

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-011

CORRESPONDENCE



Boehringer Ingelheim
Roxane Laboratories

August 31, 2000

Roxane Laboratories, Inc.

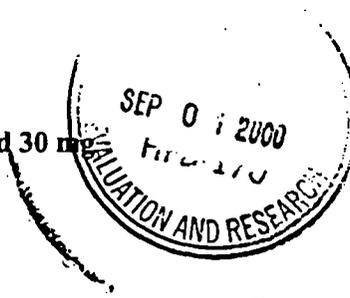
Cynthia McCormick, M.D.
Director, Div. of Anesthetic, Critical Care & Addiction Drug Products
Center for Drug Evaluation and Research, HFD-170
Food and Drug Administration
Park Lawn Building, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

SUPPL NEW CORRESP

ATTENTION: Judit Milstein, Regulatory Project Manager

SUBJECT: NDA #21-011 - Oxycodone HCl Tablets, 15 mg and 30 mg
GENERAL CORRESPONDENCE



Dear Dr. McCormick,

Attached please find color copies of the following Roxicodone™ Tablet container labeling:

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

- 100-count bottle label, 15 mg (6 copies)
- 100-count bottle label, 30 mg (6 copies)
- 25-count reverse-number card, 15 mg (6 copies)
- 25-count reverse-number card, 30 mg (6 copies)

copy taken for Action book
[/S/]
8/21/00-

The only change made to the previously submitted version is removal of the _____ statement.

I have also included 6 copies of the blister-backing for the reverse-numbered card as well as a copy of the labeling (package insert) that has my signature on the front indicating our acceptance.

Please do not hesitate to contact the undersigned if there are any additional questions or requests (phone 614-241-4134, fax 614-276-8061).

Sincerely,

Robert W. Pfeifer, M.S., R.Ph.
Associate Director, Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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6 Draft Labeling Page(s) Withheld

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II**



TO: Bob Pfeifer/Roxane Laboratories

Phone Number: (614) 241-4134

Fax Number: (614) 276-8061

FROM: Judit Milstein, Regulatory Project Manager

**DIVISION OF ANESTHETIC, CRITICAL CARE AND
ADDICTION DRUG PRODUCTS**

**CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857**

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 18 Date: 8-31-00

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**COMMENTS: Find enclosed the copy of the approval letter for
NDA 21-011, Roxicodone.**



Boehringer Ingelheim
Roxane Laboratories

August 31, 2000

Roxane Laboratories, Inc.

Cynthia McCormick, M.D.
Director, Div. of Anesthetic, Critical Care & Addiction Drug Products
Center for Drug Evaluation and Research, HFD-170
Food and Drug Administration
Park Lawn Building, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

ATTENTION: Judit Milstein, Regulatory Project Manager

**SUBJECT: NDA #21-011 – Oxycodone HCl Tablets, 15 mg and 30 mg
GENERAL CORRESPONDENCE**

Dear Dr. McCormick,

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

We write in follow-up to our phone conversation and your electronic mail message on 31-August-2000 concerning Phase IV commitments for Roxicodone™ Tablets (NDA 21-011). Based on those discussions, Roxane commits to the following:

- 1) Roxane will conduct mutagenicity studies for *Salmonella typhimurium*-*E. coli*/mammalian-chromosome reverse mutation (with confirmatory assay), mouse lymphoma forward mutation, and *in vivo* mouse micronucleous assays. Final reports will be submitted within 3 months following approval of NDA 21-011.
- 2) Roxane will conduct carcinogenicity studies in either two-year bioassays with two species or one rat two-year bioassay and one alternative model. Protocols for these studies will be submitted for FDA review within 2 months following approval. Assuming the studies are reviewed by the Agency in a timely fashion, the studies will initiated within 6 months following approval. Final reports for the studies will be submitted within 42 months following approval of NDA 21-011.

Roxicodone Tablets, 15 & 30 mg
NDA 21-011
08/31/00



Boehringer Ingelheim
Roxane Laboratories

Please do not hesitate to contact the undersigned if there are any additional questions or requests (phone 614-241-4134, fax 614-276-8061).

Sincerely,

Robert W. Pfeifer, M.S., R.Ph.
Associate Director, Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL



Boehringer Ingelheim
Roxane Laboratories

Telefax

Roxane Laboratories, Inc.

Judit Milstein
Regulatory Project Manager, CDER, HFD-170
301-827-7440 (phone)
301-443-7068 (fax)

Page: 1 of 7 (including cover)

August 29, 2000

**NDA 21-011 General Correspondence - Response to Request
for Additional Information**

Robert W. Pfeifer, M.S., R.Ph.
Telephone 614-241-4134
Telefax 614-276-0321
E-Mail bpfeifer@col.boehringer-
ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-6000

Dear Judit,

Per your verbal request on 29-August-2000, enclosed you will find revised label containers for the following packages:

- NDC 0054-8658-24 (15 mg, reverse numbered unit dose card)
- NDC 0054-8665-24 (30 mg, reverse numbered unit dose card)
- NDC 0054-4658-25 (15 mg, bottle label)
- NDC 0054-4665-25 (30 mg, bottle label)

The changes were as follows:

1. Deleted _____ and moved _____ in it's place.
2. Increased size of generic name as well as the Rx only.
3. Matched the temperature storage statement to match the package insert.

