

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-321**

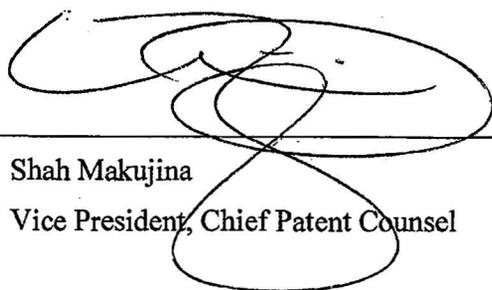
**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

1.3. Administrative Information

**PATENT CERTIFICATION**

As part of the present Application for EMBEDA™ (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsules, Applicant, Alpharma Pharmaceuticals LLC, makes reference to data contained in NDA 18-932 filed by Duramed for naltrexone hydrochloride oral tablets 50 mg strength. These tablets are sold under the proprietary name ReVia®. As the present Application references data associated with NDA 18-932, pursuant to 21 U.S.C. § 355(b)(2), Applicant hereby certifies that there are no known unexpired patents associated with that NDA. Specifically, the electronic version of the publication *Approved Drug Products With Therapeutic Equivalence Evaluations*, promulgated by the Center for Drug Evaluation & Research of the U.S. Food and Drug Administration ("the Orange Book"), current through the end of February 2008, stated, "[T]here are no unexpired patents for this product in the Orange Book Database." Accordingly, Applicant hereby certifies pursuant to 21 U.S.C. § 355(b)(2)(A)(ii) that to the extent that any patents had been listed in connection with NDA 18-932, such patents have expired. Since certification is made pursuant to 21 U.S.C. § 355(b)(2)(A)(ii), no notice need be provided to each owner of a patent or holder of an approved application.

Furthermore, pursuant to §314.52(a),(c) and §314.54(a)(1)(vi), Applicant hereby makes a certification under §314.50(i)(3) and §314.50(i)(1)(i)(A)(4) "Paragraph IV Certification" certifying that U.S. 5,378,474 and U.S. 5,202,128 which are listed in the Orange Book under NDA 20-616 for KADIAN® (morphine sulfate extended-release) Capsules will not be infringed by the manufacture, use or sale of EMBEDA™ (morphine sulfate extended-release with sequestered naltrexone hydrochloride) Capsules because Applicant, Alpharma Pharmaceuticals LLC, is the owner of the entire right, title and interest for said patents. Furthermore, Applicant as owner of said patents represents and consents to an immediate effective date upon approval of the application.



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Shah Makujina  
Vice President, Chief Patent Counsel

4/1/2008

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Date

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

22-321

NAME OF APPLICANT / NDA HOLDER

Alpharma Pharmaceuticals, LLC

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

EMBEDA

ACTIVE INGREDIENT(S)

Morphine Sulfate

STRENGTH(S)

20 mg, 30 mg, 50 mg, 60 mg,  
80 mg and 100 mg

DOSAGE FORM

Capsules

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,202,128

b. Issue Date of Patent

April 13, 1993

c. Expiration Date of Patent

April 13, 2010

d. Name of Patent Owner  
Alpharma Pharmaceuticals, LLC

Address (of Patent Owner)  
One New England Avenue

City/State  
Piscataway, New Jersey

ZIP Code  
08854

FAX Number (if available)  
908-566-4139

Telephone Number  
908-566-4108

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Shah Makujina

Address (of agent or representative named in 1.e.)  
440 U.S. Highway 22 East

City/State  
Bridgewater, New Jersey

ZIP Code  
08807

FAX Number (if available)  
908-566-4139

Telephone Number  
908-566-4108

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. Drug Product (Composition/Formulation)**

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time	

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

*Samantha Hanley*  
(for Shah Makujina)

6/25/08

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
Shah Makujina

Address  
Alpharma, Inc.  
440 US Highway 22 East

City/State  
Bridgewater, NJ

ZIP Code  
08807

Telephone Number  
908 566 4108

FAX Number (if available)  
908-566-4139

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**  
*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

22-321

NAME OF APPLICANT / NDA HOLDER

Alpharma Pharmaceuticals, LLC

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

EMBEDA

ACTIVE INGREDIENT(S)

Morphine Sulfate

STRENGTH(S)

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80 mg and 100 mg

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Capsules

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**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,378,474

b. Issue Date of Patent

January 3, 1995

c. Expiration Date of Patent

March 23, 2010

d. Name of Patent Owner

Alpharma Pharmaceuticals, LLC

Address (of Patent Owner)

One New England Avenue

City/State

Piscataway, New Jersey

ZIP Code

08854

FAX Number (if available)

908-566-4139

Telephone Number

908-566-4108

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Shah Makujina

Address (of agent or representative named in 1.e.)

