

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22382Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-382

SUPPL #

HFD # 170

Trade Name Sprix Nasal Spray

Generic Name ketorolac tromethamine

Applicant Name Roxro Pharma Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

3 years

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# 021528 Acular

NDA# 074761 + other Ketorolac tablets (generic of Toradol tablets, which are generics discontinued, not for reasons of safety or efficacy)

NDA# 075222 + other Ketorolac injection (generic of Toradol injection, which is generics discontinued, not for reasons of safety or efficacy)

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 2003-01, 2005-01

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"):

Studies 2003-01, 2005-01

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 # 062829

YES

!

!

! NO

! Explain:

Study 2003-01 was not conducted under IND (study conducted in New Zealand). Thus, there is no 1571.

However, the protocol, clinical study report, and CRO delegation forms clearly indicate that Roxro was the sponsor. There is nothing to indicate that Roxro was not the sponsor.

Investigation #2

IND # 062829

YES

!

!

! NO

! Explain:

For Study 2005-01, the 1571 and all other documents clearly indicate that Roxro was the sponsor.

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

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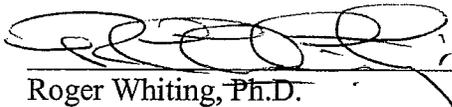
/s/

JESSICA M BENJAMIN
10/02/2009

SHARON H HERTZ
10/05/2009

Certification Statement for Generic Drug Enforcement Act of 1992

ROXRO PHARMA, Inc. ("ROXRO") has made a diligent effort to ensure that no person debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act has provided any services in connection with this application. Relying on this effort, ROXRO certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.



Roger Whiting, Ph.D.
President and Chief Scientific Officer
ROXRO PHARMA, Inc.

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22382 Sprix
Date: Friday, April 16, 2010 1:38:14 PM
Attachments:

Hi Bonnie,

Please refer to NDA 22-382 for ketorolac tromethamine nasal spray. We have the following comments regarding the carton and container labels for Sprix:

A. *Container Label*

1. Revise the proprietary name, established name, dosage form and product strength to appear in the following format. Healthcare practitioners are accustomed to this layout and variance from it may result in difficulty in identifying this important information. In order to ensure there is room for this presentation, decrease the size of the proprietary name, as currently presented it utilizes half of the principle display panel.

Sprix

(Ketorolac
Tromethamine)
Nasal Spray

15.75 mg per spray

2. As currently presented, the established name still does not appear to be one half the size of the proprietary name. Ensure the prominence of the established name is in accordance with 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the

established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

3. Delete the statement [REDACTED] ^{(b) (4)} as this information is not useful and will provide space on the label to include the discard statement below (Comment A4).

4. Prominently include the statement on the principle display panel: “Discard 24 hours after first dose, even if drug product remains”. This will help ensure the product is used as intended. If space does not permit, consider presenting the statement horizontally on the right side panel.

B. Carton Labeling (1 count)

1. See Comment A2.

2. In order to increase readability, insert a line space between the dosage form and strength and between the strength and route of administration. As currently presented this information appears crowded.

3. Increase the prominence of the product strength.

4. Relocate the “Dispense the accompanying Medication Guide to each patient” to the principle display panel, so that this information is not overlooked.

5. De-bold and relocate the “Rx only” statement to the bottom of the principle display panel, in order to make room for the Medication Guide Statement.

6. Increase the prominence by bolding the statement: “Discard 24 hours after first dose, even if drug product remains”. This will help ensure the product is used as intended and that the statement is not overlooked.

C. Carton Labeling (5 count)

1. See Comment A2.
2. See Comments B3, B4, and B6.
3. Insert a line space between the dosage form and product strength.
4. “ROXRO” is rather prominent. Decrease the size and prominence of “ROXRO” in order to help ensure there is adequate room for the above recommendations.

We request a prompt response due to the upcoming PDUFA date for this application. Let me know if you have any questions.

Regards,

Jessica

Jessica M. Benjamin

Regulatory Project Manager

Division of Pulmonary, Allergy, and Rheumatology Products

Office of New Drugs II

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9713 *fax*

From: [Bonnie Horner](#)
To: [Benjamin, Jessica;](#)
CC:
Subject: RE: Roxro NDA 22-382 - new labeling version
Date: Monday, October 05, 2009 4:47:15 PM
Attachments: [Final Label FDA changes accepted noon Oct 5.doc](#)

Jessica, here's the labeling with all the agreed changes accepted and the cross-references included.

Thanks.
Bonnie

--- On **Mon, 10/5/09**, Benjamin, Jessica <[Jessica..Benjamin@fda.hhs.gov](mailto:Jessica.Benjamin@fda.hhs.gov)> wrote:

From: Benjamin, Jessica <Jessica.Benjamin@fda.hhs.gov>
Subject: RE: Roxro NDA 22-382 - new labeling version
To: "Bonnie Horner" (b) (4)
Cc: "Benjamin, Jessica" <Jessica.Benjamin@fda.hhs.gov>
Date: Monday, October 5, 2009, 10:20 AM

Hi Bonnie,
Please refer to NDA 22-382 for ketorolac tromethamine nasal spray. I have attached a pdf version of the label with our changes and a clean copy with our changes to the label we received on Saturday. Please review the label and make any edits to the clean copy with track changes. We made our changes before we received your corrected cross-references copy, so you will need to make those updates to this version. Please let me know if you have any questions.
Thanks,
Jessica

From: Bonnie Horner (b) (4)
Sent: Saturday, October 03, 2009 4:54 PM
To: Benjamin, Jessica; Hertz, Sharon H

Subject: Roxro NDA 22-382 - new labeling version

Dear Dr. Hertz and Ms Benjamin,

As discussed in our teleconference on Friday afternoon, we have completely revised our comments on FDA's proposed label and a new version is attached. Please read the explanatory notes, which are very short, before you review the label. As stated there, I plan to send you this same label tomorrow, but with all of the corrections to the internal labeling section cross-references included.