The bottle labels contain both an actual size and a 200% enlargement on the same page. The reverse numbered cards contain an actual size as well as a separate page for the 200% enlargement. I will send hard copies to get there tomorrow. Let me know if you need anything else on these container labels.

Thanks so much,

Bob Pfeifer

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6 Draft Labeling Page(s) Withheld



Boehringer Ingelheim
Roxane Laboratories

Telefax

Judit Milstein
Regulatory Project Manager, CDER, HFD-170
301-827-7440 (phone)
301-443-7068 (fax)

Roxane Laboratories, Inc.

Page: 1 of 4 (including cover)

August 24, 2000

NDA 21-011 General Correspondence - Response to Request for Additional Information

Robert W. Pfeifer, M.S., R.Ph.
Telephone 614-241-4134
Telefax 614-276-0321
E-Mail bpfeifer@col.boehringer-
ingelheim.com

Dear Judit,

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

As promised, here are samples of the unit dose blister backings showing the location of the lot and expiration date. I apologize that this appears not to have been part of the original application. I will send the hard copy today to arrive tomorrow morning.

We are still hoping to sit down and briefly discuss the package insert labeling whenever you folks are available. Let me know.

Thanks so much,

Bob Pfeifer

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Boehringer Ingelheim
Roxane Laboratories

August 24, 2000

Roxane Laboratories, Inc.

Cynthia McCormick, M.D.
Director, Div. of Anesthetic, Critical Care & Addiction Drug Products
Center for Drug Evaluation and Research, HFD-170
Food and Drug Administration
Park Lawn Building, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

ATTENTION: Judit Milstein, Regulatory Project Manager

**SUBJECT: NDA #21-011 – Roxycodone™ Tablets, 15 mg and 30 mg
GENERAL CORRESPONDANCE – Response to Request
for Information**

Dear Dr. McCormick,

Per your verbal request on 23-August-2000, enclosed you will find blister backing artwork for the following packages:

- NDC 0054-8658-24 (15 mg, reverse numbered unit dose card)
- NDC 0054-8665-24 (30 mg, reverse numbered unit dose card)

Each sample includes actual size artwork as well as one enlargement for ease of review. This information is printed onto the back of each unit dose tablet blister. It contains the lot number and expiration date for the product. We apologize for not including this as part of the original submission. This should clear up the question of where the lot and expiration date are printed on the unit dose package.

Please do not hesitate to contact the undersigned if there are any additional questions or requests (phone: 614-241-4134; fax: 614-276-8061).

Sincerely,

Robert W. Pfeifer, M.S., R.Ph.
Associate Director, Drug Regulatory Affairs

BEST POSSIBLE COPY

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

2 Draft Labeling Page(s) Withheld



Boehringer Ingelheim
Roxane Laboratories

Telefax

Judit Milstein
Regulatory Project Manager, CDER, HFD-170
301-827-7440 (phone)
301-443-7068 (fax)

Roxane Laboratories, Inc.

Page: 1 of 4 (including cover)

August 24, 2000

NDA 21-011 General Correspondence - Response to Request for Additional Information

Robert W. Pfeifer, M.S., R.Ph.
Telephone 614-241-4134
Telefax 614-276-0321
E-Mail bpfeifer@col.boehringer-
ingelheim.com

Dear Judit,

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

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Bob Pfeifer

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Boehringer Ingelheim
Roxane Laboratories

August 24, 2000

Roxane Laboratories, Inc.

Cynthia McCormick, M.D.
Director, Div. of Anesthetic, Critical Care & Addiction Drug Products
Center for Drug Evaluation and Research, HFD-170
Food and Drug Administration
Park Lawn Building, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

ATTENTION: Judit Milstein, Regulatory Project Manager

**SUBJECT: NDA #21-011 – Roxycodone™ Tablets, 15 mg and 30 mg
GENERAL CORRESPONDANCE – Response to Request
for Information**

Dear Dr. McCormick,

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

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Please do not hesitate to contact the undersigned if there are any additional questions or requests (phone: 614-241-4134; fax: 614-276-8061).

Sincerely,

Robert W. Pfeifer, M.S., R.Ph.
Associate Director, Drug Regulatory Affairs

2 Draft Labeling Page(s) Withheld

[_____]

Fax Document

Date: 31 Aug 00

To: Dr. Judith Melstein
DACCADP

Fax: 301-443-7068

Phone:

From: [_____]
[_____]

Fax: _____

Phone: [_____]

Re: NDA 21-011

Pages: 3 total

Dr. Melstein,

Please accept my apologies. I tried to FAX this to you yesterday afternoon, but it didn't go through. You should receive it today via Fed Ex.