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City/State

Bridgewater, New Jersey

ZIP Code

08807

FAX Number (if available)

908-566-4139

Telephone Number

908-566-4108

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Samantha Hanley  
(for Shah Makujina)

6/25/08

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
Shah Makujina

Address  
Alpharma, Inc.  
440 US Highway 22 East

City/State  
Bridgewater, NJ

ZIP Code  
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Telephone Number  
908 566 4108

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Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.

Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

## EXCLUSIVITY SUMMARY

NDA # 22-321

SUPPL #

HFD # 170

Trade Name Embeda

Generic Name (morphine sulfate and naltrexone hydrochloride) Extended-Release Capsules

Applicant Name ALPharma Pharmaceuticals/King Pharmaceuticals

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(2)

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

3

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

YES  NO

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

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA# See attached list

NDA#

NDA#

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

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Study ALO-KNT-301: A multi-center, randomized, double-blind, placebo-controlled, 12-week, multiple-dose Phase 3 efficacy trial of Embeda utilizing a randomized withdrawal design, and carried out in adult patients with moderate to severe pain due to osteoarthritis of the hip or knee.

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Study ALO-KNT-301: A multi-center, randomized, double-blind, placebo-controlled, 12-week, multiple-dose Phase 3 efficacy trial of Embeda utilizing a randomized withdrawal design, and carried out in adult patients with moderate to severe pain due to osteoarthritis of the hip or knee

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

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

Investigation #1  
IND # 70853            YES             ! NO   
! Explain:

Investigation #2  
IND #                    YES             ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

---

---

Name of person completing form: Lisa Basham

Title: Senior Regulatory Project Manager

Date: 7/31/09

Name of Office/Division Director signing form: Bob A. Rappaport, MD

Title: Division Director, DAARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-321 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DAARP PDUFA Goal Date: \_\_\_\_\_ Stamp Date: 6/30/2008  
December 30, 2008

Proprietary Name: EMBEDA

Established/Generic Name: morphine sulfate and naltrexone

Dosage Form: Capsule

Applicant/Sponsor: King Pharma

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

---

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** The management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
---

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>0</u> yr. <u>0</u> mo.	<u>1</u> yr. <u>11</u> mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

# Not feasible:

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the*

pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>12</u> yr. <u>0</u> mo.	<u>17</u> yr. <u>0</u> mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>2</u> yr. <u>0</u> mo.	<u>12</u> yr. <u>0</u> mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): <u>Ages 12-17: February 2011; Ages 2-12 February 2012</u>							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: age-appropriate formulation needs to be developed for age 2-12 years

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.**

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

**Δ** Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition **AND** (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

**This page was completed by:**

{See appended electronic signature page}

\_\_\_\_\_  
**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 6/2008)**

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

-----  
Lisa Basham  
7/16/2009 03:43:10 PM



One New England Avenue  
Piscataway, NJ 08854  
United States

Telephone  
1-732-465-3684  
Facsimile  
1-732-465-0383

### cGMP STATEMENT

The following is to provide information concerning the credentials of AlphaPharma Pharmaceuticals located at One New England Avenue, Piscataway, New Jersey 08854.

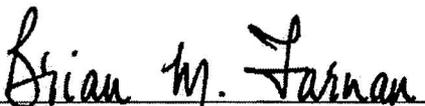
The methods, facilities and controls used at the aforementioned facility are in conformity with current Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP), i.e., in accordance with 21 CFR Part 58 and Part 210 and 211.

AlphaPharma Pharmaceuticals LLC  
One New England Avenue  
Piscataway, New Jersey 08854

### DEBARMENT CERTIFICATION

Pursuant to Chapter III, Section 306(k), of the Federal Food, Drug and Cosmetic Act, AlphaPharma Pharmaceuticals LLC hereby certifies that it did not and will not use in any capacity the services of any person who is debarred under subsection (a) or (b).

AlphaPharma Pharmaceuticals LLC further certifies that it has not sustained a conviction as described in subsections (a) and (b) of Chapter III, Section 306(k), of the Federal Food, Drug and Cosmetic Act. In addition, to the best of our knowledge, no affiliated persons have been convicted of an offense described in subsections (a) and (b) of Chapter III, Section 306(k), of the Federal Food, Drug and Cosmetic Act.

  
\_\_\_\_\_  
Brian M. Farnan  
Senior Manager, Compliance & QA  
AlphaPharma Pharmaceuticals LLC

Mar. 26<sup>th</sup>, 2008.

