CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-195 & 22-207

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Boehringer Ingelheim
Roxane Laboratories

Ms. Kathleen D. Culver
Pre-Approval Manager
FDA District Office
6751 Steger Drive
Cincinnati, Ohio 45237-3097

December 20, 2007

Elizabeth Ernst
Director
Drug Regulatory Affairs and Medical Affairs

Telephone: 614.272.4785
Telefax: 614.276.2470
E-Mail: eernst@

col.boehringeringelheim.com

NDA 22-207
Morphine Sulfate Tablets, 15 mg and 30 mg

PATENT AMENDMENT

Dear Ms. Culver:

Enclosed is the Certified True Copy of the Patent Amendment to the NDA for Morphine Sulfate Tablets, 15 mg and 30 mg.

The archival and review copies have been submitted to Lisa Basham, MS, Regulatory Project Manager, CDER, FDA, Division of Anesthesia, Analgesia, and Rheumatology Products, 5901-B Ammendale Road, Beltsville, Maryland 20705.

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Yongtain Ni, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst,
Director
Drug Regulatory Affairs and Medical Affairs

Certification of Submission to the District Office

Roxane Laboratories, Inc. hereby certifies that a third (field) copy of the Patent Amendment to NDA 22-207, Morphine Sulfate Tablets, 15 mg and 30 mg has been submitted to the Cincinnati, Ohio District Office in accordance with 21 CFR 314.94(d)(5) and that the field copy is a "true copy" of the technical sections contained in the archival and review copies of the original amendment.

Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

12/20/04
Date

Appears This Way
On Original

A. Certification of Compliance with Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, Roxane Laboratories, Inc. hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there have been no convictions of the applicant and affiliated persons at Roxane Laboratories, Inc. responsible for the development or submission of the application in the last five years.

Elizabeth Ernst
Associate Director, DRA-Multisource Products
Roxane Laboratories, Inc.

5/8/07
Date

In compliance with the Generic Drug Enforcement Act of 1992, Boehringer Ingelheim Roxane, Inc. (BIRI) hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there have been no convictions of the applicant and affiliated persons at BIRI responsible for the development or submission of the application in the last five years.

Robert C. Fromuth
Robert C. Fromuth
President and COO
Boehringer Ingelheim Roxane Laboratories, Inc.

EAE

4/10/07
Date

B. U.S. Agent Letter of Authorization

Not applicable.

Boehringer Ingelheim
Roxane Laboratories

Ms. Kathleen D. Culver
Pre-Approval Manager
FDA District Office
6751 Steger Drive
Cincinnati, Ohio 45237-3097

December 20, 2007

Elizabeth Ernst
Director
Drug Regulatory Affairs and Medical Affairs

Telephone: 614.272.4785
Telefax: 614.276.2470
E-Mail: eernst@

col.boehringeringelheim.com

NDA 22-195
Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL

PATENT AMENDMENT

Dear Ms. Culver:

Enclosed is the Certified True Copy of the Patent Amendment to the NDA for Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL.

The archival and review copies have been submitted to Lisa Basham, MS, Regulatory Project Manager, CDER, FDA, Division of Anesthesia, Analgesia, and Rheumatology Products, 5901-B Ammendale Road, Beltsville, Maryland 20705.

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Sarah Smith, Regulatory Affairs Associate, at (614) 241-4122.

Respectfully,

Elizabeth Ernst,
Director
Drug Regulatory Affairs and Medical Affairs

Appears This Way
On Original

Certification of Submission to the District Office

Roxane Laboratories, Inc. hereby certifies that a third (field) copy of the Patent Amendment to NDA 22-195, Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL, has been submitted to the Cincinnati, Ohio District Office in accordance with 21 CFR 314.94(d)(5) and that the field copy is a "true copy" of the technical sections contained in the archival and review copies of the original amendment.

Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

12/20/07
Date

Appears This Way
On Original

Boehringer Ingelheim
Roxane Laboratories

Lisa Basham, MS
Regulatory Project Manager
Food and Drug Administration
Division of Anesthesia, Analgesia, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

December 20, 2007

Elizabeth Ernst
Director
Drug Regulatory Affairs and
Medical Affairs

Telephone: 614.272.4785
Telefax: 614.276.2470
E-Mail: eernst@
col.boehringer-ingelheim.com

Attention: Lisa Basham

NDA 22-195
Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL

PATENT AMENDMENT

Dear Ms. Basham:

We wish to amend NDA 22-195. In accordance with 21 CFR 314.95(b), this certifies that a notice of certification of non-infringement of a patent has been sent to Elan Corporation, plc and King Pharmacueticals, Inc., owners of U.S. Patent No. 6,066,339 on October 31, 2007, (see attached copy). A separate copy of the notice was also sent to Elan's and King's General Counsels.

The notice met the content requirements in accordance with 21CFR 314.95(c). Copies of the signed return receipt of the notice letters to the President and Chief Executive Officers and the General Counsels of both Elan and King are provided in accordance with 21 CFR 314.05(e). The Paragraph IV Certification was filed in the NDA submitted to CDER on May 16, 2007. Roxane received the NDA acknowledgment of receipt dated May 29, 2007 for the filing.

In accordance with 21 CFR 312.95(f), this certifies that no legal action was taken by either Elan or King 45-days after receipt of the notice.

We have also submitted a copy of this amendment to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Sarah Smith, Regulatory Affairs Associate, at (614) 241-4122.

Respectfully,

Elizabeth Ernst
Director
Drug Regulatory Affairs and Medical Affairs

Boehringer Ingelheim
Roxane Laboratories

Lisa Basham, MS
Regulatory Project Manager
Food and Drug Administration
Division of Anesthesia, Analgesia, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

December 20, 2007

Elizabeth Ernst
Director
Drug Regulatory Affairs and Medical Affairs

Telephone: 614.272.4785
Telefax: 614.276.2470
E-Mail: eernst@col.boehringer-ingelheim.com

Attention: Lisa Basham

NDA 22-207
Morphine Sulfate Tablets, 15 mg and 30 mg

PATENT AMENDMENT

Dear Ms. Basham:

We wish to amend NDA 22-207. In accordance with 21 CFR 314.95(b), this certifies that a notice of certification of non-infringement of a patent has been sent to Elan Corporation, plc and King Pharmacueticals, Inc., owners of U.S. Patent No. 6,066,339 on October 31, 2007, (see attached copy). A separate copy of the notice was also sent to Elan's and King's General Counsels.

The notice met the content requirements in accordance with 21CFR 314.95(c). Copies of the signed return receipt of the notice letters to the President and Chief Executive Officers and the General Counsels of both Elan and King are provided in accordance with 21 CFR 314.05(e). The Paragraph IV Certification was filed in the NDA submitted to CDER on June 7, 2007. Roxane received the NDA acknowledgment of receipt dated August 15, 2007 for the filing.

In accordance with 21 CFR 312.95(f), this certifies that no legal action was taken by either Elan or King 45-days after receipt of the notice.

