011
From **Through**	Timothy Jiang, M.D. Ellen Fields, MD, Clinical Team Leader
Subject	Clinical Review
NDA# **Type**	(b) (4) 505(b)(2) application
Applicant	Hospira, Inc.
Date of Submission	January 14, 2011
PDUFA Goal Date	November 14, 2011
Proprietary Name / Established (USAN) names	Morphine Sulfate Injection USP
Proposed Dosage forms / Strength	IV (b) (4) Injections (pre-filled syringes (b) (4))/ 2 to (b) (4) mg/mL
Proposed Indication(s)	Management of pain not responsive to non-narcotic analgesics
Recommended:	Complete Response

1. Introduction

There are numerous unapproved narcotic analgesics marketed under the mistaken belief that as very old products the applications were not subject to review under the Drug Efficacy Study Implementation in support of continued marketing. However, the Agency has deemed that morphine sulfate and other marketed unapproved opioids must be subject to approval requirements in order to be in compliance with Agency regulations.

This NDA is for marketed, but unapproved morphine sulfate injection via the intravenous (IV) (b) (4) routes of administration. Hospira, Inc. currently markets multiple configurations of morphine products for the management of pain not responsive to non-narcotic analgesics. The drug product is supplied in following multiple strengths in the specified containers:

- 2 mg/ml, 4 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml of morphine sulfate packaged in a Carpuject™ with Luer Lock or iSecure™ Prefilled syringe

(b) (4)

In response to the FDA 2006 guidance entitled "Marketed Unapproved Drugs - Compliance Policy Guide," Hospira, Inc. has filed an NDA for their morphine sulfate product. They have submitted a 505(b)(2) application that references literature and the Agency's previous findings of efficacy and safety for Duramorph (NDA 18,565) by Baxter Healthcare for the IV injection, (b) (4)

The proposed indication for Morphine Sulfate Injection is management of pain not responsive to non-narcotic analgesics.

The Applicant has also relied on published literature to support the non-clinical aspects of this submission. No new clinical efficacy or safety studies and no new non-clinical studies were performed in support of this NDA. A waiver for bioavailability and bioequivalence studies was requested for (b) (4) the IV (b) (4) routes of administration,

(b) (4)

2. Background and Regulatory History

Morphine was isolated from opium as early as 1806. Opiate receptors were first identified in the early 1970's. Morphine, along with most of the clinically used opioids, is relatively selective for the mu subtype of opiate receptor and it is through the mu receptor that it exerts its clinical effects.

A Pre-IND (IND 105936) meeting was held on October 28, 2009, at which time the Division agreed to a regulatory path forward via a 505(b)(2) application that would rely on published literature and the Agency's previous findings of safety and efficacy for Duramorph (b) (4)

During the meeting, the Agency made the following specific comments:

- The Applicant must provide an adequate basis for reliance through appropriate bridging data (e.g., comparative bioavailability data) for (b) (4) routes of administration.
- Since neither reference product is approved for (b) (4) administration, additional pharmacokinetic studies may be required using this route of administration unless adequate support is available from the literature.
- The maximum daily dose of morphine will be established and justification for safety of the drug substance impurities, drug product degradants and excipients must be provided, based on the maximum daily dose.
- (b) (4)
- (b) (4)
- If the Sponsor requests a Biowaiver, they must submit appropriate rationale and supporting information in order to assess the request.

The NDA application, which was submitted on January 14, 2011, is only seeking IV (b) (4) routes of administration. This submission therefore, does not trigger PREA.

3. CMC/Device

Please see Dr. Ying Wang's review for details.

The following is a summary of Dr. Wang's review:
Drug Substance:

- Morphine Sulfate USP is referenced in DMF (b) (4), and is manufactured by (b) (4).
- Acceptance criteria for total impurity and some specified impurity have been tightened during the review cycle.
- Specifications for related substances all meet ICH Q3A.

Drug Product:

- Morphine Sulfate Injection USP
  - (b) (4) container closure systems
  - (b) (4) strengths
- The acceptance criteria for pH, Edetate Disodium and total impurity have been tightened during the review cycle.
- Drug product is very stable and 24 month expiry for long term storage condition is acceptable from a CMC perspective.

Manufacturing Issues:

- (b) (4)

Dr. Wang concluded that this NDA must receive Complete Response due to OC recommendation of withhold.