## Attachment B: Sample PMR/PMC Development Template

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

---

PMR/PMC Description: Efficacy, safety and pharmacokinetic (single and multiple dose) study (ies) of Embeda in pediatric patients with moderate to severe pain when the use of an around the clock analgesic is needed for an extended period of time in patients 2-12 years old.

---

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>11/01/2010</u>
	Study/Clinical trial Completion Date:	<u>11/2011</u>
	Final Report Submission Date:	<u>02/2012</u>
	Other:	_____

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

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

Studies were ready for approval in adults  
Studies in pediatric patients 2-12 years must be completed first for reasons of safety in the younger age group.

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

To obtain pharmacokinetic, efficacy and safety data in pediatric patients ages 2-12 years to inform dosing in this age group.

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

- **Which regulation?**

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

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

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

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

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

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

Pediatric patients ages 2-12 years.
-------------------------------------

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

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

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

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

---

**PMR/PMC Development Coordinator:**

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

---

(signature line for BLAs)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22321	ORIG 1		EMBEDA

---

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

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/s/

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LISA E BASHAM  
08/12/2009

LARISSA LAPTEVA  
08/13/2009

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-321 BLA#	NDA Supplement #-S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: EMBEDA Established/Proper Name: morphine sulfate and naltrexone extended release capsules Dosage Form: extended-release capsules Strengths: 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2.0 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4.0 mg		
Applicant: Alpharma Agent for Applicant (if applicable):		
Date of Application: June 30, 2008 Date of Receipt: June 30, 2008 Date clock started after UN:		
PDUFA Goal Date: December 30, 2008		Action Goal Date (if different):
Filing Date: August 28, 2008		
Date of Filing Meeting: August 12, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed Indication(s): management of moderate to severe chronic pain		
Type of Original NDA: AND (if applicable)		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification:		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal?	<input checked="" type="checkbox"/>	
Resubmission after refuse to file?	<input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <ul style="list-style-type: none"> <li><input type="checkbox"/> FDAAA [505(o)]</li> <li><input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]</li> <li><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)</li> <li><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)</li> </ul>	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 70,853	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a></i>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	

<b>Exclusivity</b>	
<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p><b>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b></p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made</p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
---	--

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b></p> <p>If yes, please list below:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
--	--

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

*If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.*

**Format and Content**

<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
--	---

<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>	
--	--

<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
---	--

<p><b>If electronic submission, does it follow the eCTD guidance?</b>  (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not, explain (e.g., waiver granted):</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
--	--

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b> Schedule II Drug</p>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b> 5,202,128;5,378,474</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input checked="" type="checkbox"/> Not Applicable ( <i>electronic submission or no CMC technical section</i> ) <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Pediatrics</b>	
<p><b>PREA</b></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <p>• <i>If no, request in 74-day letter.</i></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Prescription Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input type="checkbox"/> <b>Not applicable</b> <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Package insert (PI) submitted in PLR format?</p> <p><b>If no</b>, was a waiver or deferral requested before the application was received or in the submission?  <b>If before</b>, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b> submitted post 6/30/08 submission</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>REMS consulted to OSE/DRISK?</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES

<b>Comments:</b> to be complete post filing	<input checked="" type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<b>OTC Labeling</b>	
Check all types of labeling submitted.	<input type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<b>Comments:</b>	
Is electronic content of labeling submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<b>Meeting Minutes/SPA Agreements</b>	
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>	<input checked="" type="checkbox"/> YES Date(s): October 2, 2007 <input type="checkbox"/> NO
<b>Comments:</b>	
Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i>	<input type="checkbox"/> YES Date(s):

**Comments:**

NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** November 26, 2008

**NDA/BLA #:** 22-321

**PROPRIETARY/ESTABLISHED NAMES:** EMBEDA

**APPLICANT:** AlPharma

**BACKGROUND:** Developed under IND 70,853. Pre-NDA meeting cancelled, responses sent October 10, 2007. EMBEDA was previously referred to as KADIAN NT and ALO-01. EMBEDA™ is a capsule comprised of individual pellets containing morphine sulfate with a sequestered naltrexone hydrochloride inner core. Withdrawn April 23, 2007 and resubmitted under same NDA number on June 30, 3008.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christopher Hilfiger	Y
	CPMS/TL:	Parinda Jani/Lisa Basham	N/Y
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	Jin Chen	Y
	TL:	Ellen Fields	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OSE	Reviewer:	James Tolliver	Y
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	Katherine Meaker	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	Y
	TL:	Dan Mellon	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Elsbeth Chikale	Y
	TL:	Danae Christodoulou	Y
Facility (for BLAs/BLA supplements)	Reviewer:		
	TL:		
Microbiology, sterility (for NDAs/NDA efficacy supplements)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