We have also submitted a copy of this amendment to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Yongtian Ni, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Director
Drug Regulatory Affairs and Medical Affairs

ORIGINAL

Boehringer Ingelheim
Roxane Laboratories

Lisa Basham, MS
Regulatory Project Manager
Food and Drug Administration
Division of Anesthesia, Analgesia, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

November 2, 2007

NEW CORRESP
N-000-(C)

Attention: Lisa Basham

NDA 22-195
Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL

Elizabeth A. Ernst
Director,
Drug Regulatory Affairs and
Medical Affairs

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

AMENDMENT-Patent Certification

Dear Ms. Basham:

We wish to amend NDA 22-195 for Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL in response to your October 23, 2007 telephone request. Enclosed please find our updated Patent Certification. In accordance with 21 CFR 314.52 we have also provided notice to the owner of U.S Patent No. 6,066,339 and to the holder of the approved application for the listed drug product.

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Sarah Smith, Associate, Drug Regulatory Affairs, at (614) 241-4122.

Respectfully,

Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

Roxane Laboratories, Inc.
NDA – Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL
Module 1: Administrative Information and Prescribing Information

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Paragraph II Certification [21 CFR 314.50(i)(1)(i)(A)(2)]

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our 505(b)(2) application for Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL. Roxane Laboratories, Inc. hereby certifies that, in its opinion, and to the best of its knowledge, there are no unexpired patents as listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 27th Edition and supplements) for the drug Duramorph PF.

Paragraph IV Certification [21 CFR 314.50(i)(1)(i)(A)(4)]

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our 505(b)(2) application for Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL. Roxane Laboratories, Inc. certifies that in its opinion and to the best of its knowledge U.S. Patent No. 6,066,339 which expires on November 25, 2017 as listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 27th Edition and supplements) for the drug Avinza ® is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of Morphine Oral Solution, 10 mg/5 mL and 20 mg/5 mL for which this application is submitted. Roxane Laboratories, Inc. also certifies that it will comply with the notice requirements under 314.52(a) by providing a notice to the owner of the U.S. Patent listed above or its representative and to the holder of the approved application for the listed drug product, and with the requirements under 314.52(c) with respect to the content of the notice.

Prepared by: _____ 11/1/07
Elizabeth Ernst — Date
Director, Drug Regulatory and Medical Affairs - Multisource Products

Reviewed by: _____ 11/1/07
Julia Economou — Date
Director, Product Development Strategy

Approved by: _____ 11/1/07
for Randall S. Wilson — Date
Vice President, Scientific and Regulatory Affairs

ORIGINAL

Boehringer Ingelheim
Roxane Laboratories

N-022 (9)
NEW CORRESP

Lisa Basham, MS
Regulatory Project Manager
Food and Drug Administration
Division of Anesthesia, Analgesia, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

November 2, 2007

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Attention: Lisa Basham

NDA 22-207
Morphine Sulfate Tablets, 15 mg and 30 mg

AMENDMENT-Patent Certification

Dear Ms. Basham:

We wish to amend NDA 22-207 for Morphine Sulfate Tablets, 15 mg and 30 mg in response to your October 23, 2007 telephone request. Enclosed please find our updated Patent Certification. In accordance with 21 CFR 314.52 we have also provided notice to the owner of U.S Patent No. 6,066,339 and to the holder of the approved application for the listed drug product.

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Yongtian Ni, Associate, Drug Regulatory Affairs, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

Roxane Laboratories, Inc.
NDA – Morphine Sulfate Tablets, 15mg and 30mg.
Module 1: Administrative Information and Prescribing Information

---

Paragraph II Certification [21 CFR 314.50(i)(1)(i)(A)(2)]

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our 505(b)(2) application for Morphine Sulfate Tablets, 15mg and 30mg. Roxane Laboratories, Inc. hereby certifies that, in its opinion, and to the best of its knowledge, there are no unexpired patents as listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 27th Edition and supplements) for the drug Duramorph PF.

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In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our 505(b)(2) application for Morphine Sulfate Tablets, 15mg and 30mg. Roxane Laboratories, Inc. certifies that in its opinion and to the best of its knowledge U.S. Patent No. 6,066,339 which expires on November 25, 2017 as listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 27th Edition and supplements) for the drug Avinza ® is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of Morphine Sulfate Tablets, 15mg and 30mg for which this application is submitted. Roxane Laboratories, Inc. also certifies that it will comply with the notice requirements under 314.52(a) by providing a notice to the owner of the U.S. Patent listed above or its representative and to the holder of the approved application for the listed drug product, and with the requirements under 314.52(c) with respect to the content of the notice.

Prepared by: _____ 11/1/07
Elizabeth Ernst — Date
Director, Drug Regulatory and Medical Affairs - Multisource Products

Reviewed by: _____ 11/1/07
Julia Economou — Date
Director, Product Development Strategy

Approved by: _____ 11/1/07
for: Randall S. Wilson — Date
Vice President, Scientific and Regulatory Affairs

EXCLUSIVITY SUMMARY

NDA # 22-195 SUPPL # HFD # 170

Trade Name

Generic Name Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/ 5 mL

Applicant Name Roxane Laboratories

Approval Date, If Known March 17, 2008

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.

This marketed unapproved drug was evaluated in a comparative bioavailability study with Avinza (morphine sulfate extended-release) Capsules (NDA 21-260) and Duramorph (morphine sulfate) injection (NDA 18-565).

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?

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#

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:

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"):

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 # 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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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: Regulatory Project Manager
Date: March 7, 2009

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Deputy Division Director

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

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

/s/

Sharon Hertz
3/13/2008 09:14:42 PM

EXCLUSIVITY SUMMARY

NDA # 22-207 SUPPL # HFD # 170

Trade Name

Generic Name Morphine Sulfate Tablets, 15 mg & 30 mg

Applicant Name Roxane Laboratories

Approval Date, If Known March 17, 2008

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.

This marketed unapproved drug was evaluated in a comparative bioavailability study with Avinza (morphine sulfate extended-release) Capsules (NDA 21-260) and Duramorph (morphine sulfate) injection (NDA 18-565).

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?

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#

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:

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"):

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 #	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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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: Regulatory Project Manager
Date: March 7, 2009

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Deputy Division Director

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

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/s/

Sharon Hertz
3/13/2008 09:15:17 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-195 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: May 16, 2007 **PDUFA Goal Date:** March 17, 2008

HFD 170 **Trade and generic names/dosage form:** morphine sulfate oral solution, 10 mg/5 mL, 20 mg/5 mL

Applicant: Roxane Laboratories **Therapeutic Class:** chronic pain opioid

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

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

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** _____

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): 1

Indication #1: relief of moderate to severe acute and chronic pain

Is this an orphan indication?

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

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo.__0____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__17___ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Lisa Basham, MS
Regulatory Project Manager

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

(Revised: 10/10/2006)

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

Indication #2: _____

Is this an orphan indication?

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

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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.

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: 10/10/2006)

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/s/

Lisa Basham
3/14/2008 09:56:35 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-207 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: June 8, 2007 **PDUFA Goal Date:** April 8, 2008

HFD 170 **Trade and generic names/dosage form:** morphine sulfate Immediate-Release Tablets, 15 mg & 30 mg
Applicant: Roxane Laboratories **Therapeutic Class:** chronic pain opioid

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

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

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** _____

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): 1

Indication #1: relief of moderate to severe acute and chronic pain

Is this an orphan indication?