Thank you very much for making the time to talk to us on Friday and for offering to review our new version over the week-end. Please phone me at any time if you have changes to the label or any other issues you want to discuss before 10 am Eastern time on Monday. You can reach me via cell phone [REDACTED] ^{(b) (6)} From 10 am your time on Monday we will be in the Roxro office in California, from which time you can also reach me on the central Roxro number (650) 322-4554. Please do not hesitate to call my cell phone listed above at any time.

Best regards.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	Sprix (ketorolac tromethamine) nasal spray

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/s/

JESSICA M BENJAMIN
04/29/2010

MEMORANDUM

Date: 26-Jan-2010

From: Joseph Leginus, Review Chemist, Branch II/DPA I/ONDQA

To: NDA 22-382, Sprix (ketorolac tromethamine) Nasal Spray

Through: Prasad Peri, Branch Chief (Acting), Branch II/DPA I/ONDQA

Subject: Approval Recommendation

Background:

- On 08-Sep-2009, an overall recommendation of Withhold was made by the Office of Compliance for NDA 22-382 due to the unresolved GMP issues associated with the drug product manufacturing facility at Hollister Stier Laboratories. As a result of this recommendation, NDA 22-382 was considered to be Not Approvable from a CMC perspective (see Quality Reviews by J. Leginus (10/1/2009) and A. Al-Hakim (10/1/2009)).
- In late December 2009, the Seattle District Office (DO) received a complete response from Hollister Stier Laboratories which was reviewed and determined to adequately address the GMP issues. The DO recommended Acceptable on 22-Jan-2010.
- Based on the District recommendation of Acceptable, the Office of Compliance recommended Acceptable for the drug product manufacturing facility at Hollister Stier Laboratories on 25-Jan-2010.
- Acceptable recommendations have been provided for all manufacturing and testing facilities submitted to EES for NDA 22-382 and an Overall Compliance recommendation of Acceptable was provided on 25-Jan-2010.

Conclusion:

- With the GMP issues resolved at the drug product manufacturer for Sprix (Hollister Stier Laboratories) and an overall Office of Compliance recommendation of Acceptable, NDA 22-382 is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

Joseph Leginus, Ph.D.
Review Chemist

Prasad Peri, Ph.D.
Branch II Chief (Acting), ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JOSEPH M LEGINUS
01/26/2010

PRASAD PERI
01/26/2010
I Concur

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	Sprix (ketorolac tromethamine) nasal spray

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/s/

JESSICA M BENJAMIN
02/01/2010



NDA 022382

ACKNOWLEDGE CLASS 2 RESPONSE

Roxro Pharma, Inc.
535 Middlefield Road
Suite 180
Menlo Park, CA 94025

Attention: Roger Whiting, PhD
President and Chief Scientific Officer

Dear Dr. Whiting:

We acknowledge receipt on November 20, 2009 of your November 19, 2009 resubmission to your new drug application for Sprix™ (ketorolac tromethamine) Nasal Spray.

We consider this a complete, class 2 response to our October 5, 2009 action letter. Therefore, the user fee goal date is May 20, 2010.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22382	----- ORIG-1	----- ROXRO PHARMA INC	----- KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

SARA E STRADLEY
12/04/2009

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: label
Date: Wednesday, September 30, 2009 12:19:37 PM
Attachments: [Draft Label NDA 22-382 30Sep.pdf](#)
[Draft Label NDA 22-382 sponsor clean.doc](#)

Hi Bonnie,

Please refer to NDA 22-382 for ketorolac tromethamine nasal spray. I have attached a pdf version of the label with our changes and a clean copy with our changes accepted. Please review the label and make any edits to the clean copy with track changes. Please note that the label has not been finalized by senior management. Depending on the edits, we may need to have further discussions. We request a prompt response to this request.

Let me know if you have any questions.

Thanks,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22382	----- ORIG-1	----- ROXRO PHARMA INC	----- KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JESSICA M BENJAMIN
10/05/2009

From: [Greeley, George](#)
To: [Benjamin, Jessica](#);
CC: [Stowe, Ginneh D.](#);
Subject: NDA 22-382 Sprix
Date: Friday, October 02, 2009 4:33:02 PM
Attachments:

Hi Jessica,

The Sprix (ketorolac tromethamine) deferral and plan was reviewed by the PeRC PREA Subcommittee on August 26, 2009.

The Division recommended a deferral or studies for patients 0-16 years because the product is ready for approval in adults.

The PeRC agreed with the Division to grant a deferral because the product is ready for approval in adults.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JESSICA M BENJAMIN
10/02/2009

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: carton and container labeling - Sprix
Date: Wednesday, September 30, 2009 3:21:54 PM
Attachments: [carton container comments.doc](#)

Hi Bonnie,

Please see our attached comments for the carton and container labeling for Sprix.

Please let me know if you have any questions.

Regards,
Jessica

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22382	----- ORIG-1	----- ROXRO PHARMA INC	----- KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JESSICA M BENJAMIN
10/05/2009



NDA 22-382

INFORMATION REQUEST

Roxro Pharma, Inc.
Attention: Roger Whiting, Ph.D.
President and Chief Scientific Officer
535 Middlefield Road, Suite 180
Menlo Park, CA 94025

Dear Dr. Whiting:

Please refer to your December 5, 2008 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ketolorac tromethamine nasal spray.

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. It is noted that the batch formula provided in the submission (Section 3.2.P.3.2, page 1 of 1), as well as the description of the manufacturing process (Section 3.2.P.3.3, pages 1-2) list (b) (4) "Water for Injection, USP" as a formulation ingredient. However, this is not completely accurate as the batch records submitted (from Hollister-Stier) for submission batches #7279 and #7133 indicate that drug product is formulated (b) (4). Such (b) (4) generally does not meet the strict requirements of (b) (4) "Water for Injection, USP". Therefore, you should amend the submission accordingly.
2. Since microbial control of the drug product during manufacturing relies on maintaining a low-bioburden of components and processes, it is recommended that you consider establishing formal acceptance criteria for (b) (4) bioburden as well as production hold-time limits for the formulated bulk (b) (4).