**OTHER ATTENDEES:**

505(b)(2) filing issues?  If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>Electronic Submission comments</b>  <b>List comments:</b>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <b>Comments:</b>  <i>If no, for an original NME or BLA application, include the reason. For example:</i> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: 11/14/08 <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> Add sub group analysis</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> Label needs updating</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Biowaiver request</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul> <p><b>If yes</b>, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<b>FACILITY (BLAs only)</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Bob A. Rappaport

**GRMP Timeline Milestones:** Mid-Cycle Meeting 9/19/08, Team Meeting 10/23/08, Wrap-Up Meeting 12/11/08, AC Meeting 11/14/08

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review

**ACTIONS ITEMS**

<input type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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this page is the manifestation of the electronic signature.**  
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/s/

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Lisa Basham  
7/15/2009 05:01:00 PM  
CSO

Parinda Jani  
7/15/2009 05:19:15 PM  
CSO

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-321	NDA Supplement #-	Efficacy Supplement Type SE-
Proprietary Name: EMBEDA Established/Proper Name: Morphine Sulfate and Naltrexone Dosage Form: casule Strengths: 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2.0 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4.0 mg		
Applicant: Alpharma		
Date of Receipt: June 30, 2008		
PDUFA Goal Date: December 31, 2008		Action Goal Date (if different):
Proposed Indication(s): management of moderate to severe chronic pain		

**GENERAL INFORMATION**

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES  NO

*If "YES," proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES  NO

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

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

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

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Kadian	Previous finding of safety and efficacy
ReVia	Previous finding of safety and efficacy

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)  
Bio-Availability Studies

**RELIANCE ON PUBLISHED LITERATURE**

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?
- YES  NO

*If “NO,” proceed to question #6.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?
- YES  NO

*If “NO,” proceed to question #6  
If “YES”, list the listed drug(s) identified by name and answer question #5(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
- YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.*

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
- YES  NO

*If "NO," proceed to question #11.*

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

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Kadian	20,616	y
ReVia	18,932	y

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

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
- YES  NO

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

9. Were any of the listed drug(s) relied upon for this application:

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

YES  NO

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

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

- b. Approved by the DESI process?

YES  NO

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

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

- c. Described in a monograph?

YES  NO

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

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d.1.

If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

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

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

This application propose a new combination of previously approved drugs

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

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

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

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

YES  NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

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

If "YES" and there are no additional pharmaceutical equivalents listed, proceed to question #13.

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

Pharmaceutical equivalent(s):

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

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

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

YES  NO

If "NO", proceed to question #13.

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

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

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):



PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s): 3,332,950; 5,202,128; 5,378,474

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES  NO

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

Listed drug/Patent number(s):

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

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- Patent number(s): 3332950
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
- Patent number(s):

*If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?*

YES  NO

*Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.*

YES  NO

Date Received:

*Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.*

YES  NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

*If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?*

YES  NO

*Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.*

YES  NO

Date Received:

*Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.*

YES  NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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/s/

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Christopher M Hilfiger  
7/14/2009 03:03:19 PM  
CSO



NDA 22-321

**NDA ACKNOWLEDGMENT**

Alpharma Pharmaceuticals, LLC  
One New England Avenue  
Piscataway, NJ 08854

Attention: Isabelle Lefebvre, BSc, RAC US & EU  
Director, Regulatory Affairs

Dear Ms. Lefebvre:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: EMBEDA (Morphine Sulfate ER w/ naltrexone HCl) extended-release capsules, 20mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

Date of Application: June 30, 2008

Date of Receipt: June 30, 2008

Our Reference Number: NDA 22-321

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 29, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-4131.

Sincerely,

*{See appended electronic signature page}*

Christopher Hilfiger  
Regulatory Project Manager  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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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.**  
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/s/

-----  
Christopher M Hilfiger  
7/15/2008 08:03:27 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-321

*ACKNOWLEDGE WD*

Alpharma Pharmaceuticals, LLC  
One New England Avenue  
Piscataway, NJ 08854

Attention: Isabelle Lefebvre, BSc, RAC US & EU  
Director, Regulatory Affairs

Dear Ms. Lefebvre:

We have received your April 21, 2008, correspondence on April 22, 2008, notifying us that you are withdrawing your new drug application (NDA) for EMBEDA (Morphine Sulfate ER w/ naltrexone HCl) capsules, 20mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, prior to its filing date.

In accordance with 21 CFR 314.65, this application is withdrawn as of April 22, 2008. If you have paid a user fee, we will refund 75% of your payment.