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

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- X **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo.__0__ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__17__ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Lisa Basham, MS
Regulatory Project Manager

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

(Revised: 10/10/2006)

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

Indication #2: _____

Is this an orphan indication?

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

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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.

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: 10/10/2006)

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/s/

Lisa Basham
3/14/2008 09:56:09 AM

A. Certification of Compliance with Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, Roxane Laboratories, Inc. hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there have been no convictions of the applicant and affiliated persons at Roxane Laboratories, Inc. responsible for the development or submission of the application in the last five years.

Elizabeth Ernst
Associate Director, DRA-Multisource Products
Roxane Laboratories, Inc.

6/4/07
Date

In compliance with the Generic Drug Enforcement Act of 1992, Boehringer Ingelheim Roxane, Inc. (BIRI) hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there have been no convictions of the applicant and affiliated persons at BIRI responsible for the development or submission of the application in the last five years.

Robert C. Fromuth EAE

Robert C. Fromuth
President and COO
Boehringer Ingelheim Roxane Laboratories, Inc.

5/24/07
Date

B. U.S. Agent Letter of Authorization

Not applicable.

Date: August 1, 2006

Generic Drug Enforcement Act Certification of Debarment and Conviction

and its wholly owned subsidiary,
hereby certify 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 any services performed for Roxane Laboratories, Inc. b(4)

and its wholly owned subsidiary,
further certify that it has not used any individuals convicted of any offense described under section 306(a) and 306(b) of the Act within the past 5 years. b(4)

b(4)

Basham, Lisa

From: Basham, Lisa
Sent: Monday, March 17, 2008 10:55 AM
To: 'elizabeth.ernst@boehringer-ingelheim.com'
Subject: Another Phase 4 commitment needed...

Liz, please provide your agreement to perform the following as a post-marketing commitment:

1. Conduct a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) tested up to the limit dose for the assay, for each of the following drug substance impurities that exceed ICHQ3A qualification thresholds of NMT 0.15%:

Your quick response would be most appreciated!

b(4)

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

Lisa Basham
3/25/2008 11:35:28 AM
CSO

Basham, Lisa

From:	elizabeth.ernst@boehringer-ingelheim.com
Sent:	Monday, March 17, 2008 3:42 PM
To:	Basham, Lisa
Cc:	elizabeth.ernst@boehringer-ingelheim.com; corina.posey@boehringer-ingelheim.com
Subject:	RLI commits to conduct the following tox studies post-approval and file them to the morphine NDA 22-207
Attachments:	emfinfo.txt

Hello Lisa,

RLI will commit to run a minimal genetic toxicology screen (two in vitro genetic toxicology studies) post-approval [redacted] b(4)

- One point mutation assay
- Chromosome aberration assay

A total of 6 studies will be conducted.

Thanks

Elizabeth Ernst
Director of Regulatory & Medical Affairs
Roxane Laboratories
614-272-4785 phone
614-276-2470 fax

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/s/

Lisa Basham
3/17/2008 03:47:35 PM
CSO

Basham, Lisa

From: Basham, Lisa
Sent: Wednesday, December 05, 2007 10:15 AM
To: 'eernst@col.boehringer-ingelheim.com'
Subject: Two requests for info (pertains to both NDAs)....

Hi, Liz,

Below, please see two requests from the clinical pharmacologist and pharm/tox reviewer, respectively.

1. Please provide *in vitro* and/or *in vivo* information, if available, on the intestinal permeability of morphine.

b(4)

2. According to the morphine drug substance contains the following impurities: reported that they are at a level of NMT which exceeds ICH Q3A safety qualification threshold. You should either reduce the specifications to NMT or provide adequate safety qualification as per ICH Q3A. Adequate qualification should include:

- Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- Repeat dose toxicology of appropriate duration to support the proposed indication.

If you are unable to reduce the specifications, you may justify the safety based on the above toxicology data or via reference to such data in the published literature.

Please keep in touch and let me know when we should expect your response to these requests. You may send your responses informally via email in addition to formally responding to both NDAs. The emailed response will allow me to expedite distribution. Also, please provide two copies of each submission.

Thanks!!

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

Lisa Basham
3/14/2008 10:28:30 AM
CSO

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, October 30, 2007 9:51 AM
To: 'eernst@col.boehringer-ingelheim.com'
Subject: 10-30-07 505(b)(2) guidance

Liz, The following is the guidance provided by our legal staff pertaining to 505(b)(2) applications and patent certification.

You are required to provide an appropriate patent certification or statement for each listed drug for which you are relying upon the Agency's finding of safety and/or effectiveness to support your 505(b)(2) application (see 21 CFR 314.54(a)(1)(vi)). Your amended patent certification or statement should specify each listed drug(s) (identified elsewhere in your application) upon which you are relying and, as applicable, provide the patent number for each listed patent for which you are providing a certification or statement. Your current paragraph II patent certifications are inadequate as they state that there are "no unexpired patents ... for Morphine Sulfate Tablets" (with respect to your pending NDA 22-207) and "there are no unexpired patents ... for Morphine Sulfate Oral Solution" (with respect to your pending NDA 22-195). However, you are relying upon the Agency's finding of safety and/or effectiveness for a morphine sulfate extended-release capsule (Avinza; NDA 21-260) and a morphine sulfate injection (Duramorph PF; NDA 18-565) to support your 505(b)(2) applications and these products are not encompassed within your current patent certifications.

As we previously advised, you need to provide an appropriate patent certification with respect to Avinza (NDA 21-260), for which there is an unexpired patent listed in the Orange Book, and comply with any applicable regulatory requirements related to your patent certification. In addition, your patent certifications reference the statutory and regulatory provisions for abbreviated new drug applications rather than 505(b)(2) applications. We refer you to section 505(b)(2)(A)-(B) of the Food, Drug, and Cosmetic Act and our regulations at 21 CFR 314.50(i) regarding patent certification.

Feel free to call me with any questions.

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

Lisa Basham
3/14/2008 10:26:39 AM
CSO

Basham, Lisa

From: Basham, Lisa
Sent: Tuesday, October 23, 2007 5:17 PM
To: 'eernst@col.boehringer-ingelheim.com'
Subject: 10-23-07 Clinical/biopharm request for NDA 22-195

Liz,

As discussed, following is an inquiry from the clinical/biopharm reviewers for pending NDA 22-195:

Approval is sought for two strengths of morphine sulfate oral solution 10 mg/5 mL and 20 mg/5 mL. The two strengths are not compositionally proportional in that they differ substantially in the percentage composition of sorbitol — and glycerin. In addition, the 20 mg/5 mL strength contains parabens —. In the pharmacokinetic studies MORP-T30-PLFS-1 and MORP-T30-PVFS-3 submitted to the NDA, the 10mg/5 mL strength was investigated and therefore its bioavailability has been determined. However, the NDA does not seem to contain any pharmacokinetic data obtained with the 20 mg/5 mL strength. As such, the bioavailability of the 20 mg/5 mL strength is unknown and the basis for its approval has not been addressed. In light of this, provide your rationale for support of the approval of the 20 mg/5 mL strength. b(4)

Please respond as soon as possible. Thank you!