[_____]

APPEARS THIS WAY
ON ORIGINAL

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FAX TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG
PRODUCTS

5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: Bob Pfeifer/Roxane Labs Date: 8/30/00 —

Fax #: (614) 276-8061

Pages: 14

(INCLUDING THIS COVER SHEET)

From: (614) 241-~~4~~34

Subject: ~~Final~~ Draft Package Insert

Comments: Find enclosed the draft of Package Insert.
If agreed, please initialize and fax back
Thanks - [/S/] —

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content of this communication is not authorized. If you have received this document in error, please
notify us immediately by telephone and return it to us at the above address.

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Return Receipt Requested

30 August 2000

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Document Control Room #9B23
CDER, FDA
5600 Fishers Lane
Rockville, Maryland 20857

Re: **NDA 21-011**
Amendment 15.01
ROXICODONE™ Tablets, 15mg and 30mg
Safety update report

ATTN: Judith Milstein, Regulatory Project Manager

Dear Dr. McCormick:

In accordance with 21 CFR 314.50 (d) (5) (vi), a safety update report was requested. On behalf of Roxane Laboratories, Inc., this letter is submitted to meet that requirement.

The following table reviews the significant events relevant to the safety update:

Date	Event	Comment
29 Sep 98	NDA 21-011 submitted	.
11 Feb 99	4-month safety update submitted	No new information provided
30 Sep 99	Protocol XIR0199 (RL-001) submitted to IND 46,618, SS021	Single-dose study in dental pain model to evaluate the efficacy of one strength of oxycodone extended-release and two strengths of immediate-release oxycodone (15 and 30 mg).
14 Oct 99	Protocol XIR0299 submitted in IND 46,618, SS023	Bioequivalence study
27 Jan 00	Protocol XSR0999 submitted in IND 46,618, SS024	Single-dose study in dental pain model to evaluate the efficacy of 4 strengths of oxycodone extended-release. Immediate-release oxycodone (30 mg) serves as reference group.
28 Feb 00	Response to approvable letter	Included XIR0299 report

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Date	Event	Comment
10 Mar 00	3 mutagenicity protocols submitted for approval (XIRT100, 200 and 300)	
30 Jun 00	2 developmental toxicity studies (XIRT0399 and 0499) submitted to IND 46,518, SS029	

Roxane's response of 28 Feb 00 to the approvable letter includes and summarizes all the available safety data. To the best of our knowledge, there are no additional data to include in a safety update report except for the two clinical studies listed above (XIR0199 and XSR0999). Both XIR0199 and XSR0999 have been unblinded and are pending finalization of the study reports. No serious adverse events were reported for either study. Since these studies involved single-doses in a dental patient population, Roxane does not believe that the data in these studies will change the safety profile of oxycodone. Roxane commits to provide these study reports as part of the "rolling NDA" for extended-release oxycodone tablets (NDA 20-932) once the reports are available in the next few months.

No additional information from other sources has manifested which would alter the safety conclusions submitted in NDA 21-011 or its amendments.

Should you have any questions, please feel free to contact me at _____

Sincerely,

xc: Roxane Laboratories, Inc.

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Boehringer Ingelheim
Roxane Laboratories

August 24, 2000

Roxane Laboratories, Inc.

Cynthia McCormick, M.D.
Director, Div. of Anesthetic, Critical Care & Addiction Drug Products
Center for Drug Evaluation and Research, HFD-170
Food and Drug Administration
Park Lawn Building, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

ATTENTION: Judit Milstein, Regulatory Project Manager

**SUBJECT: NDA #21-011 – Oxycodone HCl Tablets, 15 mg and 30 mg
GENERAL CORRESPONDENCE**

Dear Dr. McCormick,

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

We write in follow-up to our two teleconferences (4-August-2000 and 22-August-2000) and our letter dated 8-August-2000 concerning the proposed proprietary name of Roxicodone™ Tablets for our pending application NDA 21-011. In the teleconferences, the Agency expressed a desire to have Roxane re-evaluate the use of the name "Roxicodone" due to the Agency's concern regarding potential confusion with the root name "Rox" in several of our analgesic products. We appreciate the opportunity to have a continuing discussion on the subject.

Roxane is a company that has been built on caring for the health and welfare of our patients. Our introduction of unit dose packaging in the early 1980's was an important and vital step towards reducing medication errors and providing a safe and convenient way to dispense and administer individualized patient doses in an institutional setting. Roxane has been a leader in supporting the palliative care movement here in the United States. To that end, we have become an established and well-recognized name for providing safe and effective medications designed to ease the pain and suffering of those in need of symptom management. Our products and services have helped countless healthcare professionals and patients cope with the challenges of receiving an improved quality of life during difficult struggles with often terminal diseases.