If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission. However, because we retain only the archival copy of a withdrawn application in our files, you should resubmit appropriate review copies of all information. Retain the above NDA number for the resubmitted application but obtain a new user fee identification number. The new user fee identification number must be on the check as well as on the User Fee Cover Sheet in the resubmitted application. Submit the check for the appropriate user fee to the following address:

Food and Drug Administration  
P.O. Box 360909  
Pittsburgh, PA 15251-6909

For courier delivery, write the NDA number, the FDA Post Office box number (P.O. Box 360909), and the user fee identification number on the check and deliver it to the following address:

Food and drug Administration (360909)  
Mellon Client Service Center, Room 670  
500 Ross Street  
Pittsburgh, PA 15262-0001

In addition, the resubmitted application should address the following deficiencies identified before receipt of your withdrawal request:

1. You have not submitted the agreed upon safety database. As documented in the pre-NDA meeting on March 16, 2005, the safety database was to include 50 patients for one year as noted from the following excerpt taken from the meeting minutes

Since both morphine sulfate and naltrexone are approved products, the safety database can consist of:

- A total population of 500
  - 100 exposed for at least 6 months
  - 50 exposed for at least 1 year

As noted in the following table, you have submitted the NDA with only 5 patients dosed longer than 9 months. We note your proposal to submit the remainder with the 120-day safety update. However, an application should be complete at the time of submission including the long-term safety data.

#### 2.7.4 Summary of Clinical Safety

Alpharma Pharmaceuticals LI

**Table 7: Summary of ALO - 01 Dose and Exposure - All Studies (Safety Population)**

Dose Duration (days)	Total Drug Received (mg)											
	0-500	501-1000	1001-2000	2001-3000	3001-4000	4001-5000	5001-10000	10001-15000	15001-20000	20001-30000	30001-50000	50001-100000
0-1	69	1	0	0	0	0	0	0	0	0	0	0
2-5	198	0	0	0	0	0	0	0	0	0	0	0
6-10	67	6	2	2	0	0	0	0	0	0	0	0
11-20	25	38	52	13	4	4	0	1	0	0	0	0
21-30	9	21	28	5	2	1	3	0	0	0	0	0
31-90	1	12	45	49	32	16	28	6	3	0	0	0
91-180	2	0	1	1	59	19	181	91	45	19	10	3
181-370	0	0	0	0	0	1	6	5	3	1	1	0
371-360	0	0	0	0	0	0	1	3	1	0	0	0
<b>TOTAL</b>	<b>371</b>	<b>98</b>	<b>128</b>	<b>70</b>	<b>97</b>	<b>41</b>	<b>219</b>	<b>106</b>	<b>52</b>	<b>20</b>	<b>11</b>	<b>3</b>

2. You have not submitted an integrated safety database. In the letter dated October 1, 2007, in which the Division provided responses to the questions from your meeting package for the meeting scheduled for October 2, 2007, it is stated:

Additional Comments

The division requests the following for the submitted datasets:

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The safety datasets you have provided have not integrated the data from the Phase 2 and Phase 3 trials.

3. You have not conducted subgroup analyses of efficacy based on age, race or gender as required by 21CFR 314.50(d)(5)(v), "The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dosing interval needed for specific subgroups."

As noted in your submission in the study report for Study ALO-KNT-301:

**11.4.2.8. Examination of Subgroups**

No subgroup analyses were performed.

4. You have not conducted subgroup analyses of safety based on age, race or gender as required by 21CFR 314.50(d)(5)(vi(a)), "The safety data shall be presented by gender, age, and racial subgroups."

We note that you have stated:

"Analyses of intrinsic factors were not performed. The controlled clinical studies could not be pooled and the studies individually had insufficient power to detect clinically meaningful differences. Further, subgroup analyses of adverse events in the controlled Phase 2/3 clinical studies would be limited, as subjects who were unable to tolerate study drug in the Titration Phase were to be dropped from the study. The ongoing long-term Study ALO-KNT-302 had no control group to provide an estimate of intrinsic differences among subpopulations."

We note that you did not power the study for subgroup analyses. However, subgroup analyses do not need to be powered for inferential statistics.

Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Bob Rappaport, MD, Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Central Document Room

5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Christopher Hilfiger, Regulatory Project Manager, at 301-796-4131.