Regards,

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

Lisa Basham
3/14/2008 10:22:09 AM
CSO

Basham, Lisa

From: elizabeth.ernst@boehringer-ingelheim.com
Sent: Friday, March 14, 2008 7:59 AM
To: Basham, Lisa
Cc: elizabeth.ernst@boehringer-ingelheim.com
Subject: FW: Comments and commitments for Morphine OS NDA 22-195 and morphine Tablets NDA 22-207
Attachments: emfinfo.txt

Hello Lisa,

As per your request, RLI will commit to amend both of our NDAs to include an updated validation technical report which will contain (accuracy, linearity, precision, and a LOQ) for in the first annual report. b(4)

If you need anything else from me please advise.

Thanks

Elizabeth Ernst
Director of Regulatory & Medical Affairs
Roxane Laboratories
614-272-4785 phone
614-276-2470 fax

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/s/

Lisa Basham
3/14/2008 09:51:25 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-195
NDA 22-207

DISCIPLINE REVIEW LETTER

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228

Attention: Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

Dear Ms. Ernst:

Please refer to your May 16, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate oral solution and morphine sulfate immediate-release tablets.

The Division of Medication Errors and Technical Support, Office of Surveillance and Epidemiology, has completed their review of your submissions and they have identified the following deficiencies:

1. General Comment for Tablets and Oral Solution: Delete [redacted] from the labels and labeling. It is not approved USP nomenclature for the dosage form. b(4)

2. Blister Label: Morphine Sulfate Tablets

   a. Increase the prominence of the product strength. If possible further differentiate the strengths by using the same colors used on the container labels.

   b. When highlighting the strength (15 mg and 30 mg), include the unit of measure (mg), not just the numerical portion of the strength (15 and 30) in the box or color block.

   c. [redacted] b(4)

Delete [redacted] b(4)

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d. Relocate the barcode to the side of the blister to allow more space to increase the prominence of the product strength.

3. Container Label and Carton Labeling: Morphine Sulfate Tablets

   a. Use tall man format for the middle portion of the NDC number (e.g., 0054-0235-25).

   b. Relocate "Sulfate" juxtapose to Morphine so the proprietary name is on the same line (e.g., Morphine Sulfate).

b(4)

   d. Increase the prominence of the product strength.

   e. Delete the Applicant's logo. If this is not achieved then at a minimum, decrease the prominence of the Applicant name (Roxane Laboratories) and logo.

   f. On the carton, revise the net quantity statement as: 4 cards x 25 tablets each.

4. Unit-Dose Container label: Morphine Sulfate Oral Solution

   a. Use tall man format for the middle portion of the NDC number (e.g., 0054-**0235**-25).

   b. Relocate "Sulfate" next to "Morphine" so the proprietary name is on the same line (e.g., Morphine Sulfate).

   c. Increase the prominence of the product strength.

   d. Differentiate the strengths (10 mg/5 mL and 20 mg/10 mL) by using contrasting colors, boxing or some other means. The entire strength (including the unit of measure) should be highlighted if such measures are employed. If contrasting color is use, use another color other than blue in order to avoid confusion with the 20 mg/5 mL strength.

b(4)

   f. Delete the Applicant's logo. If this is not achieved then, at a minimum, decrease the prominence of the Applicant name (Roxane Laboratories) and logo.

5. Container Label: Morphine Sulfate Oral Solution 100-mL and 500-mL Bulk Bottles

   a. Use tall man format for the middle portion of the NDC number (e.g., 0054-**0235**-25).

   b. Relocate "Sulfate" next to "Morphine" so that the proprietary name is on the same line (e.g., Morphine Sulfate).

c.

d. Delete the usual adult dose statement since the dose is individualized.

b(4)

e. Delete —— that appears beneath the product strength.

f. Increase the prominence of the product strength.

g. Delete the Applicant's logo. If this is not achieved then, at a minimum, decrease the prominence of the Applicant name (Roxane Laboratories) and logo.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa E. Basham, Regulatory Project Manager, at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
2/25/2008 03:56:57 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-195
NDA 22-207

INFORMATION REQUEST LETTER

Roxane Laboratories
1809 Wilson Road
Columbus, Ohio 43228

Attention: Elizabeth Ernst
Associate Director, DRA-Multisource Products

Dear Ms. Ernst:

Please refer to your new drug applications (NDA) dated May 16, 2007 (morphine sulfate oral solution) and June 7, 2007 (morphine sulfate oral tablets) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

We are reviewing the labels provided in your submissions for adherence to the format proposed by the Physician's Labeling Rule. Provided below is a list of comments based upon Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review Divisions. Additional comments, derived from review of data provided in the NDAs, will be forthcoming. We request a prompt written response in order to continue our evaluation of your NDAs.

The following issues/deficiencies have been identified in your proposed labeling.

You may wish to consider combining the package inserts for morphine sulfate oral tablets and morphine sulfate oral solution. Please submit, as soon as possible, revised, combined labeling to both NDAs, that includes the revisions noted below.

Highlights:

1. The highlights limitation statement must read as follows: **These highlights do not include all of the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].** The word "use" is missing from the latest version. [See 21 CFR201.57(d)(8)]

2. Under Highlights the Initial U.S. Approval date should be the date of the first morphine approval in the U.S.

3. The new rule [See 21 CFR 201.57(a)(6)] requires that if a product is a member of an

established pharmacologic class, the following statement must appear under the INDICATIONS AND USAGE heading in Highlights:

"(Drug) is a (name of class) indicated for (indications(s))."

Please propose as established pharmacologic class that is scientifically valid and clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

4. Under Dosage and Administration, the referenced sections are incorrect for the statement, "Caution in patients with hepatic failure and renal insufficiency." The referenced sections should read: b(4)

5. In the Contraindications section, only known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug) should be listed. If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction. You may wish to consider removing the statement "Morphine Sulfate is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product."

6. Refer to 21 CFR 201.57(a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

7. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57(a)(11)].

8. In Use in Specific Populations, the references sections in the FPI are incorrect.

9. The revision date will be edited to the month/year of application approval. In the mean time, it should be left blank.

10. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]. Add a horizontal line to separate the Contents from the FPI.

Contents:

Pregnancy and Labor and Delivery subsections should be in section 8 (Use in Specific Populations), rather than section 13 (Nonclinical Toxicology).

Full Prescribing Information:

1. In the Contraindications section, only known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug) should be listed. If the contraindication is not

theoretical, then it must be worded to explain the type and nature of the adverse reaction. You may wish to consider removing the statement, "Morphine Sulfate is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product."

2. Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biologic Products – Content and Format," available at http://www.fda.gov/cder/guidance.

3. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numeric identifier. For example. [*see Use in Specific Populations (8.4)* not *See Pediatric Use (8.4).* The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
12/5/2007 02:24:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-207

DISCIPLINE REVIEW LETTER

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228

Attention: Elizabeth Ernst
Associate Director, DRA-Multisource Products

Dear Ms. Ernst:

Please refer to your June 7, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Immediate Release Tablets, 15 mg and 30 mg.