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22382	----- ORIG-1	----- ROXRO PHARMA INC	----- KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

ALI H AL HAKIM
09/24/2009

MEMORANDUM

Date: 24-Aug-2009

From: Joseph Leginus, Review Chemist, Branch II/DPA I/ONDQA

To: NDA 22-382 Sprix® (ketorolac tromethamine) Nasal Spray

Subject: Status of Inspections of Manufacturing and Testing Sites

Background:

On August 7, 2009, Chemistry Review #2 of NDA 22-382 was completed. From a CMC perspective, the applicant provided adequate responses to each of the 7 deficiency comments outlined in the CMC IR letter dated May 13, 2009. However, The EER for the NDA was pending.

Current Status:

- CMC is recommending Not Approvable for NDA 22-382. This is based on an Office of Compliance recommendation of "Withhold" following the 26-Mar-2009 inspection of the drug product manufacturer, Hollister Stier Laboratories.
- In addition, inspections have not yet been completed at two dosage testing sites:

(b) (4)

Acceptable cGMP recommendations are required for all manufacturing and testing facilities before approval.

(This recommendation was forwarded to Cross Discipline Team Leader, Rob Shibuya, via email on August 24, 2009.)

- The microbiology review is pending. Robert Mello is the microbiology reviewer.
- Pharmacology/toxicology has recommended approval. Newton Woo is the pharmacology/toxicology reviewer.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JOSEPH M LEGINUS
08/24/2009

ALI H AL HAKIM
08/24/2009

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22382	----- ORIG 1	----- ROXRO PHARMA INC	----- KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JESSICA M BENJAMIN
08/21/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **CDER Pediatric and Maternal Health Staff, Maternal Health Team**

FROM (Name, Office/Division, and Phone Number of Requestor): **Jessica Benjamin, DARRP, 6-3924**

DATE
8/13/09

IND NO.

NDA NO.
22-382

TYPE OF DOCUMENT

DATE OF DOCUMENT
December 5, 2008

NAME OF DRUG
Sprix (ketorolac tromethamine nasal spray)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
August 28, 2009

NAME OF FIRM: **Roxto Pharma**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: New NDA application for nasal spray containing ketorolac tromethamine for short term management of moderate to severe pain. Please review proposed labeling in section 8.4, Nursing Mothers.

Paper submission - will email label
PDUFA date: October 5, 2009
PM - Jessica Benjamin X6-3924
CDTL - Rob Shibuya X6-1292

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

JESSICA M BENJAMIN

08/14/2009

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22-382 Information Request
Date: Wednesday, July 01, 2009 10:03:31 AM
Attachments:

Hi Bonnie,

We have the following information request from our clinical team.

We note that in Study 2005-01 and 2003-01 no subjects on ROX-888 65 years of age or older had a nasal exam but several subjects 65 years old and on ROX-888 in Study 2001-03 had nasal exams. For Study 2001-03, provide a list of every patient 65 years of age and older on ROX-888 that had a nasal exam and include the findings, number of doses and comparison to placebo. Provide a list of any other subjects 65 years of age or older on ROX-888 that had nasal exams.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: RE: Roxro NDA 22-382
Date: Monday, August 10, 2009 11:21:00 AM
Attachments:

Hi Bonnie,

In order to complete our PeRC assessment, we need your pediatric plan no later than Thursday, August 13th.

Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 office
301-796-9713 fax

-----Original Message-----

From: Bonnie Horner  (b) (4)
Sent: Tuesday, July 21, 2009 1:10 PM
To: Benjamin, Jessica
Subject: Roxro NDA 22-382

Hi Jessica,

I wanted to confirm that we sent in the carton and vial labels for our product on Friday, so they arrived at the mail room yesterday. Please let me know if they don't reach you within a reasonable time frame.

Then I also thought I'd do a quick status check with you. According to my

list, we now have 2 items that you have asked for still pending response from us. One is the revised SPL, updated to version 4, of the labeling. We should have that back from the vendor to send you within the next few days. The other thing we still owe you is our response to item 4 of the CMC questions that you e-mailed us on May 13th. We've answered all the other points from that e-mail, and expect to have item 4 data ready to submit by the end of July. If there is anything else pending from us at this time, please let me know.

I have a couple of questions for you. Can you tell me the dates of the Pediatric Committee's meetings between now and end of September. We are working on our pediatric plan and would like to submit it in time for the Pediatric Committee's review before our PDUFA date, so it would help us to know when they meet.

We have not received any questions on PK/clinical pharmacology. Do you have any idea what the timing might be of receipt of any questions from that review group?

Finally, there was an inspection of our drug product manufacturer (Hollister-Stier Laboratories in Spokane, WA) that has led to some additional discussions between the manufacturer and their District Office. Is there anything that you need from us to make sure the loop is closed on all of those discussions - do we need to copy you on any of the agreements between the manufacturer and the District Office, for example - or will that be taken care of between the Division and the Dist. Office without the need for us to do anything?

Thanks again for all your help.

Best regards.

Bonnie

(b) (4)

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22-382; Information Request
Date: Wednesday, August 19, 2009 10:31:08 AM
Attachments:

Hi Bonnie,

Please refer to NDA 22-382 for Sprix. We have the following clinical question:

Regarding your initial NDA submission and all follow up submissions to your NDA, have you reported to FDA all treatment-emergent deaths, serious adverse events, and adverse events that led to discontinuation from all studies and from all sites for the entire intranasal ketorolac development program?

We request a prompt response to this request. Please feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To:  (b) (4)
CC: [Benjamin, Jessica;](#)
Subject: Sprix label
Date: Friday, August 21, 2009 10:46:06 AM
Attachments:

Hi Karin,

Please confirm that the black and white labels you submitted are the labels that you intend to introduce to the market place? Additionally, although we appreciate the mock-up for the multipack, we would also like an electronic copy of the multipack.