Sincerely,

*{See appended electronic signature page}*

Bob Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Bob Rappaport  
5/13/2008 11:48:19 AM



NDA 22-321

**NDA ACKNOWLEDGMENT**

Alpharma Pharmaceuticals, LLC  
One New England Avenue  
Piscataway, NJ

Attention: Isabelle Lefebvre, BSc, RAC US & EU  
Director, Regulatory Affairs

Dear Ms. Lefebvre:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: EMBEDA (morphine sulfate extended release with sequestered naltrexone HCl) tablets; 20 mg, 30 mg, 50 mg, 60 mg, 80 mg and 100 mg

Date of Application: February 28, 2008

Date of Receipt: February 28, 2008

Our Reference Number: NDA 22-321

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 28, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-4131.

Sincerely,

*{See appended electronic signature page}*

Christopher Hilfiger  
Regulatory Project Manager  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/

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Christopher M Hilfiger  
3/14/2008 02:40:31 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 70,853

ALPHARMA Pharmaceuticals  
One New England Ave.  
Piscataway, NJ 08854

Attention: Carolyn Zimmer  
Senior Manager, Regulatory Affairs

Dear Ms. Zimmer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALO-01 (morphine sulfate and naltrexone hydrochloride extended-release) Capsules.

Attached are the Division's responses to the questions from your meeting package for our upcoming meeting, scheduled for October 2, 2007, to discuss your NDA for ALO-01. Your questions are in italics and the Division's responses are in bold.

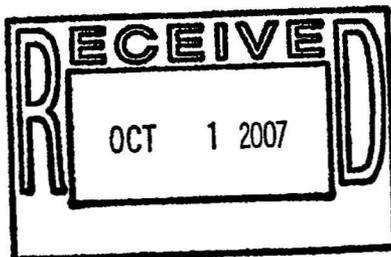
The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, please call me at 301-796-1175.

Sincerely,

*{See appended electronic signature page}*



Lisa Basham, MS  
Regulatory Project Manager  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

### SPONSOR MEETING AGENDA

**MEETING DATE/TIME:** October 2, 2007/3-4 PM

**LOCATION:** 10903 New Hampshire Ave., Bldg 22, Room 1313, Silver Spring, MD, 20993

**APPLICATION:** IND 70,853

**STATUS OF APPLICATION:** Active

**PRODUCT:** ALO-01 (morphine sulfate and naltrexone HCL extended-release) Capsules

**INDICATION:** moderate to severe chronic pain

**SPONSOR:** ALPHARMA Pharmaceuticals

**TYPE OF MEETING:** Pre-NDA

**MEETING CHAIR:** Sharon Hertz, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

**MEETING RECORDER:** Lisa Basham, Regulatory Project Manager

FDA Attendees	Title
Curtis Rosebraugh, MD	Deputy Direct, ODE II
Bob Rappaport, MD	Division Director
Sharon Hertz, MD	Deputy Division Director
Suresh Doddapaneni, PhD	Team Leader, Clinical Pharmacology
Dionne Price, PhD	Statistics Team Leader
Danae Christdoulou, PhD	CMC Pharmaceutical Assessment Lead
Ellen Fields, MD	Clinical Reviewer
David Lee, PhD	Clinical Pharmacology Reviewer
Katherine Meaker, PhD	Statistics Reviewer
Alan Schroeder, PhD	CMC Reviewer
Janice Weiner, JD, MPH	Regulatory Counsel, ORP
Silvia Calderon, PhD	Team Leader, Controlled Substance Staff (CSS)
Katherine Bonson, PhD	Pharmacologist, CSS
Lisa Basham, MS	Regulatory Project Manager
(Sponsor) Attendees	Title
Ron Warner, PhD	President and CEO
Joseph Stauffer, DO	Chief Medical Officer, VP, Clinical Research & Medical Affairs
Bill Vincek	Senior Vice President, R&D – Regulatory Affairs
James Jones, MD, PharmD, FACEP	VP, Clinical Development
Franklin Johnson	Director, Clinical Pharmacology
George Wagner	Director, Regulatory Affairs
Joann Stevoli	Sr, Manager, Regulatory Affairs
Carolyn Zimmer	Sr. Manager, Reg. Affairs
Jaffrey Isaacson	Statistical Consultant
Matthew Giles	Associate Director, Analytical Development

**Meeting Questions/Responses**

**CMC**

*Question 1. Does the Division agree that no additional toxicology testing is necessary for this degradants at the expected shelf life concentration of (b) (4)?*