We also refer to your submissions dated August 30, and September 7, 2007.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

Regarding the drug substance

1. Provide the results of testing ALL of the batches of drug substance using your own procedures. In particular report the amounts of [redacted]. b(4)

2. Provide the specifications for the [redacted] used to prepare the Resolution Solutions in the tests for related substances, as requested in our letter dated December 20, 2007. It is important to ensure the identity and purity of these compounds in order to ensure the validity of the Resolution determination as part of the System Suitability Test. b(4)

Regarding the drug product

1. There can be only one set of regulatory specifications for products marketed in the U.S. See ICH Q6A Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products : Chemical Substances, Section 2.2 Release vs. Shelf-life Acceptance Criteria

   "The concept of different acceptance criteria for release vs. shelf-life specifications applies to drug products only; it pertains to the establishment of more restrictive criteria

for the release of a drug product than are applied to the shelf-life. Examples where this may be applicable include assay and impurity (degradation product) levels. In Japan and the United States, this concept may only be applicable to in-house criteria, and not to the regulatory release criteria. Thus, in these regions, the regulatory acceptance criteria are the same from release throughout shelf-life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf-life. In the European Union there is a regulatory requirement for distinct specifications for release and for shelf-life where different."

Any sample must meet the acceptance criteria in the specification when tested. In order to prevent a sample from failing if it is tested after storage within the labeled expiration dating period, we recommend that you choose the "Stability Specifications" as your regulatory specifications. You may use the release specification for in-house testing.

2. The upper limit for — should be set at — based on a toxicological evaluation of this compound. b(4)

3. To avoid confusion, remove the "specified impurities" — from the "Test: Degradation Products" in the drug product specifications or rename the test. b(4)

4. Amend the test procedures directions regarding storage time of sample solutions, to be "3 days, stored at 4°C", since that is the storage time and condition supported by the data in the Methods Validation Report (Pages 450-451 in the original submission"

5. Amend Procedure 1667-03-01 (Identification B) to specify the criteria used to establish the identity of the morphine sulfate in the tablets.

6. The expiration date should be 18 months, based on the upper limit of — for — and a statistical analysis of the data. b(4)

7. Submit a revised methods validation package when all of the data collection and analysis is complete

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa E. Basham, Regulatory Project Manager, at 301-796-1175.

Sincerely,

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lisa Basham
2/14/2008 05:50:22 PM
For Parinda Jani

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-207

DISCIPLINE REVIEW LETTER

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228

Attention: Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

Dear Ms. Ernst:

Please refer to your June 7, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate immediate-release tablets.

We also refer to your submissions dated August 30 and September 7, 2007.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. **Drug Substance**

   a. **Specifications and Batch Analysis**

   (1) Explain why neither the Certificate of Analysis (COA) [redacted] (Page 112) nor your internal COA (Page 110) includes the acceptance criteria or results for [redacted]. Explain why the table of batch results on Page 87 contains no results for [redacted]. Your specification for morphine sulfate from [redacted] specifies an acceptance criterion for [redacted] of NMT [redacted] (Page 11.) b(4)

   (2) Provide data for residual [redacted] from the CoA for drug substance lots obtained [redacted].

   (3) Provide a Batch Analysis of the drug substance using your test procedures.

   (4) Provide the results for measurement of [redacted] for drug substance batch 06BW019 used to manufacture drug product batches 657258 and 657259. b(4)

   b. **Test Procedures**

   (1) Amend the test procedures to include directions regarding storage time of sample and standard solutions. Provide data to support the storage time. We note the following:

(a) The results of the Precision experiment on Page 73 show a decrease of 4% over four days.

(b) The acceptance criterion of NMT change in the Methods Validation for the solution stability (Page 77) should be decreased to an appropriate level to ensure that all compounds of interest are measured accurately when the sample solution is stored under the recommended conditions. b(4)

(2) Provide the determination of the Quantitation Limits (QLs) and Detection Limits (DLs) for the individual impurities. The QLs should be close the concentrations that yield a signal to noise ratio close to and the DLs should be close the concentrations that yield a signal to noise ratio close to . b(4)

c. Reference Standards
Provide the source and specifications for the used to prepare the Resolution Solutions in the tests for Related substances. b(4)

d. **Impurities**
Explain the statement on Page 463 that the peak identified as is present at "approximately " b(4)

2. **Drug Product**

a. **Composition**
Explain why the tablets contain a overage of the active ingredient. b(4)

b. **Manufacturing Procedure**

(1) Explain why the Speed Setting for the in the Manufacturing Batch Record (Page 170) is while the speed of the in the flow chart on Page 158. b(4)

(2) Amend the Master Batch Record to include directions for taking a sample for Blend Uniformity testing. Include directions on how to proceed if the sample fails the Blend Uniformity test.

c. **Excipients**
Provide a statement from the supplier(s) of the stearic acid that it is not obtained form sources that can transmit bovine spongiform encephalopathy

d. **Specifications**

(1) Specify whether the release or stability specifications are the regulatory specifications.

(2) Explain why [redacted] are listed under "Degradation Products" in the Specification table when you state (Page383): [redacted] are considered process impurities in the API..." We note that data from forced degradation studies reported in table 18 on Page 420 show that [redacted] is a degradant. b(4)

e. **Analytical Procedure BIRI Internal No. [redacted] Assay and Degradation Products, Identification A and Uniformity of Dosage Units** b(4)

(1) Include a test for resolution in the System Suitability.

(2) Amend the test procedures to include directions regarding storage time of sample and standard solutions, supported by data from the Methods Validation report.

f. **Test Procedure for Identity:**
Provide the specific procedure for preparing the solution for the identification test by UV absorption rather than including it in BIRI Internal [redacted] Dissolution and Identification B.

g. **Validation report for Analytical Procedure BIRI Internal No. [redacted] Assay and Degradation Products, Identification A and Uniformity of Dosage Units** b(4)

(1) Provide data to show the accuracy, linearity, precision, and limit of quantitation for [redacted].

b(4)

(2) Provide data to support the validation for the precision [redacted].

(3) Provide an evaluation of the Quantitation Limits (QLs) for the morphine sulfate and degradants based on concentrations that yield a signal to noise ratio of [redacted]. b(4)

(4) Explain how it was determined that "Run 19 represents the optimized conditions." (Page 447).

(5) Explain why the conditions reported as the "optimized conditions" (Run 19) (Page 447) are not reflected in the actual test procedure [redacted]. b(4)

	Run 19	[redacted]
pH	4.7	4.60 ±0.5
[redacted] (mM) in Mobile Phase	3.3	3
Buffer concentration (M) in Mobile Phase	0.0525	0.0565

b(4)

(6) Provide the acceptance criteria for the resolutions in the Method Robustness leading to the conclusion that "The method for the impurities of morphine sulfate is not robust within the conditions studied." Specify the modifications "to more stringently control buffer content and amount of [redacted] to assure robustness of the method." b(4)

h. **Stability Data**

(1) Explain the discrepancies in the values for in the Certificates of Analysis (Pages 518 and 523) and the Zero Time in the stability table on Page 534. b(4)

(2) Provide updated stability data, reported at two significant figures.