Thanks,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: [REDACTED] (b) (4)
CC: [Benjamin, Jessica;](#)
Subject: FW: Sprix label
Date: Monday, August 24, 2009 1:10:52 PM
Attachments:

Hi Karin,

In addition to the request below, please confirm whether or not you will continue to have the carton labeling for the 1 day supply.

We appreciate your quick response to these requests.

Regards,
Jessica

From: Benjamin, Jessica
Sent: Friday, August 21, 2009 10:46 AM
To: [REDACTED] (b) (4)
Cc: Benjamin, Jessica
Subject: Sprix label

Hi Karin,

Please confirm that the black and white labels you submitted are the labels that you intend to introduce to the market place? Additionally, although we appreciate the mock-up for the multipack, we would also like an electronic copy of the multipack.

Thanks,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC:
Subject: NDA 22-382
Date: Friday, August 28, 2009 3:40:38 PM
Attachments:

Hi Bonnie,

In reference to your application for Sprix, do you intend to use (b) (4) for the intended purposed described in your NDA, which is that it may be used as an alternative facility for (b) (4) the packaged product?

Thanks,
Jessica

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: REMS
Date: Monday, September 28, 2009 3:02:03 PM
Attachments:

Bonnie,

The current FDAAA regulation requires all products that have a Medication Guide to have a REMS. Since Sprix already has the FDA-approved NSAID Medication Guide, we will need to convert it to a REMS. In order to do this, we will need a timetable for submission of assessments. The assessments need to include an evaluation of the effectiveness of the Medication Guide in communicating the risks of Sprix.

Please let me know if you have any questions.

Are there any updates on the mixing study?

Regards,
Jessica

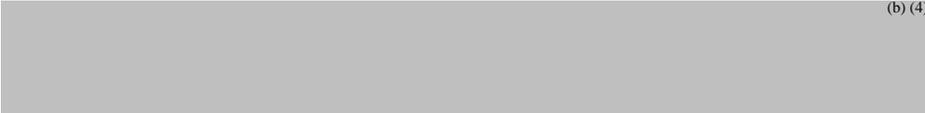
Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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

/s/

JESSICA M BENJAMIN
10/02/2009

From: [Benjamin, Jessica](#)
To:  (b) (4)
CC: [Benjamin, Jessica](#);
Subject: NDA 22-382 Information Request
Date: Wednesday, May 13, 2009 1:14:45 PM
Attachments:

Hello,

Please refer to [NDA 22-382](#) for ketorolac tromethamine. See below for an information request from our CMC review team.

1. Provide accurate and consistent batch manufacturing dates for the drug product. For example, manufacturing dates differ for drug product batch numbers 7029A, 7087, 7090, 7279 and 7304 referred to in Tables 3.2.P.5.4-1 (Analytical and Related Data for Drug Product Batches) and Tables 3.2.P.8.1-1 and 3.2.P.8.1-2 (Summary of Drug Product ICH Stability Batches/Studies).
2. Provide a single acceptance criterion for tests for a) color (L, a, b, ΔE), and b) impurities (individual and total) in the drug product specifications. Having two sets of acceptance criteria (release and stability) for tests in the drug product specification is not acceptable. Also, provide justification for the proposed acceptable ranges/levels for each test.
3. Include a test and acceptance criterion for percentage of droplets less than  (b) (4) as part of the droplet size distribution (DSD) specification for the drug product.
4. Clarify the conditions of the multi-day study, "Priming and Repriming in Various Orientations." It is unclear how samples were maintained during non-use periods (1, 2, 3, or 5 days), i.e., were samples protected from light within their secondary containers (cartons)? If samples were maintained within cartons during these studies, provide representative data from similar studies conducted with

samples exposed to ambient light during non-use periods.

5. Lower the proposed acceptance criteria for the 1-keto impurity in the drug product specifications to no more than 1.0%. Qualification data to support acceptable levels of this impurity above 1.0% has not been provided.

6. Include a test and acceptance criterion for osmolality as part of the drug product specifications as recommended in the 2002 FDA Guidance for Nasal Spray Drug Products.

7. Note: The proposed shelf life of 24 months at refrigerated (2° - 8°C) temperatures and an in-use period of one day at ambient conditions for ketorolac tromethamine is unacceptable. This is due to the level of 1-keto impurity, which has been qualified at no more than 1.0% (below the proposed level of (b) (4)). Your Shelf Life Projection graph (Figure 3.2.P.8.3.3-9) of ketorolac tromethamine shows the 1-keto degradant exceeding this limit prior to the proposed shelf life for 24 months under real time conditions (2° - 8°C). In addition, at the 18 month time point in the real time stability study, the average impurity level of the 1-keto impurity was (b) (4) for the 5 batches stored at 2° - 8°C suggesting that the acceptable level of this impurity would be exceeded at 24 months. Therefore, your proposal of a 24 month shelf life period for ketorolac tromethamine nasal spray is not warranted. A shelf life of 18 months at 2 – 8°C plus 24 hours at ambient conditions will be granted for the drug product.

Upon your receipt and review of these requests, please provide a timeline for submission of the requested information. Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research

301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: (b) (4)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22-382; Information Requests
Date: Monday, June 01, 2009 2:05:43 PM
Attachments:

Hi Bonnie,

Please refer to NDA 22-382 for ketorolac tromethamine. See below for an information request from our clinical review team.

1. For Studies 2003-01 and 2005-01, indicate how many subjects took ROX-888 and placebo after hospital discharge. Provide the average and maximum number of doses and number of days ROX-888 and placebo were taken during the outpatient period and the average total duration (inpatient and outpatient use) in doses and days for these patients. Provide a line listing of each subject including the number of doses of outpatient use, the number of days of outpatient use, the total number of days and doses of combined inpatient and outpatient use.
2. Three subjects (Subject 81238, Subject 82055 and Subject 82057) were reported to have discontinued ROX-888 due to the adverse event of elevated creatinine and BUN. However, review of the CRFs for these subjects did not reveal any worsening except for Subject 82057 who had a baseline creatinine of 1.1 mg/dl and follow-up creatinine of 1.2 mg/dl. Explain why these patients were coded as discontinuing due to elevated creatinine and provide any additional laboratory results used in making this determination.
3. In follow up to item 6 of our request from April 21, 2009 for additional information, verify that only two patients (Subject 81275 and Subject 81187) had a shift from normal creatinine defined as creatinine \leq 1.5 mg/dl at baseline to abnormal defined as creatinine $>$ 1.5 mg/dl at follow-up.
4. Provide a list of subjects that have follow-up creatinine $>$ 1.0 mg/dl AND an

increase from baseline of > 0.2 mg/dl for both IN ketorolac and placebo groups. Determine the incidence of increased creatinine in both groups.