4. Nonclinical Pharmacology/Toxicology

Please see Dr. Elizabeth Bolan's review for details.

The Applicant did not submit any new preclinical studies. The Pharmacology and Toxicology team amended certain sections of the label based on their review of the literature in order to make all morphine labels consistent.

Dr. Bolan sent the Applicant the following comments and received acceptable responses:

1. The drug substance acceptance specification of (b) (4) for (b) (4) exceeds the ICH Q3A (R2) qualification threshold. We recommend that you consult with your DMF holder and tighten your acceptance specification to NMT 0.15% in order to comply with ICH Q3A (R2) guidelines.

2. The drug product specifications for (b) (4) exceed the ICH Q3B (R2) qualification threshold of NMT 0.2%. After formal review, it has been determined that your literature-based justification is not adequate to support the safety of your proposed drug product specifications. However, the genetic toxicology studies with (b) (4) are acceptable and no further genetic toxicology qualification of (b) (4) will be required. The impurities/degradants must either be reduced to below ICH Q3B (R2) qualification threshold of NMT 0.2% or adequately qualified via toxicology studies. Adequate qualification would include:
    - Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) for (b) (4), tested up to the limit dose for the assay.
    - Repeat dose toxicology studies of 90 days duration with (b) (4)

There are no pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Since the Applicant did not submit any new clinical pharmacology data, there is no clinical pharmacology review. Dr. David Lee of Clinical Pharmacology team reviewed articles submitted by the Applicant that contained pharmacokinetic data for morphine in pediatric patients. Please see Pediatric section of this review for details.

Please see Dr. Minerva Hughes's biopharmaceutics review for details.

As summarized by Dr. Hughes, a waiver of the CFR's requirement to provide data from in vivo bioavailability or bioequivalence studies for (b) (4) the IV (b) (4) routes of administration, to support the approval of Morphine Sulfate Injection was requested on the basis that the product is an injectable solution and its bioavailability is self-evident, as per 21 CFR §320.22 (Criteria for waiver of evidence of in vivo bioavailability or bioequivalence). In support of the requested biowaiver for Morphine

Sulfate Injection, NDA 202-515 included the following information for review and evaluation:

- Formulation comparison table which included composition data for approved products
- Literature references for bioavailability and pharmacokinetic performance

Dr. Hughes concluded that a waiver of the CFR's requirement to provide vivo bioavailability or bioequivalence data is granted for Morphine Sulfate Injection administered by the intravenous route only. (b) (4)

6. Clinical Microbiology

Please see Dr. Bryan S. Riley's review for details.

The following is a summary of Dr. Riley's review:

- The drug product is (b) (4) filled.
- (b) (4)
-

As stated in Dr. Riley's review, a microbiological deficiency related to (b) (4) in the product labeling was sent to the applicant. Pending submission of microbiological data to support a (b) (4)

Dr. Riley concluded that "this submission is approvable pending resolution of product quality microbiology deficiencies." However, if the labeling includes the language for (b) (4) the product is approvable from a microbiological perspective.

7. Clinical/Statistical- Efficacy

No new clinical efficacy studies were performed in support of this application. In order to meet the requirements for approval for morphine sulfate IV, (b) (4) the Applicant relied on the Agency's previous sindings of efficacy and safety for the reference drugs Duramorph (NDA 018565) by Baxter by Baxter Healthcare (b) (4) They also submitted published literature.

The Applicant submitted 59 published articles that included randomized controlled trials of morphine (55 for acute pain, and four for chronic pain) which have been reviewed. Overall, the literature is consistent with what would be expected regarding the efficacy of morphine sulfate; that IV (b) (4) morphine effectively treat a variety of painful conditions, such as post-surgical, acute, and chronic pain. The literature-based information is not required for approval, since the Applicant has relied on reference drugs as noted above.

Since the biowaiver (b) (4) only the Agency's previous findings of efficacy for the reference product Duramorph for the IV route of administration will contribute to the approval of this NDA.

8. Safety

No new clinical safety data were submitted in support of this application. Safety for morphine sulfate IV (b) (4) is supported by the Agency's prior findings of safety for the reference products Duramorph (NDA 018565) by Baxter by Baxter Healthcare, (b) (4)

The safety data from the 59 published articles submitted by the Applicant have been reviewed. The safety profile described in the literature is consistent with the known safety profile of morphine sulfate.