(3) The acceptability of the specifications and the determination of the expiration date will be assessed in conjunction with a toxicology review.

i. **Labeling**

(1) Provide the structural formula of the drug in the DESCRIPTION section (11).

(2) Provide the storage conditions for the drug product in the HOW SUPPLIED section (16).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa E. Basham, Regulatory Project Manager, at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
12/20/2007 08:55:31 AM

Basham, Lisa

From: Basham, Lisa
Sent: Friday, September 07, 2007 1:58 PM
To: 'eernst@col.boehringer-ingelheim.com'
Subject: NDA 22-195: CMC request 9-7-07

Liz,

See an additional CMC request below....

b(4)

As the drug product may be used chronically, and it contains the co-solvent Glycerin, USP at up to ~~~~ demonstrate the safety of the drug product in terms of potential leachables from either the bottles or the unit dose cups. For pertinent information, it is recommended that you refer to section III. F of the Agency guidance entitled *Container Closure Systems for Packaging Human Drugs and Biologics* (1999). It is also recommended that you communicate with the suppliers of these container closures (DMFs ~~~~) prior to preparing your response to address the issue of potential leachables.

This will be your only notification of this request. I will archive this email as an official communication.

Thanks!

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
301-796-1175
New email: lisa.basham@fda.hhs.gov

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/s/

Lisa Basham
9/7/2007 04:27:13 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-207

INFORMATION REQUEST LETTER

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228

Attention: Elizabeth Ernst
Associate Director, DRA-Multisource Products

Dear Ms. Ernst:

Please refer to your June 7, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Immediate-Release Tablets, 15 mg and 30 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide information regarding polymorphs of the drug substance and how this may affect the dissolution properties of the drug product.

2. Provide a sample of executed batch record for manufacture of the drug product.

3. Provide information to indicate which stability batches are "historical" batches. Explain why there is only one data point for some batches, e.g. Batch 456304A has a data point at 34 months.

4. Provide statements that the chemical composition of the packaging components that are in contact with the drug product materials are safe for use in packaging tablets for oral administration. This can be done by citing the correct sections of the Code of Federal Regulations applicable to indirect food contact. For the aluminum foil/paper peelable blister backing, this information should be provided b(4)

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If you have any questions, call Lisa E. Basham, Regulatory Project Manager, at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
8/16/2007 04:58:46 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-207

Roxane Laboratories, Inc.
1809 Wilson Rd.
Columbus, OH 43228

Attention: Elizabeth Ernst
Associate Director, DRA-Multisource Products

Dear Ms. Ernst:

Please refer to your June 7, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Immediate-Release Tablets, 15 mg and 30 mg.

We also refer to your submission dated July 27, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 7, 2007, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

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

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/s/

Parinda Jani
8/16/2007 04:25:10 PM
for Bob Rappaport, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-195

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228

Attention: Elizabeth Ernst
Associate Director, DRA-Multisource Products

Dear Ms. Ernst:

Please refer to your May 16, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL.

We also refer to your submissions dated May 30, June 8, and July 5 and 11, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on July 16, 2007, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DISCIPLINE REVIEW LETTER

NDA 22-195

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 73228

Attention: Elizabeth Ernst
Associate Director, DRA-Multisource Products

Dear Ms. Ernst:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Oral Solution.

Our review of the chemistry section of your submission is complete, and we have identified the following deficiencies:

1. Provide confirmation that , which contains a chemical structural alert moiety for mutagenicity, which can be quantified by your related substances method, but is not a specified impurity for the sourced API, is limited by default to NMT as an unspecified impurity in the acceptance specification for sourced API. It is noted that your validation report 1397-027 demonstrates that does form by degradation of the API under stress conditions with heat, peroxide, and light. Clarify the specification acceptance criteria in light of the footnote in your method (v3, p. 27) that indicates this "impurity is not tracked in the API." b(4)

2. Depending on the determination of adequacy of DMF to support your application, you may need to provide evidence that leachables from the bottles are consistently below levels that are demonstrated to be acceptable and safe. b(4)

3. We recommend that you revise the HPLC method to include a system suitability criterion or criteria for resolution, considering the results of the robustness studies reported (v7, p. 1912). b(4)

4. The methods used for determination of the degradants would appear to calculate the total degradation by summing the individual degradants (both known and unspecified) that are quantitated at a level above the quantitation limit. Provide confirmation that this is the case since there are several instances where the data reported do not appear to be derived in that fashion. Rounding may be the reason for most of the apparent discrepancies (e.g., v5, p. 1034, initial), but cannot account for all instances (v5, p. 1058, 3 month time point).

5. With regard to the revisions to the gradient method (v7, p. 1841) due to the failures seen in the robustness study (validation report 1397-026, p. 2018), it is stated that the method was modified ' It is not evident what modifications were made to the method to provide greater assurance of correct mobile phase composition. Provide clarification *and* add the appropriate minimum resolution limit(s) to the system suitability requirements for the method for the most critical pair(s) of degradants. b(4)

6. DMF — was reviewed and was found to be deficient. A letter has been forwarded to the holder. b(4)

7. As it is evident that morphine sulfate degrades when exposed to light (e.g., v7, p. 1883), provide data that support the adequacy of the bottle packages that you propose to use with regard to light exposure (e.g., results of ICH photostability studies, light transmission test results as per USP <661>).

8. The following is a preliminary comment regarding your labels and labeling. Additional comments may be forthcoming: Revise the package insert to indicate the storage conditions that should be followed for the drug product.

9. Additional comments regarding the microbiological aspects of your application may be forthcoming.

10. Additional comments regarding the qualification of the drug substance and drug product impurities may be forthcoming.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 75,041

Roxane Laboratories
1809 Wilson Road
Columbus, OH 43228

Attention: Elizabeth A. Ernst
Associate Director, Regulatory Affairs

Dear Ms. Ernst:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Morphine Sulfate Immediate-Release Tablets, 15 mg and 30 mg, and Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL.