5. Provide summary statistics (mean, median, range) for vital signs (SBP, DBP, HR) per timepoint.

Upon your receipt and review of these requests, please provide a timeline for submission of the requested information. Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: [REDACTED] (b) (4)
CC: [Benjamin, Jessica;](#)
Subject: Sprix carton/container labels
Date: Thursday, June 04, 2009 10:50:48 AM
Attachments:

Hi Bonnie,

Please refer to NDA 22-382 for ketorolac tromethamine. Do you have any mock-up carton/container labels at this point? When the tradename request was submitted, we only received basic black and white draft labels. If you are any farther along with the carton/container labels, please officially submit them to your NDA for review.

Let me know if you have any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22-382 information request
Date: Thursday, June 18, 2009 11:15:45 AM
Attachments:

Hello,

Please refer to NDA 22-382 for ketorolac tromethamine. See below for an information request from our CMC review team.

Provide labeling content using the Structured Product Labeling (SPL) stylesheet including Drug Listing Data Elements.

Upon your receipt and review of this request, please provide a timeline for submission of the requested information. Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: RE: Sprix carton/container labels
Date: Thursday, June 18, 2009 11:20:20 AM
Attachments:

Hi Bonnie,

We do not advise you to wait to submit carton/container labels. Final review of the tradename will not occur until we are within 90 days of the anticipated PDUFA date and you will only be notified if the name is found unacceptable following the re-review.

Applicants typically submit the container label and carton labeling that they intend to introduce into the marketplace (e.g., in color) with the anticipated name incorporated.

Our initial review of the container label and carton labeling can take up to thirty days. Additionally, multiple review and revision cycles may be necessary. You should plan accordingly to ensure that adequate time is allotted for such prior to the PDUFA date.

We request you submit proposed container label and carton labeling as soon as possible.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Bonnie Horner [REDACTED] (b) (4)
Sent: Friday, June 12, 2009 7:04 PM
To: Benjamin, Jessica
Subject: RE: Sprix carton/container labels

Jessica, We don't have actual mock-ups as yet. We were waiting to have final approval of our tradename, and also to complete some internal decisions based on marketing choices, shipping tests, etc., before finalizing the appearance of the labels and cartons. I understand from the group reviewing the tradename that we should not expect to receive final approval until September.

Is there a specific time within the review process by which you would like us to have finalized mock-ups available (even if still provisional based on final tradename approval)? If so, let me know and we will certainly do our best.

Thanks.
Bonnie

-----Original Message-----

From: Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
Sent: Thursday, June 04, 2009 7:51 AM
To: [REDACTED] (b) (4)
Cc: Benjamin, Jessica
Subject: Sprix carton/container labels

Hi Bonnie,

Please refer to NDA 22-382 for ketorolac tromethamine. Do you have any mock-up carton/container labels at this point? When the tradename request was submitted, we only received basic black and white draft labels. If you are any farther along with the carton/container labels, please officially submit them to your NDA for review.

Let me know if you have any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

No virus found in this incoming message.
Checked by AVG - www.avg.com
Version: 8.5.339 / Virus Database: 270.12.53/2154 - Release Date:
06/04/09 05:53:00

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22-382 (Sprix) - request for additional information
Date: Tuesday, June 30, 2009 1:52:06 PM
Attachments:

Hi Bonnie,

We have the following request for clarification from your response.

Thanks,
Jessica

1. We note that in your response dated June 23, 2009 to question #1 about the nasal exam findings, Table 1.2 (below) reports an incidence of ulceration or erosion in 6 subjects and erythema or bleeding in 10 subjects in the ROX-888 group at termination visit for Study 2005-01. Table 1.3 (below) at the 14 day follow-up visit reports an incidence of ulceration or erosion in 3 subjects and erythema or bleeding in 25 subjects. Explain how after 14 days off medication there is an increased incidence of bleeding.

2. Please clarify for Study 2003-01, if at the 14 day follow-up visit a nasal exam was performed or just the questionnaire and was this completed over the phone.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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

/s/

JESSICA M BENJAMIN
10/02/2009

From: [Benjamin, Jessica](#)
To: [REDACTED] (b) (4)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22-382 Information requests
Date: Tuesday, April 21, 2009 2:33:06 PM
Attachments:

Hi Bonnie,

Please refer to NDA 22-382 for ketorolac tromethamine. Please see below for information requests (7) from our statisticians and clinical reviewers.

1. For Study 2003-01, the Analysis Rules for Population 2 on page 6 of the file titled "Study200301_SPID24_48.doc" submitted on 16FEB2009, states:

If PI evaluations for any of these time points are missing, the dates and times with non-missing PI values provided on the lower half of Form 17 and Form 32 (i.e., 8 hours Post-Op time point) will be reviewed to see if any of those non-missing PI data can be used for the missing PI evaluations in the top half. Data from the closest non-missing time point to the scheduled missing time point will be used.

There appear to be discrepancies in the data where the above rule was not applied. For example for patient 81090, the pain intensity (PI) value at the 16 hours time point was missing and substituted by the PI evaluation done at 0.5 hour post-op Day 1. However, the assessment at the post-op Day 1 time point appears to be closer to the scheduled 16 hours time point. (The scheduled 16 hours time point was at 9:05 am on [REDACTED] (b) (6). The post-op Day 1 assessment was done at 9:00 am on [REDACTED] (b) (6). The 0.5 hour post-op Day 1 was at 9:30 am on [REDACTED] (b) (6).) Clarify the discrepancies in the data whereby the rule was seemingly not applied.