Morphine sulfate is a Schedule II controlled substance and like all opioids, its' use can result in abuse, misuse, psychological and physical dependence, and tolerance.

According to the labels of the referenced morphine products, the most serious adverse events encountered during administration of morphine sulfate IV (b) (4) are respiratory depression, respiratory arrest, central nervous system depression, overdose, coma and death. Anaphylaxis resulting from morphine administration has also been described.

Common adverse events associated with morphine sulfate are similar to those of other opioids and include sedation, constipation, lightheadedness, dizziness, nausea, vomiting, and sweating.

(b) (4)

Since the biowaiver (b) (4) only the Agency's previous findings of safety for the IV route of administration for the reference product Duramorph will contribute to the approval of this NDA.

9. Advisory Committee Meeting

No Advisory Committee meeting was held regarding this application.

10. Pediatrics

As the products that are the subject of this application do not represent a change in active ingredient, dosage form, route of administration, indication or dosing regimen, the pediatric study requirements under PREA are not applicable, and there are no required pediatric studies associated with this NDA. (b) (4)

Duramorph is administrated by the intravenous, epidural or intrathecal routes. The label includes the following language in reference to pediatric usage: "Adequate studies, to establish the safety and effectiveness of spinal morphine in pediatric patients, have not been performed, and usage in this population is not recommended."

(b) (4)

(b) (4)

The Agency sent the Applicant an information request explaining that their application did not trigger PREA, (b) (4)

The following was conveyed to the Applicant on March 7, 2011:

- We acknowledge your submission of a pediatric waiver request and literature review in NDA 202515 for morphine sulfate injection. Since approved versions of morphine sulfate exist for both IV (b) (4) injection and for the same proposed indication of your product, NDA 202515 does not trigger PREA, and therefore no pediatric studies are required for this NDA.

- (b) (4)

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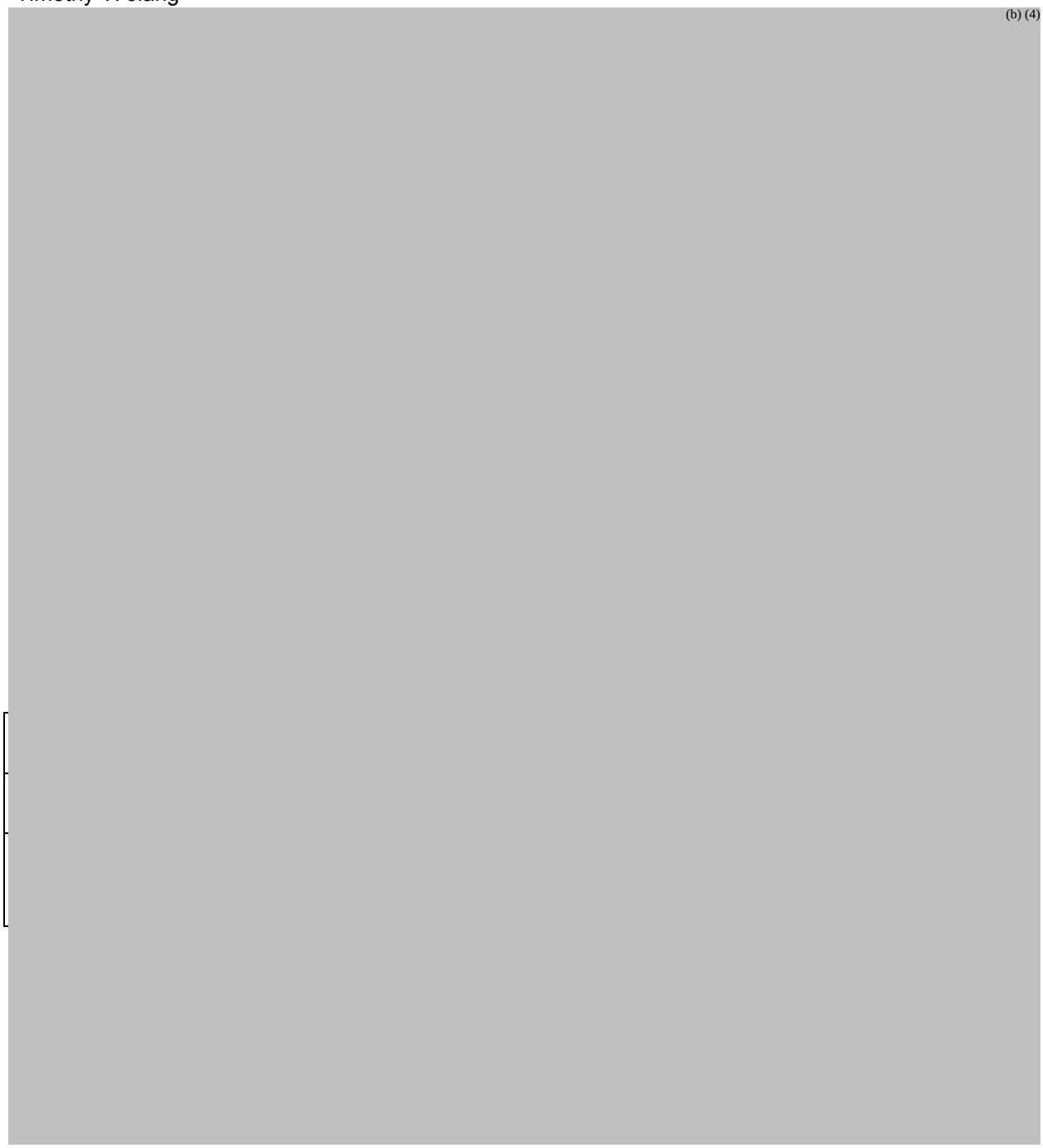
(b) (4)