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Roxicodone Tablets, 15 & 30 mg
NDA 21-011
08/24/00



Boehringer Ingelheim
Roxane Laboratories

We share the Agency's concern for public health and are committed to minimizing to the extent possible any misadventures in the medication delivery system involving our products, and specifically Roxicodone in the case of this pending application. In coming to a decision about the proprietary name of our oxycodone hydrochloride tablets, we need to carefully weigh the potential benefits and risks associated with each option - leaving the Roxicodone™ name as it has been in the marketplace for nearly 20 years or changing it to something else.

As you are aware, we have transmitted an internal review of complaints and adverse events associated with Roxicodone Tablet name confusion in our August 8, 2000 letter. That review, comprising nearly 20 years of safety data that we have compiled regarding products bearing the Roxicodone name, turned up only three complaints and one report of a medication error (with no associated adverse events) that involved Roxicodone Tablet name confusion. We also have reviewed reports submitted directly to the Agency and transmitted to us on August 23, 2000. That information included only three additional reports involving Roxicodone Tablets, however, none of those reported a problem with name confusion.

Given the low rate of complaints and adverse event reports involving Roxicodone Tablet name confusion, it is our strong belief that changing the name would create a greater negative impact on public health than keeping the name Roxicodone. As stated previously, the name Roxicodone is well entrenched in the minds of both patients and healthcare practitioners. If the name was removed from the marketplace and replaced with something else, considerable confusion would result and this could ultimately jeopardize the timely provision of much-needed pain medication to those who depend on it. Patients who have long relied upon and trusted the Roxicodone name may become confused as to why they are suddenly getting a new medication. Physicians will write prescriptions for Roxicodone Tablets and, when no such product is available, pharmacists will likely require the physician to issue a new written prescription due to the strict requirements relating to Schedule II prescriptions. Also, because Schedule II narcotics must be ordered on a DEA Form 222 in a precise manner without error, ordering an unavailable product will likely require reissuance of corrected DEA forms and cause delays in fulfilling orders from wholesalers and pharmacists.

In summary, we believe that the public health risks of changing the currently marketed Roxicodone Tablet name outweigh the potential benefits given a thorough review of available data. However, to address the Agency's concerns, and to help avoid any future medication misadventures involving our products, we propose the following:

BEST POSSIBLE COPY

Roxicodone Tablets, 15 & 30 mg
NDA 21-011
08/24/00



Boehringer Ingelheim
Roxane Laboratories

Please do not hesitate to contact the undersigned if there are any additional questions or requests in the meantime (phone 614-241-4134, fax 614-276-8061).

Sincerely,

Robert W. Pfeifer, M.S., R.Ph.
Associate Director, Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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Boehringer Ingelheim
Roxane Laboratories

Telefax

Judit Milstein
Regulatory Project Manager, CDER, HFD-170
301-827-7440 (phone)
301-480-8682 (fax)
443-7068

Page: 1 of 5 (including cover)

Roxane Laboratories, Inc.

August 24, 2000

**NDA 21-011 General Correspondence - Response to 22-August-2000
Telecom**

Robert W. Pfeifer, M.S., R.Ph.
Telephone 614-241-4134
Telefax 614-276-0321
E-Mail bpfeifer@col.boehringer-
ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

Dear Judit,

As promised, here is our response to the 22-August-2000 Teleconference concerning the "Roxicodone" name. I will send the hard copy today to arrive tomorrow morning.

As I have said in the letter, we would like to maintain an open dialog on this issue prior to the targeted user fee action date of 8/29/00. Please let me know if you need anything else on this issue.

Thanks,

Bob Pfeifer

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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG
PRODUCTS

5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: Bob Pfeifer

Date: 8/23/00

Fax #: 1-614-276-8061

Pages: 4

(INCLUDING THIS COVER SHEET)

From: Judith Kulster

Subject: Label Draft

Comments: Dr. Mc. Couch will be out of the office Friday & Monday. Let's try to work with this label as much as we can tomorrow is possible.

Thanks [JS]

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PRODUCTS

5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: Bob Pfeifer
Fax #: 301-276-8981

Date: 08-23-02
Pages: 20
(INCLUDING THIS COVER SHEET)

From: Judith Miltner

Subject:

Comments:

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notify us immediately by telephone and return it to us at the above address.

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO 0448
CONNECTION TEL 4916142768061
SUBADDRESS
CONNECTION ID
ST. TIME 08/23 11:33
USAGE T 02'47
PGS. SENT 30
RESULT OK



**FAX
TRANSMISSION**
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG
PRODUCTS

5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

Date: 08-23-00
Pages: 27 (INCLUDING THIS COVER SHEET)

To: Bob Pfeifer
Fax #: 614-276-8061
From: Judith Milstein

Subject:

Comments:

PLEASE CALL (301) 827-7410 IF RE-TRANSMISSION IS NECESSARY
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5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: *Rob Pfeifer* Date: *08-23-2000*
Fax #: *614-276-8061* Pages: *30*
(INCLUDING THIS COVER SHEET)
From: *Judith Mulstein*
Subject:
Comments: *To Roxane Laboratories*

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Milstein



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-011

Roxane Laboratories, Inc.
P. O. Box 16532
Columbus, Ohio 43216-6532

AUG 15 2000

Attention: Robert W. Pfeifer, M.S., R. Ph.
Manager, Drug Regulatory Affairs

Dear Mr. Pfeifer:

Please refer to the telecon between representatives of your firm and FDA on August 4, 2000.