2. According to the clinical study report (CSR) for Study 2003-01, patients were assessed immediately before the study drug administration and immediately before each subsequent dose during the first 48 hours of the study, ie, at 8, 16, 24, 32, 40, and 48 hours.

However for some patients, assessments were made after doses were administered. For example for patient 81087, the 3rd dose (16 hours) was given at 8:50 am on [REDACTED] (b) (6) and the PI at 16 hours time point was evaluated at 9:45 am on [REDACTED] (b) (6), which was about 1 hour after dosing. Clarify the discrepancies.

3. Explain the need for extrapolation of morphine sulfate use in Study 2003-01 and Study 2005-01 for subjects who withdrew prematurely since these subjects were in the hospital where the exact amount of morphine sulfate used should be available from the nursing records.

4. How many patients required extrapolation of morphine sulfate use and specify which patients this affected?

5. Provide a table of total opioid usage for all subjects in Study 2003-01 and Study 2005-01 for 0 to 24 hours, 24 to 48 hours, and 0 to 48 hours to include the following column headers:

Unique Subject Identifier	Treatment allocation	PCA morphine used	Oral opioid used	Oral opioid used in morphine IV mg equivalent	Total morphine used (morphine IV equivalents)
---------------------------	----------------------	-------------------	------------------	---	---

Provide a separate table for each study. Calculate descriptive statistics for the amount of opioid used per subject in each treatment arm based on these tables.

6. Provide a list and narratives for all subjects requiring blood transfusions or with a drop of HCT greater than 30% from screening. Include the study number, patient ID, treatment arm, initial surgical

procedure, whether any follow-up surgical procedure was required, all CBC values, the number of doses of ketorolac and relationship of dosing to the other requested information. Indicate whether the follow-up CBC was done prior to or after any blood transfusion. List concomitant medication with specific attention to drugs effecting coagulation or platelet function.

7. Identify the subjects identified in Table 1.26 (page 82) of the Integrated Summary of Safety who had an increase in serum creatinine from normal to high (one was treated with active; one with placebo) and provide narratives for those subjects.

Upon your receipt and review of these requests, please provide a timeline for submission of the requested information. Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*

From: [Benjamin, Jessica](#)
To: [REDACTED] (b) (4)
CC: [Benjamin, Jessica](#);
Subject: NDA 22-382 Information Request
Date: Tuesday, April 28, 2009 11:29:55 AM
Attachments:

Good morning,

Please refer to NDA 22-382 for ketorolac tromethamine. Please see below for an information request from our CMC review team.

In NDA 22-382, Hollister-Stier Laboratories (3525 N. Regal St. Spokane, WA 99207) is identified as the drug product release and stability testing facility. However, upon inspection by FDA officials in March 2009, it was determined that Hollister-Stier is not conducting stability testing as described in the NDA. Additionally, the method "Identification, Assay, Impurities and Degradation Products" for the drug product at Hollister-Stier is identified as [REDACTED] (b) (4). Again, it was found that this method is not the method used at Hollister-Stier to generate data submitted in the NDA (for example, see table 3.2.P.5.4-1), but rather method [REDACTED] (b) (4) was used by Hollister-Stier for these purposes.

1. Verify that the information contained in NDA 22-382 is accurate with respect to the facility(ies) conducting release and stability testing of the drug product.
2. Provide the proper method used for a) Assay, and b) Impurities/Degradants determination of the drug product, as well as analytical validation data for this method

Upon your receipt and review of these requests, please provide a timeline for submission of the requested information. Do you have a status on the previous information request regarding clinical and statistical information? Feel free to contact me with any questions.

Regards,

Jessica

Jessica Benjamin

Regulatory Project Manager

Division of Anesthesia, Analgesia and

Rheumatology Products

Office of New Drugs II

Center for Drug Evaluation and Research

301-796-3924 *office*

301-796-9713 *fax*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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

/s/

JESSICA M BENJAMIN
10/02/2009



NDA 22-382

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

Roxro Pharma, Inc.
535 Middlefield Road, Suite 180
Menlo Park, CA 94025

Attention: Bonnie Horner
Regulatory Consultant

Dear Ms. Horner:

Please refer to your NDA dated December 5, 2008, received December 5, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ketorolac Tromethamine Nasal Spray.

We also refer to your December 12, 2008 correspondence, received December 15, 2008, requesting review of your proposed proprietary name, Sprix. We have completed our review of the proposed proprietary name, Sprix, and have concluded that it is acceptable.

The proposed proprietary name, Sprix, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 5, 2008 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Chris Wheeler, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0151. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

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

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/s/

Sharon Hertz
3/13/2009 02:56:38 PM
Signing for Bob Rappaport, M.D.



FILING COMMUNICATION

NDA 22-382

Roxro Pharma
535 Middlefield Road
Suite 180
Menlo Park, CA 94025

Attention: Roger Whiting, PhD
President and Chief Scientific Officer

Dear Dr. Whiting:

Please refer to your new drug application (NDA) dated December 5, 2008, received December 5, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for ketorolac tromethamine, 15% solution spray.

We also refer to your submissions dated December 12, 2008, and January 6, 8, 13, 26 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is **October 5, 2009**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September, 14, 2009.

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

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

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

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/s/

Bob Rappaport
2/17/2009 02:22:45 PM

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/s/

Jessica Benjamin
2/9/2009 04:24:09 PM

From: [Quaintance, Kim M](#)
To: [Benjamin, Jessica](#); [Duvall Miller, Beth A](#);
CC:
Subject: RE: b1/b2 issue for NDA 22-382 Letter of Reference/Letter of Authorization to Toradol Information
Date: Tuesday, January 13, 2009 5:29:40 PM
Attachments:

Jessica,

I sincerely apologize - I did not read page 2... Page 2 is a letter from Roche authorizing us to use the information in their NDAs to support the approval of the proposed intranasal product (and only that product - we can use it to support any other Roxro product.) We also have to treat the Toradol applications like a master file - we cannot communicate deficiencies/questions regarding the data themselves to Roxro (hence the paragraph regarding the confidential nature of Toradol applications.)