**FDA Response:**

1. Significantly more than 9 months of data will be needed to support an expiration dating period of (b) (4) months.
2. The ICH Q3B (R2) thresholds are based on the maximum dose of the drug substance administered per day. The development of tolerance to opioids precludes the determination of a maximum daily dose (MDD). The MDD for this drug product will be determined by the maximum feasible daily intake (MFDI) of morphine in an opioid-tolerant patient population. Please determine and provide justification for the MFDI for morphine in an opioid-tolerant patient. You should provide a clear rationale for the MFDI proposed.
3. The regulatory limit for the impurity qualification will be based on the total amount of naltrexone in the drug product using the MFDI of morphine unless you can provide clear data-driven justification that only a portion of the total naltrexone is released from the drug product during labeled use AND that (b) (4) would be released at a similar rate or magnitude as naltrexone (*i.e.* it is not preferentially leached out). If this can be shown, then your impurity specifications can be based on the amount of naltrexone that is released when the product is used as labeled.
4. If safety qualification is necessary, you will need to submit the data to support your assertion that (b) (4) is not toxic.
5. Any impurity or degradation product that exceeds ICH thresholds will need to be adequately qualified. Adequate qualification should include:
  - a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
  - b. Repeat dose toxicology of appropriate duration to support the proposed indication, unless otherwise justified.

**ADDITIONAL CMC COMMENTS:**

**We note that there was no End of Phase 2 meeting for this IND and there is little CMC information in the August 31, 2007 pre-meeting package. We therefore provide the following comments pertaining to your NDA submission.**

- 1. We strongly recommend that you request a pre-NDA meeting with a focus on CMC issues for this drug product.**
- 2. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.**
- 3. It is expected that at least 12 months of real time data and 6 months of accelerated data be included in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiration dating period.**
- 4. At the beginning of the CMC section, include a table of all facilities, and state specifically what is the function of each facility, the contact name and address, the CFN number, and the complete name and address of the facility.**
- 5. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in the NDA cover letter.**
- 6. We strongly recommend that you submit all necessary data to support your proposed expiry in the initial NDA and do not rely on stability updates submitted during the review cycle. Under good review management practices, reviews must be completed according to a timeline. While every effort will be made to review stability updates submitted during the review cycle, whether they are reviewed will depend on the timing of the submission, the extent of submitted data, and the available resources. Thus, the expiration dating period may be commensurate with the stability data from the initial submission if updates cannot be accommodated during the review cycle.**
- 7. Provide the stability data summary for your NDA stability batches on a parameter-by-parameter basis (instead of on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.**
- 8. We recommend use of the ICH Q1 guidances for your stability protocol and your stability studies. Consult the ICH Q3 guidances pertaining to impurities in the drug substances and drug products, and the ICH Q6A guidance pertaining to drug substance and drug product specifications. Provide a drug product specification for brittleness at release and for shelf-life, or provide justification with data for the**

absence of this attribute.

9. We reiterate the CMC comments provided by the Agency at the pre-IND meeting on March 16, 2005, as recorded in the official minutes of that meeting.

Non-Clinical

*Question 1. <orphine sulfate and naltrexone hydrochloride are both approved products and extensive preclinical databases exist for them. For the preclinical section of the NDA, AlPharma will rely on the finding of safety based on the nonclinical section of the SBA and package inserts of KADIAN®, Avinza®, and Revia® and a review of the literature published since 2002. A detailed proposal citing our plan is provided in Attachment 2.*

*Will this information be sufficient for inclusion in a 505(b)(2) submission?*

**FDA Response:**

1. Your question suggests that you are proposing to reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries to support the safety and/or effectiveness of your proposed product. We note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug. In this regard, we also note that your comments in Attachment 2 of your pre-NDA meeting package appear to propose reliance on the "Agency's prior knowledge," which is vague and does not describe an acceptable regulatory approach.
2. A 505(b)(2) application would be an acceptable approach at this time based on the information provided. If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.
3. Based on the information in your pre-NDA meeting package, it appears that you are proposing to rely upon FDA's finding of safety and/or effectiveness for Kadian, Avinza, and Revia, and published literature to support your proposed 505(b)(2) application. Clarify the intent of your reference to ANDA 75-434 for naltrexone hydrochloride in section 1.3.2 of your meeting package.

4. **If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor chooses to rely.**
5. **The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).**
6. **Include copies of all referenced literature with the NDA submission.**

**ADDITIONAL NONCLINICAL COMMENTS:**

1. **For the NDA submission, any impurity or degradation product in the drug product must be reduced below the threshold for qualification as described in the ICH guidelines "Impurities in New Drug Substances" (ICH Q3A R2) and "Impurities in New Drug Products" (ICH Q3B R2) or adequate toxicologic qualification of these impurities will be required. Several of the current specifications of individual impurities in morphine sulfate and naltrexone hydrochloride stated in the NDA Nonclinical Plan (Attachment 2) exceed current ICH guidelines for qualification.**
2. **Morphine and naltrexone may contain impurities with an (b) (4) moiety, such as (b) (4) and (b) (4), respectively, which have a structural alert for mutagenicity. We acknowledge that in the Pre-IND meeting on March 16, 2005 we stated that the specification for the compounds containing (b) (4) was (b) (4). Be advised that current Agency thinking regarding acceptable levels for potentially genotoxic impurities requires a specification of NMT 1.5 mcg/day and is based on the maximal feasible daily exposure to morphine in an opioid-tolerant patient.**
3. **We recommend that you consult with your DMF holder to determine the levels of impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities.**