The purpose of the telecon was to request that Roxane Laboratories reconsider the proposed proprietary name Roxicodone® for the pending oxycodone hydrochloride (NDA 21-011) application.

A copy of our minutes of that telecon is enclosed. These minutes are the official minutes of the telecon. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

[/S/]

Judit Milstein
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Center for Drug Evaluation and Research

Enclosure: Minutes of the telecon

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: August 4, 2000

APPLICATION NUMBER: NDA 21-011 Roxicodone (oxycodone hydrochloride)
immediate release Tablets

BETWEEN:

Name: Robert W. Pfeifer, M.S., R.Ph., Manager, Drug Regulatory Affairs
Ann Maloney, Director, Drug Regulatory Affairs, Approved Products
Michael Schobelock, Pharm.D., Associate Director, Medical Affairs
Ann Kline, B.A., Clinical Research Manager
Bence Boelcskev, Ph. D., Director, Project Management
Phone: (614) 276-4000 (Extension 2502)
Representing: Roxane Laboratories

AND

Name: Cynthia G. McCormick, M.D., Director, Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Bob Rappaport, M.D. Deputy Director
Judith Milstein, Regulatory Project Manager
Jerry Phillips, R.Ph., Associate Director for Medication Error Prevention (OPDRA),
HFD-400
Peter Tam, R. Ph., Safety Evaluator, HFD-400

SUBJECT: Request for re-evaluation of the proposed proprietary name Roxicodone® for the pending application (NDA 21-011) for oxycodone hydrochloride.

BACKGROUND: The Division consulted OPDRA, to conduct a post-marketing and pre-marketing review on the reported confusion with the root name "Rox" utilized for the analgesic products manufactured by Roxane Laboratories.

DISCUSSION: Dr. McCormick expressed the Division's concern about the frequency of medical errors that occurred between several products that share the "Rox" root name. In that context, three main areas are identified:

- Confusion due to similar packaging and labeling
- Confusion between "mL" and "mg" in the dispensing of Roxanol
- Confusion among the products that share the root name "Rox"

The Division is also aware of communication between the Office of Generic Drugs and Roxane Laboratories, with respect to the medical errors occurring between Roxanol, Roxicet tablets, and Roxicet oral solution, and more specifically to the suggestion to add color to differentiate the products within the "Rox" family.

Based on the available medical errors information, Dr. McCormick indicated that it would be the Division's preference that Roxane Laboratories take this opportunity to choose a new name for their new oxycodone hydrochloride product.

Mr. Pfeiffer replied that Roxane Laboratories will begin internal discussions to address Dr. McCormick's suggestion.

OUTCOMES: Roxane Laboratories will provide the following information within a week:

1. All reports of medical errors, regardless of outcome, including the customer complaints file, for all "Roxi" products, going back to 1992.
2. Mock-up copies for the proposed colored carton and container labels for Roxane's oxycodone hydrochloride pending application.
3. A clear rationale for their refusal to change the name, in the event that Roxane Laboratories decides to pursue the name Roxicodone for their pending application.

[/S/]

Judith Milstein, Regulatory Project Manager

[/S/]

Cynthia McCormick, M.D., Division Director concurrence

**APPEARS THIS WAY
ON ORIGINAL**

cc: Original NDA
HFD-170/Div. File
HFD-170/Judit Milstein/C. Schumaker
HFD-170/B.Rappaort
HFD-400/Jerry Phillips/Peter Tam

[S/]
8/15/00.

Drafted by: JM 8-9-00

Initialized by: P. Tam 8-9-00, J. Phillips 8-10-00, B.Rappaort 8-9-00, C. Schumaker 8-14-00

Final

File:N:\CSO\MILSTEIN\N21011 Roxicodone\minutes of telecon 5-24-00 sent.doc

TELECON

APPEARS THIS WAY
ON ORIGINAL

Telefax**Boehringer Ingelheim
Roxane Laboratories**

Judit Milstein
Regulatory Project Manager, CDER, HFD-170
301-827-7440 (phone)
301-480-8682 (fax)

Roxane Laboratories, Inc.

Page: 1 of 7

August 11, 2000

NDA 21-011 General Correspondance - Response to 4-August-2000 Telecon

Robert W. Pfeifer, M.S., R.Ph.
Telephone 614-261-6134
Telefax 614-276-0321
E-Mail bpfeifer@col.boehringer-
ingelheim.com

Dear Judit,

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

As promised, here is our response to the 4-August-2000 Teleconference concerning the "Roxicodone" name. I will send the hard copy today to arrive Monday morning. Please let me know if you need anything else.