If there is no other information that Roxro does not own or have right of reference to that is needed to support the approval of their intranasal product, then this is a (b)(1).

Kim

From: Benjamin, Jessica
Sent: Tuesday, January 13, 2009 3:54 PM
To: Quaintance, Kim M; Duvall Miller, Beth A
Subject: RE: b1/b2 issue for NDA 22-382 Letter of Reference/Letter of Authorization to Toradol Information

Hi Kim,

Thanks for your reply. There still may be some confusion because their submission does include a letter from Roche authorizing us to cross reference their NDAs. The attachment contains their Statement of Right

of Reference and their Letter of Authorization (page 2).

<< File: letter of cross-reference to 19-645 and 19-698 Toradol.pdf >>
Thanks for your help!

Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: Quaintance, Kim M
Sent: Friday, January 09, 2009 5:01 PM
To: Benjamin, Jessica; Duvall Miller, Beth A
Subject: RE: b1/b2 issue for NDA 22-382 Letter of Reference/Letter of
Authorization to Toradol Information

Jessica,

I completely agree - it is confusing as written!

Basically, unless they have a letter from Hoffman LaRoche (current holders of the referenced Toradol applications) authorizing us to use the data in those applications to support their application, they are a (b)(2). I am guessing that what they are terming "cross reference" in the section entitled "Statement of Right of Reference", is more a statement of reliance on our previous findings of safety and effectiveness for the two products to support their application as contemplated for applications submitted pursuant to section 505 (b)(2) of the Act.

Does that help?

Kim

Kim Quaintance
Associate Director for Regulatory Affairs
Office of New Drugs
CDER/FDA
301-796-0700 (OND IO main)
301-796-0140 (direct)
301-796-9856 (facsimile)
Please note new email address
Kim.Quaintance@fda.hhs.gov

From: Benjamin, Jessica
Sent: Friday, January 09, 2009 4:19 PM
To: Quaintance, Kim M; Duvall Miller, Beth A
Subject: FW: b1/b2 issue for NDA 22-382 Letter of Reference/Letter of Authorization to Toradol Information

Hello,

Please see the email below. We assume that this application is a b (2) but their language is causing confusion with the review team. Could you confirm?

Thanks for your help.
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 office
301-796-9713 fax

From: Leshin, Lawrence
Sent: Friday, January 09, 2009 3:54 PM
To: Rappaport, Bob A; Shibuya, Robert
Cc: Wasserman, Adam; Levin, Robert A; Benjamin, Jessica
Subject: b1/b2 issue for NDA 22-382 Letter of Reference/Letter of Authorization to Toradol Information

Attached is a copy of the Letter of Reference to Toradol NDAs. I used the term letter of authorization in my presentation, perhaps inappropriately.

They referred to the letters to use the DMF's as "Letters of Authorization," but letters to reference the Toradol information as "Letters of Reference."

Hopefully, you can make the determination as what they really are so that the b1/b2 issue can be clarified.

Steve

<< File: letter of cross-reference to 19-645 and 19-698 Toradol.pdf
>> letter is on page 2

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JESSICA M BENJAMIN
10/02/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **Sylvia Gantt/Jim McVey New Drug Microbiology Staff OC/OO/CDER/OPS/NDMS**

FROM (Name, Office/Division, and Phone Number of Requestor): **Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of Danae Christodoulou/Joseph Leginus**

DATE
January 13, 2009

IND NO.

NDA NO.
22-382

TYPE OF DOCUMENT
NDA submission

DATE OF DOCUMENT
December 5, 2008

NAME OF DRUG
Ketorolac Tromethamine

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
Analgesics

DESIRED COMPLETION DATE
May 1, 2009

NAME OF FIRM: **Roxro Pharma Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology consultation is requested to review the specifications for this product and the manufacturing process.

SIGNATURE OF REQUESTOR
{See appended electronic signature page }

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Ali Al-Hakim
1/13/2009 09:40:08 PM

From: [Benjamin, Jessica](#)
To: [REDACTED] (b) (4)
CC:
Subject: NDA 22-382 (Ketorolac Tromethamine Nasal Spray)
Date: Wednesday, January 07, 2009 11:24:03 AM
Attachments:

Hi Bonnie,

Thank you for your voice mail. To answer your question, three copies of Form FDA 3674 that you referenced in your message are fine.

After initial review of NDA 22-382, we have the following information requests:

- Submit the SAS transport files
- Submit the proposed label in a Word file

Feel free to contact me with any questions or concerns. I look forward to working with you in the future.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22-382 Information requests
Date: Friday, January 16, 2009 10:57:21 AM
Attachments:

Hi Bonnie,

Please refer to NDA 22-382 for ketorolac tromethamine. As a follow-up to our phone conversation yesterday, I have attached the information requests from our statisticians and clinical reviewers.

1. You submitted SDTM datasets which generally conform to a specific format. The format may not include variables denoting the efficacy assessments from the case report forms. For Studies 2001-03, 2003-02, 2003-05, and 2005-01, we therefore request that you submit raw datasets for all efficacy assessments taken from the case report form and analysis-ready datasets which should be derived from the raw data. For each study, at least two analysis-ready datasets should be submitted. One should contain subject-level efficacy (i.e. one record per subject), and another analysis-ready dataset should contain assessment-level efficacy (i.e. one record per subject per assessment time -- example, subject 1, pain intensity difference at time 0 is 5, pain intensity difference at time 0.5 hours is 4, etc...). The analysis-ready datasets should include all derived variables used to generate the results presented in the study reports. Most importantly, your primary and secondary endpoints should be included.

Provide a data definition file for these datasets with detailed information on how the variables are derived (i.e. formula) and which variables in the raw data or case report form were used in the calculation of the variables.

2. Perform analyses on SPID 24 and SPID 48 using the same analytical approaches applied to your primary endpoint (i.e. SPID 6)

3. We note that you have only submitted Amendment 3 for Study 2003-01. Provide the initial version of Study 2003-01 and protocol amendments 1 and 2 for this study.