We also refer to the meeting between representatives of your firm and FDA on September 12, 2006. The purpose of the meeting was to discuss the requirements for NDA applications for the above drug products.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

ENCLOSURE

Signature Page

MEETING DATE: September 12, 2006
TIME: 3-4 PM
LOCATION: 10903 New Hampshire Avenue, Silver Spring, MD 20993, Building 22, Conference Room 1311
APPLICATION: PIND 75,041
STATUS OF APPLICATION: Presubmission
PRODUCT: Morphine Sulfate Immediate-Release Tablets, 15 mg and 30 mg, and Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL
INDICATION: relief of moderate to severe pain
SPONSOR: Roxane Laboratories
TYPE OF MEETING: Pre-IND
MEETING CHAIR: Sharon Hertz, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
MEETING RECORDER: Lisa Basham, Regulatory Project Manager

FDA Attendees	Title
Bob Rappaport, MD	Division Director
Sharon Hertz, MD	Deputy Division Director
Dan Mellon, PhD	Supervisory Pharmacologist
Howard Josefberg, MD	Clinical Reviewer
David J. Lee, PhD	Clinical Pharmacology Reviewer
William M. Adams, PhD	Chemistry Reviewer
Janice Weiner, JD, MPH	Regulatory Counsel, Office of Regulatory Policy
Lisa Basham, MS	Regulatory Project Manager
Kathleen Davies	Regulatory Project Manager
Sponsor Attendees	**Title**
Elizabeth A. Ernst	Associate Director of Medical and Regulatory Affairs
Marilynn F. Davis	Regulatory Manager
Gregory M. Hicks, PharmD	Clinical Research Manager
Mukul A. Agrawal, PhD	Clinical Research Manager
Joseph Mc Phillips, PhD	Consultant - Toxicologist
Megan Stojic, PharmD	Medical Consultant

b(4)

Background: The sponsor submitted a request for a Pre-IND meeting, dated May 3, 2006. This meeting was scheduled for September 12, 2006. The subject products are marketed but unapproved. The purpose of this meeting is to discuss the requirements for bringing these products into regulatory compliance. Prior to the meeting, the Agency prepared responses to the questions posed in the August 15, 2006, meeting package. These responses were forwarded to the sponsor on September 8, 2006. Prior to the Pre-IND meeting, the sponsor requested that discussion be allowed for all items.

Note: The questions included in the meeting package are shown below in italicized text. Agency responses/comments/questions, forwarded to the sponsor prior to the meeting, are shown below in bolded text. Discussion during the meeting is presented in normal text.

Roxane's application would include the following:

Full Index and CTD outline of the 505(b)(2) application:

Roxane proposes one (1) 505(b)(2) application, with one (1) label to address both the oral immediate-release tablets and solutions.

Question 8a: Is one application and label for these products acceptable to the Agency?

FDA Response:

- **The prescription drug user fee bundling policy described in our guidance on *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (December 2004) states that "[d]ifferent dosage forms ... should be submitted in separate original applications unless the products are identical ... in quantitative and qualitative composition..." Accordingly, we would expect separate NDAs for the immediate-release tablets and oral solution. ~~Whether your two formulations can be submitted as one application is under review.~~ User fees may be applicable; for further information contact Michael D. Jones in the Office of Regulatory Policy.**

- **One label for both of these immediate-release formulations is acceptable.**

Discussion: Ms. Basham noted that the next to the last sentence in the first bullet of the FDA Response should be removed, as indicated above. This sentence was a remnant of an earlier version of our response, prior to obtaining input from the USER FEE staff.

The sponsor stated that they have no issue with filing two NDAs for the two products, but wish to pay one user fee for both NDAs. Dr. Rappaport stated that the Division has no authority over user fee issues, but added that the Division will inform the User Fee group regarding the specifics of these applications to assist with their decision making. He suggested that the sponsor speak with Michael Jones directly regarding this issue.

Proposed labeling - Reference Drug:

Roxane proposes to rely on the Agency's previous findings on Avinza® (MSO_4 extended-release capsules, Ligand Pharmaceuticals), as the baseline reference drug (Approved: 3/20/02, NDA #021260). The labeling would be appropriately adjusted for the Roxane-specific immediate release products.

Question 8b: Is it agreeable that Roxane will appropriately reference Avinza® labeling as the baseline reference drug for the application?

FDA Response:

- **You may rely, in part and as described in further detail below, on the Agency's finding of safety and efficacy for Avinza if you provide an adequate basis for such reliance through appropriate bridging data (e.g., comparative bioavailability data).**

- **You may support your proposed indication for chronic pain by reliance upon the Agency's finding of efficacy for chronic pain for Avinza® or by reliance on published literature.**

- **The Avinza® package insert can also provide a fair amount of support for safety, and when accompanied by post-marketing data and supportive literature, should be sufficient to adequately inform the label.**

- **Avinza® is not approved for the treatment of acute pain and thus cannot provide support for your proposed indication, which includes the treatment of acute in addition to chronic pain. You will need to provide sufficient supportive evidence for the treatment of acute pain, through reliance on the Agency's finding of safety and efficacy for a morphine product approved for this indication and/or adequate references in the literature.**
    - **Literature references to support efficacy must be from analgesic studies.**
    - **Constraining your literature search to studies published after the 2002 Avinza® approval limits the likelihood of finding adequate data.**

- **The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 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/guidance.htm for further information. 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.**

Discussion: The sponsor stated their intent to submit 15-20 published literature references regarding breakthrough pain to support the acute indication. Dr. Hertz stated that this is problematic since the literature references are old and the Division does not have access to the source data. She suggested another option, referencing an approved morphine with an acute indication. The sponsor inquired whether reference to an approved injectable morphine would be acceptable. Dr. Hertz answered affirmatively. The sponsor inquired whether their study comparing 10 mg of intravenous morphine to their oral morphine would serve as a comparative

bioavailability study. Dr. Hertz responded that this is possible and inquired what the comparator was. The sponsor responded that the comparator in that study was Baxter's Duramorph, which is an approved product.

Clinical Data Summary and Labeling:

For the clinical data sections of the labeling, Roxane proposes to examine literature published since 2002 for updated information. Specific clinical studies will not be conducted.

Question 8c: Does the Agency agree with Roxane's proposal to update the clinical data summary and labeling sections, based on a review of the literature, since the Avinza® approval date (2002)?

FDA Response: No. See above response to Question 8b.

No discussion required.

Pediatric Study Requirements:

Roxane proposes to submit information obtained from a review of the literature published since 1995. As appropriate, labeling can be updated based on review. Specific pediatric clinical studies will not be conducted.

Question 8d: Does the Agency agree that Roxane will update pediatric information based on a review of the literature since 1995?

FDA Response:

- **It is unlikely that literature review alone will provide sufficient, evidence-based pediatric dosing information to adequately address the requirements of PREA. You may request a deferral of pediatric studies at the time of your marketing application.**

Discussion: The sponsor stated their intent to submit literature references to inform the label regarding pharmacokinetics in pediatric patients. If this information is not adequate, they are amenable to conducting pediatric studies as a Phase 4 commitment. Dr. Hertz responded that pharmacokinetic data in pediatric patients is not sufficient, but that the Division will accept pediatric data as a Phase 4 commitment. She added that the Division can provide a general idea of the types of studies required as a Post Meeting note, or shortly thereafter.

POST MEETING NOTE: To address the requirements of PREA, pediatric studies would need to be performed in pediatric patients of all ages. The program would need to begin with single and multiple-dose PK studies followed by efficacy and safety studies. The efficacy studies would be for the same indication as for adults, and could be tailored to the needs of pediatric patients based on age.

Nonclinical Pharmacology and Toxicology Summary and Labeling:

Roxane proposes to use the Agency's previous findings of safety for the nonclinical pharmacology and toxicology summary, and would submit any pertinent literature references since 2002. Roxane will submit a summary of literature published since 2002 (date of Avinza® approval). Specific pharmacology and toxicology studies will not be conducted.

Question 8e: Does the Agency agree with Roxane's proposal to update the Nonclinical Pharmacology and Toxicology Summary and labeling sections with a review of available literature since the approval date of Avinza® (2002)?