Thanks,

Bob Pfeifer

PRIVILEGED AND CONFIDENTIAL: Information intended only for the addressee(s) named above. If the reader of this message is not the intended recipient or the employee or the agent responsible for delivering the message to the intended recipient(s) please note that any dissemination, distribution or copying of this communication is strictly prohibited. Anyone who receives this communication in error should notify the sender immediately by telephone and return the original message to the sender at Roxane Laboratories, Inc., 1809 Wilson Road, Columbus, OH 43216.

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Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Cynthia McCormick, M.D.
Director, Div. of Anesthetic, Critical Care & Addiction Drug Products
Center for Drug Evaluation and Research, HFD-170
Food and Drug Administration
Park Lawn Building, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

August 09, 2000

ATTENTION: Judit Milstein, Regulatory Project Manager
FAX: 301-480-8682 / 301-443-7068

SUBJECT: NDA #21-011 – Roxycodone™ Tablets, 15 mg and 30 mg
GENERAL CORRESPONDENCE – Response to Request for
Information

Robert W. Pfeifer, M.S., R.Ph.
Telephone 614.241.4134
Telefax 614.276.8061

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Dr. McCormick:

In response to your voicemail on 9-August-2000, please see below the names and titles of those from Roxane who attended the 4-August-2000 teleconference.

Bob Pfeifer, M.S., R. Ph. – Associate Director, Drug Regulatory Affairs
Ann Maloney – Director, Drug Regulatory Affairs – Approved Products
Mike Schobelock, PharmD – Associate Director, Medical Affairs
Ann Kline, B.A. – Manager, Medical Affairs
Bence Boelskevny, Ph.D. – Director, Project Management

Please do not hesitate to contact the undersigned if there are any additional questions or requests (phone: 614-241-4134; fax 614-276-8061).

Sincerely,

Robert W. Pfeifer, M.S., R.Ph.
Associate Director, Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL



Boehringer Ingelheim
Roxane Laboratories

August 8, 2000

Roxane Laboratories, Inc.

Cynthia McCormick, M.D.
Director, Div. of Anesthetic, Critical Care & Addiction Drug Products
Center for Drug Evaluation and Research, HFD-170
Food and Drug Administration
Park Lawn Building, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

ATTENTION: Judit Milstein, Regulatory Project Manager

**SUBJECT: NDA #21-011 – Roxicodone™ Tablets, 15 mg and 30 mg
GENERAL CORRESPONDANCE – Response to Request
for Information**

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone: (614) 276-6000
Telefax: (614) 274-0974

Dear Dr. McCormick,

As per your request in our 4-August-2000 teleconference, Roxane Laboratories is providing additional information concerning the proposed proprietary name of Roxicodone™ for our pending application NDA 21-011. In the teleconference, the Agency expressed their desire to have Roxane reconsider the use of the name "Roxicodone" in an attempt to minimize potential prescribing and dispensing errors.

We are somewhat concerned that this issue is just now coming to the forefront, so close to the target date for an end-of-August action letter. So much work has already been done in terms of marketing and manufacturing preparations that a change now would greatly hamper our launch efforts and delay the release of these much-anticipated dosage strengths to the palliative care marketplace. This New Drug Application (NDA 21-011) was originally filed on 29-September-1998, and we received an approvable letter on 23-September-1998. Nowhere in prior discussions, either verbally or in the approvable letter, was this issue raised. Also, Roxane's NDA 20-932 for sustained-released oxycodone was approved on 26-October-1998 with the proprietary name Roxicodone™ SR, and the name was not an issue during those deliberations. Roxane is very cognizant of the potential for name confusion, and

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Roxicodone Tablets, 15 & 30 mg
NDA 21-011
08/11/00



Roxicodone™ has a long marketing history at Roxane Laboratories. Currently, we market the following products:

- Roxicodone™ (Oxycodone HCl Tablets USP), 5 mg
- Roxicodone™ (Oxycodone HCl Oral Solution USP), 5 mg/5mL
- Roxicodone™ Intenso™ (Oxycodone HCl Oral Solution, Concentrate), 20 mg/mL

All of these products have been successfully marketed for nearly 20 years under the Roxicodone trademark. Both patients and healthcare practitioners are well acquainted with the Roxicodone name, and it has become an established brand in the pain and palliative care environment. We view the addition of the 15 mg and 30 mg strengths as simply a line extension to a product that has been marketed since 1982.

At the request of the Agency, we have reviewed our complaint and adverse event databases for instances of name confusion. Attachment 1 contains all complaints concerning the "Rox" prefix products since 1993. Other than a general complaint concerning all of our "Rox" products, there were only three complaints that specifically involved Roxicodone Tablets (complaint nos. 10158, 10820, 10828). To the best of our knowledge, only one of them (10820, Roxicodone vs. Roxicet™ [oxycodone and acetaminophen tablets USP]) involved actual medication errors. The other two reports concerned perceived similarities between the names Roxicodone and Oxycontin® (Purdue Frederick). It is worth noting that the Roxicodone name has been in the marketplace long before the name Oxycontin. Our oxycodone products with the proprietary name "Roxicodone" were filed with FDA Drug Listings on August 12, 1986. Certainly that information should have been available during the review and approval of the Oxycontin name in 1995. Perhaps Purdue Frederick would be amenable to changing the proprietary name of their drug product since it has a much shorter marketing history compared to Roxicodone. While two complaints have been filed with Roxane about similarities between Roxicodone and Oxycontin, we are not aware of the occurrence of any adverse events.