Clinical

*Question 1. We are providing in Attachment 3 unpopulated tables and listings shells for studies ALO-KNT-301 and ALO-KNT-302.*

*Are the proposed report presentations of these data acceptable for the NDA submission?*

**FDA Response:**

**The proposed report presentations appear appropriate. If during the course of the NDA review additional tables are needed, they will be requested.**

*Question 2. Does the Division agree with this proposal for data integration?*

**FDA Response:**

**We agree with the proposal; however safety data must also be presented for all Phase 1 studies.**

*Question 3. Does the Agency agree that this is adequate data to support once or twice-a-day dosing for ALO-001?*

**FDA Response:**

**With adequate evidence of bioequivalence to Kadian, similar labeling for once or twice-a-day dosing would be acceptable.**

**For the NDA submission, dose linearity information should be addressed. It is not clear in the submitted package if the dose linearity information was assessed.**

*Question 4. Does the Agency agree to granting a waiver from the requirement to conduct pediatric studies?*

**FDA Response:**

- **A deferral for pediatric studies may be granted.**
- **Justification for a waiver should be provided, keeping in mind that extended-release morphine may be useful in some pediatric patients.**

NDA Content and Format

*Question 1. eCTD questions.....*

**FDA Response:**

**We concur with your approach.**

*Question 2. AlPharma requests a waiver for providing an eCTD sample submission, as (b) (4) will be compiling the eCTD. (b) (4) filed an acceptable eCTD pilot with the Center on June 2, 2004 (pilot no. 900024). Does the Agency concur? Does the Agency have any specific comments on the proposed eCTD format and content?*

**FDA Response:**

**We concur.**

Fast Track/Priority Review

*Question 1. We wish to discuss with the Agency the designation of this program as a Fast Track/Priority Review. A justification for the Fast Track/Priority Review designations for ALO-01 NDA is provided in Attachment 6. Does the Agency agree that this program using ALO-01 dosage form may be approved for Fast Track/Priority Review?*

**FDA Response:**

**The submission appears to qualify for Priority Review status; however the final determination for Priority Review will occur at the time of NDA submission. *Fast Track* review is not applicable at this stage in the review process.**

Additional Comments

**The division requests the following for the submitted datasets:**

- 1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.**
- 2. The integrated safety dataset that should include the following fields/variables:**
  - a. A unique patient identifier**
  - b. Study/protocol number**
  - c. Patient's treatment assignment**

- d. **Demographic characteristics, including gender, chronological age (not date of birth), and race**
  - e. **Dosing at time of adverse event**
  - f. **Dosing prior to event (if different)**
  - g. **Duration of event (or start and stop dates)**
  - h. **Days on study drug at time of event**
  - i. **Outcome of event (e.g. ongoing, resolved, led to discontinuation)**
  - j. **Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).**
  - k. **Marker for serious adverse events**
  - l. **Verbatim term**
3. **The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form.**
4. **Please see the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.**
5. **In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.**
6. **The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.**
7. **Please provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.**
8. **Please perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, please provide any additional SMQ that may be useful based on your assessment of the**

**safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**

- 9. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**
- 10. Also, for the concomitant medication dataset, you should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**
- 11. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format.**
- 12. Please perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**
- 13. In every dataset, all dates should be formatted as ISO date format.**
- 14. Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.**
- 15. All datasets should contain the following variables/fields (in the same format and coding):**
  - a. Each subject should have one unique ID across the entire NDA**
  - b. Study number**
  - c. Treatment assignment**
  - d. Demographic characteristics (age, race, gender, etc.)**
- 16. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.**

- 17. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.**
- 18. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.**
- 19. If you and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).**
- 20. Please note that the HLG T and HLT level terms in this table are from the primary MedDRA mapping only. There is no need to provide HLT or HLG T terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HGLT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 2 (SOC3)
01-701-1015	1	701	1015	MedDRA Version 8.0	Redness around application site	10003058	Application Site redness	Application Site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders	

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/s/

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Lisa Basham  
10/1/2007 10:15:57 AM  
CSO