FDA Response:

- **In principle, yes. However, final review of the labeling will occur at the time of NDA submission. The Division requests that your NDA submission include copies of all referenced literature citations.**
- **Opioid drug products derived from thebaine (phenanthrene-derivatives) may contain impurities containing an , which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance should be reduced to a TDI of NMT or adequate safety qualification should be provided. Consult with your DMF holder to decrease the limit of these impurities.** b(4)

- **Adequate safety qualification for any potential genotoxic impurities should be provided with the NDA submission and should include:**
    - **Minimal genetic toxicology screen (two in vitro genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
    - **Repeat dose toxicology of appropriate duration to support the proposed indication.**

- **Should this qualification produce positive or equivocal results, the impurity specification should be set at NMT or otherwise justified. Justification may require an assessment for carcinogenic potential either in a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.** b(4)
    - **NOTE: Guidance to Industry regarding setting acceptable specifications for potential genotoxic impurities is in development in CDER OND. The specifications above represent our current thinking on this topic at this time.**

- **Adequate safety qualification should be provided for any new excipients. Please refer to Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following http://www.fda.gov/cder/guidance/guidance.htm**

- **The NDA/IND submission should contain information on potential leachables and extractable from the drug delivery system. Provide your justification for the safety**

of potential exposure to the study subjects, including supporting data/literature references. Complete characterization of leachables and extractables should be submitted with the NDA.

Discussion: The sponsor stated that their suppliers ——— is already manufacturing material that contains less than the Agency's minimum allowable amount for ——— . They are still working with ——— to determine the levels in their material. They added that they realize that, if this material is above the specification for ——— they will have to perform toxicity studies, or have ——— perform them. They added that they intend to file the NDAs with ———suppliers, but are prepared to file with ——— only, if ——— cannot meet the specification. b(4)

The sponsor stated that they intend to submit literature in support of the pharmacology/toxicology sections of the label. Dr. Mellon requested that they submit copies of the actual articles for review.

Human Pharmacokinetics and Bioavailability Summary:

Roxane proposes to conduct the following descriptive pharmacokinetic studies:

- *3-way crossover pilot study: Intravenous (IV) vs. Tablet vs. Solution (fasted)*
- *2-way crossover study: 30 mg Tablet vs. 15 mg Tablet (fasted)*

Study results to be incorporated into pharmacokinetic section of labeling. Results of the pilot study will be provided to FDA prior to the meeting.

Question 8f: Does the Agency agree that the Human Pharmacokinetics and Bioavailability Summary will be based on the descriptive pharmacokinetic studies conducted by Roxane, and that Roxane will develop a descriptive pharmacokinetic section of the labeling based on results of these studies?

FDA Response: You will need to address linearity, multiple dosing, food effect and special populations (hepatic and renal insufficiency) in the package insert either from the literature or from your in-house information.

Since you propose to submit your application as 505(b)(2) referencing Avinza® for the chronic pain indication, the Agency recommends that you have a reference arm (Avinza®) in the proposed 15- and 30-mg tablet pharmacokinetic study. Clarify if the food effect information in the meeting package (34% increase in the AUC with morphine solution) was obtained with a high-fat meal.

With respect to the intravenous formulation used in the 3-way crossover pilot study, clarify if it is approved in the U.S. In addition, provide the formulation details.

Discussion: The sponsor stated that they would like to combine single and multiple dosing in one study. This study will compare the 15- and 30-mg tablet and use Avinza 60 mg as a reference product. Additionally, the 30-mg tablet will be tested for food effect. Dr. Lee requested that the sponsor submit the protocol for review. The sponsor noted that the RLD

(Avinza) is a 120-mg dose and asked whether they may use a 60-mg dose instead. Dr. Lee responded that this is acceptable.

With respect to the intravenous formulation used in the 3-way crossover pilot study, Duramorph was used.

The sponsor stated that the protocols will be ready for submission within 30 days.

Safety Update Report:

Roxane proposes to reference information obtained from Roxane's history with the Morphine Sulfate Immediate Release 15 mg and 30 mg Tablets, and the Morphine Sulfate Immediate Release Oral Solution 10 mg/5 mL and 20 mg/5 mL Products.

Question 8g: Is this acceptable for the Safety Update Report section of the NDA?

FDA Response:
The Integrated Summary of Safety can be composed of the information from Roxane's history with the Morphine Sulfate Immediate-Release Tablets and Oral Solutions, in addition to reference to the Avinza package insert and your literature review.

No discussion necessary.

Chemistry, Manufacturing and Controls Summary:

Roxane proposes to:

- *Commit to manufacturing one demonstration lot of the finished drug product. The demonstration lot will be used for all in vivo testing and CMC testing including supporting stability data.*
- *Summarize and tabulate historical stability data (room temperature) for all batches placed on stability for the last two years.*

Question 8h: Does the Agency agree with Roxane's proposal as stated above for the Chemistry, Manufacturing, and Controls Summary?

FDA Response:

- **The application should include CMC information from at least three lots of each proposed strength of each dosage form prepared using at least three drug substance lots. At least one drug product lot should approximate commercial scale. The other two lots may be of smaller size. All three lots should be manufactured with equipment using the same operating principles as the commercial process.**

- **Stability data at the proposed storage condition should be provided for at least three drug product lots of each strength of each dosage form in each packaging configuration and size. Historical data may be accepted as supportive of the storage**

condition and/or initial expiry period if the formulations, manufacturing processes and packaging are the same as the product proposed in the application.

Discussion: The sponsor stated that, since these products are already approved, they have a large amount of historical data to support the application. They do not want to wait to manufacture three commercial lots prior to filing. They proposed filing with one commercial lot and three months accelerated and three months real-time stability data. Dr. Adams requested that the sponsor submit their proposal as a request for Special Protocol Assessment.

KEY DISCUSSION POINTS:

1. The sponsor is agreeable to filing two separate NDAs for each formulation, but wishes to pay one user fee for both applications. The Division has no authority over user fee issues, but will inform the user fee staff of the specifics of these applications. The sponsor will contact Michael Jones directly to discuss this issue.

2. Literature alone is not sufficient to support the acute indication. The sponsor should consider referencing an approved formulation. An approved intravenous formulation of morphine would serve as an acceptable reference listed drug.

3. Pharmacokinetic data in pediatric patients is not sufficient to inform the label. Pediatric studies will be accepted as a Phase 4 commitment. The Division will provide a general idea of what types of studies will be required.

4. Source material must meet the Agency's requirements regarding levels of
is manufacturing material that meets this specification. The sponsor is working with to determine whether their material meets this specification. The sponsor is willing to file with if necessary, and understands that toxicity studies of this impurity will be required for the manufactured material if they do not meet the specification. b(4)

5. The proposed PK study will add Avinza 60 mg as a reference. The food effect will be tested with 30-mg tablet. The Sponsor will submit protocols for comment.

6. The sponsor will submit, as a request for Special Protocol Assessment, their proposal to submit one commercial batch of drug product for each NDA, with three months of accelerated and real-time stability data.

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/s/

Lisa Basham-Cruz
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