Attachment 2 contains all adverse events over the past seven years that resulted from prescribing and/or dispensing errors secondary to "Rox" prefix confusion. There were no adverse events that involved Roxicodone Tablets, 5 mg.

The attachments also show complaints and adverse events received on our other "Rox" prefix products. A total of four complaints were received concerning potential confusion between Roxicet and Roxiprin™ (oxycodone and aspirin tablets USP). However, Roxiprin is no longer marketed, so that issue has been resolved. Roxilox™ (oxycodone and acetaminophen capsules USP) has received only one complaint for name confusion in seven years, so we do not feel a name change for that product is warranted.

Roxane has received six complaints about the similarity between the Roxicodone solutions (5 mg/5 mL and 20 mg/mL [Intenso™]) and Roxanol™ (morphine sulfate concentrated oral solution, 20 mg/mL). To our knowledge, none of these medication errors resulted in any adverse outcomes, probably due to the fact that oxycodone and morphine are considered equipotent on a mg per mg basis. However, we have received

Roxicodone Tablets, 15 & 30 mg
 NDA 21-011
 08/11/00



Boehringer Ingelheim
 Roxane Laboratories

adverse event reports where concentrated morphine (i.e., Roxanol) was administered instead of the regular strength solutions (which are labeled generically). In these cases it is doubtful that the Roxanol name contributed to the confusion. In fact, it is probably helpful that a "brand name" is associated with the concentrated form to help distinguish the differences from Morphine Sulfate Oral Solutions.

In cooperation of the Office of Generic Drug's request to better differentiate our "Rox" products (OGD letter dated 3/15/98, ANDA 89-775/R-015),

In summary, a review of the complaint and adverse event data attached suggests that there is little name confusion in the marketplace with regards to Roxicodone Tablets. For that reason, Roxane seeks to keep the name "Roxicodone Tablets" for the currently marketed 5 mg tablet and the 15 mg & 30 mg tablets in the pending application.

As the Agency is aware, Roxane is planning to

Again, we feel this approach is valid based on our available data. As always, we commit to continually monitor our complaint and adverse event files for developing trends in the area of name confusion, taking action when warranted.

Please do not hesitate to contact the undersigned if there are any additional questions or requests (phone 614-241-4134, fax 614-276-8061).

Sincerely,

Robert W. Pfeifer, M.S., R.Ph.
 Associate Director, Drug Regulatory Affairs

attachments

ATTACHMENT 2

Reported AE's Involving "Rox" Prefix Drugs and Name Confusion << Adverse Reactions Resulting From Prescribing and/or Dispensing Errors >>

Report No.	Date Received	Drugs Involved	Summary	Outcome
16000-029	8/14/98	<ul style="list-style-type: none"> • Morphine Sulfate Oral Solution, 20 mg/5 mL • Roxanol™ (morphine sulfate) Concentrated Oral Solution, 20 mg/mL 	Morphine OS Rx inadvertently filled with Roxanol. 68 yo cancer patient (liver mets) received 100 mg instead of 20 mg (1 st opioid dose). Also on Ativan.	Transported to hospital. Experienced renal failure and died 4 days later – cause of death unknown.
16000-031	4/14/98	<ul style="list-style-type: none"> • Roxanol™ (morphine sulfate) Concentrated Oral Solution, 20 mg/mL 	Physician order written for "Roxanol 10-15 mL pm" – administered to 77 yo terminal hospice patient.	Patient respiration decreased to 6/min – received Narcan x 2 & returned to baseline. Died 4 days later.
16000-045	2/18/00	<ul style="list-style-type: none"> • Morphine Sulfate Oral Solution, 10 mg/5 mL • Roxanol™ (morphine sulfate) Concentrated Oral Solution, 20 mg/mL 	Nurse accused of dosing 88 yo ESRD patient with Roxanol 5 mL (100 mg) instead of Morphine OS (10 mg). [USP/PRN #52886]	Patient died 12 hours after the dose.
16000-051 thru 16000-057	5/23/00	<ul style="list-style-type: none"> • Methadone HCl Oral Concentrate, 10 mg/mL • Roxanol™ (morphine sulfate) Concentrated Oral Solution, 20 mg/mL 	Pharmacist dispensed Roxanol instead of methadone. A number of patients received doses before the error was discovered.	No adverse outcome.
89775-001	1/12/00	<ul style="list-style-type: none"> • Roxicet™ (oxycodone and acetaminophen) Tablets, 5 mg/325 mg • Roxicet™ (oxycodone and acetaminophen) Caplets, 5 mg/500 mg 	Pharmacy dispensed Caplets instead of Tablets.	Consumer reported that Caplets did not work as well as the Tablets.