11. Other Relevant Regulatory Issues

There are no outstanding regulatory issues. The regulatory requirements to support this 505(b)(2) application have been adequately addressed.

The Controlled Substance Staff is in agreement that morphine sulfate should remain subject to the controls imposed by Schedule II of the Controlled Substances Act, as proposed by the Applicant.

12. Labeling

The label was submitted in PLR format and is under review at this time. No proprietary name was proposed for this product.

(b) (4)

13. Recommendations/Risk Benefit Assessment

- Regulatory Action: Complete Response

  Although Morphine Sulfate solution for injection via the IV route of administration is approvable based on review of the submitted information and reliance on the reference drug Duramorph, at this time the manufacturing issues at the (b) (4) manufacturing site preclude the approval. If these issues are resolved satisfactorily prior to the PDUFA date for this application, an Approval action may be taken.

  Approval for the following specific strengths of morphine sulfate at the specified containers only in the IV route of administration *if manufacturing issue resolves*:
  - 2 mg/ml, 4 mg/ml, 8 mg/ml, 10 mg/ml, 15 mg/ml packaged in Carpuject™ with Luer Lock or iSecure™ Prefilled syringe

    (b) (4)

- Risk Benefit Assessment: There is adequate evidence for efficacy and safety of morphine sulfate IV use in adults, based on reliance on the reference drug Duramorph. The overall benefit associated with morphine sulfate IV for treatment of management of pain not responsive to non-narcotic analgesics appears to outweigh the associated risks.

- Recommendation for Postmarketing Risk Management Activities: A medication guide is not required since this product is used primarily in hospitals or institutional settings.

- Recommendation for other Postmarketing Study Commitments: None at this time.

14. Appendix and References

Tables 1 to 4 in next six pages:

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/s/

TIMOTHY T JIANG
10/06/2011

ELLEN W FIELDS
10/06/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-515 **Applicant:** Hospira **Stamp Date:** 1/14/2011

Drug Name: Morphine sulfate inj **NDA/BLA Type:**B2

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			Literature only No clinical studies
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Duramorph MS Injection
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			x	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Literature only
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Since approved versions of morphine sulfate exist for both IV (b) (4) injection and for the same proposed indication of this product, this NDA does not trigger PREA.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	Morphine is already scheduled under the CSA
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			No clinical study
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The following has been communicated to the Sponsor on March 7, 2011:

We acknowledge your submission of a pediatric waiver request and literature review in NDA 202515 for morphine sulfate injection. Since approved versions of morphine sulfate exist for both IV (b) (4) injection and for the same proposed indication of your product, NDA 202515 does not trigger PREA, and therefore no pediatric studies are required for this NDA.

However, if you wish to obtain pediatric labeling for your product, you must submit evidence of safety and efficacy in the proposed pediatric age groups for the proposed indication and routes of administration. This evidence may be based on studies conducted by you, studies you have reference to, or literature references. (b) (4)

Timothy Jiang 3/14/2011

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

TIMOTHY T JIANG
03/14/2011

ELLEN W FIELDS
03/14/2011