4. Provide a line listing of patients discontinued from study drug due to an adverse event. The table can be in a similar format to Table 1.23 (SAEs) in the ISS.

5. We note that you have only submitted Amendment 3 for Study 2003-01. Provide the initial version of Study 2003-01 and protocol amendments

1 and 2 for this study.

6. Provide a line listing of patients discontinued from study drug due to an adverse event. The table can be in a similar

format to Table 1.23 (SAEs) in the ISS.

Upon your receipt and review of these requests, please provide a timeline for submission of the requested information. Feel free to contact me with any questions.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9713 *fax*

From: [Benjamin, Jessica](#)
To: ["Bonnie Horner";](#)
CC: [Benjamin, Jessica;](#)
Subject: NDA 22-382 - Information requests (2)
Date: Friday, January 16, 2009 2:26:33 PM
Attachments:

Hi Bonnie,

I also have the following information requests from our chemistry reviewers for NDA 22-382:

1. Provide the contact information (name, telephone, email) for the following site in (b) (4) that performs (b) (4) of the packaged nasal spray pumps.

(b) (4)

2. Provide two (2) spray/pump systems used in the Phase 3 clinical trials.
3. Provide two (2) proposed commercial spray/pump systems.

We appreciate your prompt attention to these requests.

Regards,
Jessica

Jessica Benjamin
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of New Drugs II
Center for Drug Evaluation and Research
301-796-3924 *office*

301-796-9713 *fax*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JESSICA M BENJAMIN
10/02/2009

MEMORANDUM

Date: 01-Oct-2009

From: Joseph Leginus, Review Chemist, Branch II/DPA I/ONDQA

To: NDA 22-382, Sprix (ketorolac tromethamine) Nasal Spray

Through: Ali Al-Hakim, Branch Chief, Branch II/DPA I/ONDQA

Subject: Not Approvable

Background:

- The Drug Product manufacturer for NDA 22-382, Hollister Stier Laboratories, was inspected for GMP on 1/6/09 to 1/13/09. As a result, an FDA 483 was issued for: stability failures, initiation of practices prior to change approval by the QC Unit, no formal procedure for maintaining segregated vials for non-conforming material, no formal documentation of retention sample review, increase in a product's hold time between [REDACTED] ^{(b) (4)} without formal approval from CBER, and Annual Product Reviews were not reviewed by the Quality Unit in a timely manner. The most recent inspection was conducted on 6/19/08 to 7/2/08 and resulted in an FDA 483 for failure to thoroughly review unexplained discrepancies, and a manufacturing process was not thoroughly evaluated to identify and correct possible sources of variability in critical process parameters. Because these issues have not been resolved by Hollister Stier, on 04-Aug-2009, the Office of Compliance made a recommendation of Withhold for the facility.
- On 08-Sep-2009, an overall recommendation of Withhold was made by the Office of Compliance for NDA 22-382 due to the unresolved GMP issues associated with the drug product manufacturing facility at Hollister Stier Laboratories.

Conclusion:

- NDA 22-382 is considered to be Not Approvable from a CMC perspective at this time due to the Office of Compliance overall recommendation of Withhold based on the non-GMP status of the drug product manufacturing facility.

Joseph Leginus, Ph.D.
Review Chemist

Ali Al-Hakim, Ph.D.
Branch II Chief, ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

JOSEPH M LEGINUS
10/01/2009

ALI H AL HAKIM
10/01/2009



NDA 22,382

NDA ACKNOWLEDGMENT

Roxro Pharma, Inc.
535 Middlefield Road, Suite 180
Menlo Park, CA 94025

Attention: Roger Whiting, Ph.D.
President and Chief Scientific Officer

Dear Dr. Whiting:

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

Name of Drug Product: Ketolorac tromethamine
nasal spray, 15% solution

Date of Application: December 5, 2008

Date of Receipt: December 5, 2008

Our Reference Number: NDA 22-382

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 3, 2009, in accordance with 21 CFR 314.101(a).

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

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must

be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

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

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

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

If you have any questions, call me at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

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

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/s/

Jessica Benjamin
12/18/2008 02:31:42 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 022382 Class 2 resubmission	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Sprix Established/Proper Name: ketorolac tromethamine Dosage Form: nasal spray		Applicant: Roxro Pharma Inc. Agent for Applicant (if applicable):
RPM: Jessica Benjamin		Division: DAAP
<p>NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>May 20, 2010</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR - 10/5/2009
❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p>Comments:</p>	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	included
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Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR 10/5/2009 AP 05/14/2010
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Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	11/20/2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	11/20/2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	4/18/2010
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	3/13/2009 3/4/2009; 8/26/2009; 3/30/2010
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 9/8/09; 4/14/10 <input checked="" type="checkbox"/> DRISK 10/5/2009 <input checked="" type="checkbox"/> DDMAC 8/21/2009 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	Filing Review – 9/10/2009
❖ 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC 8/26/2009 If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Ack ltr – 12/18/2008 Filing ltr 0 2/17/2009 Tradename accepted – 3/13/2009 IR letter – 9/24/2009 Resubmission Ack ltr – 12/4/2009

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 12/4/09

❖ Internal memoranda, telecons, etc.	1/13/2009 – b1/b2 issue
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 10/4/2007
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 5/17/2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Dep. Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/5/2009; 5/14/10
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/27/2009
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1 – 10/1/2009
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	8/27/2009
• Clinical review(s) (<i>indicate date for each review</i>)	8/20/2009
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical Review – 8/20/2009
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	12/5/2008; 9/30/2009; 11/20/2009
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	9/29/2009
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None 10/5/2009 - DRISK
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 7/29/2009

⁵ Filing reviews should be filed with the discipline reviews.
Version: 12/4/09

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/7/2009
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/14/2009
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/12/2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/9/2009 (MHT)
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/7/2009; 1/26/2010
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 10/2/2009
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	CMC review 8/7/2009
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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