For the following drugs, no AE's have occurred as a result of prescribing and/or dispensing errors secondary to name confusion:

- Roxicodone™ (oxycodone) Tablets, 5 mg
- Roxicodone™ (oxycodone) Oral Solution, 5 mg/5 mL
- Roxicodone™ (oxycodone) Intenso™ Oral Solution (Concentrate), 20 mg/mL
- Roxicet™ (oxycodone and acetaminophen) Oral Solution, 5 mg/325 mg per 5 mL
- Roxilox™ (oxycodone and acetaminophen) Capsules, 5 mg/500 mg
- Roxiprin™ (oxycodone HCl, oxycodone terephthalate, and aspirin) Tablets, 4.5 mg/0.38 mg/325 mg

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ATTACHEMENT 1Labeling Complaints for "ROX" Products*

Complaint No.	Complaint Date	NDC No.	Product	Complaint Type	Notes
10632	4/22/98	1368344	ROXICODONE 20MG/ML 30ML	Label Design Content	Pharmacy is adding product to its formulary. The packaging, size of bottle, concentration and drug name all look or sound very similar to Roxanol, which is already on the formulary.
10702	6/8/98	1368344	ROXICODONE 20MG/ML 30ML	Label Design Content	The pharmacy at a long term care facility dispensed Roxicodone Oral Solution instead of Roxanol. The error was discovered by a nurse; there was no adverse outcome. The customer is complaining of the similarity of the packaging and labeling of the two products.
10821	8/28/98	1375144	ROXANOL 30ML	Label Design Content	Pharmacist reported that packaging of Roxanol and Roxicodone Intensol are too similar, which makes medication errors more likely.
10820	8/28/98	1465025	ROXICET TABS #100	Label Design Content	A hospital reported three medication errors due to similar names and packaging of Roxicet Tablets and Roxicodone Tablets.
10828	9/4/98	1465725	ROXICODONE 5MG #100	Label Design Content	Source: Drug Information Nurses July 1998, Vol 27 No.3. There continues to be much confusion/misunderstanding about oxycodone product, which lead to errors. All oxycodone products are not the same. OxyContin is sustained release. Roxicodone is immediate release. If immediate release is accidentally given for sustained release, patient can receive too much oxycodone and will experience respiratory depression.
11199	5/18/99	1375144	ROXANOL 30ML	Label Design Content	The pharmacy dispensed Roxanol instead of Roxicodone. The pharmacist feels the names and packaging of the two products are too similar. The patient did not experience any adverse effects.
13367	6/5/00	1375144	ROXANOL 30ML	Label Design Content	A hospice patient was to be given oxycodone oral solution. The night shift nurse used morphine sulfate oral solution (Roxanol) instead. The labels on each product (Roxicodone and Roxanol) are very similar and they are in the same size bottle.

*Information from QSDB records from 1/3/95 to present and Filenet records from 1/1/93 to 12/31/94.

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ATTACHEMENT 1

Labeling Complaints for "ROX" Products*

Complaint No.	Complaint Date	NDC No.	Product	Complaint Type	Notes
93-072	3/22/93	1465025, 1465325	ROXICET TABLETS/ ROXIPRIN TABLETS		Roxiprin was dispensed instead of Roxicet. The potential for error to continue to be made exists due to the similarity of packaging, labeling, and tablet size and shape. The tablet ID number on the box is of little help.
93-215	8/12/93	All	ROXICET, ROXILOX, ROXICET 5/500		The names of the products are confusing to pharmacists and nurses.
01093R	3/13/95	1865024	ROXICET TABS 4X25	Label Design Content	"Reporter relayed her concern regarding the two products Roxicet (NDC 0054-8650-24) and Roxiprin (NDC 0054-8653-24). They have identical appearing packages. It is extremely easy to mixup the two products. Reporter is very concerned about giving the wrong medication to the wrong patient. An error has occurred with no adverse effect." FDA DQRS 95-01690
95-103	3/31/95		ROXI products		We need to rename our Roxi line. We were mentioned by Neil Davis & Michael Cohen for dosing errors.
01228R	8/14/95	1865324	ROXIPRIN TABS 4X25	Label Design Content	Between the two products (Roxiprin and Roxicet) they are packaged similarly causing nursing error when dispensing. Both pills are white. Both packages are white with brown lettering. Reporter's main concern is that these two products should have different colored packaging. FDA DQRS 95-03438.
01502R	4/25/96	1865024	ROXICET TABS 4X25	Label Design Content	The unit dose packages of Roxicet and Roxiprin are too similar. The hospital had a mis-dose.
01528R	5/20/96	1865024	ROXICET TABS 4X25	Label Design Content	Poor labeling of Roxicet and Roxiprin UD packages: product names too similar, product identification too similar, and same color ink on both products. two incidents reported - no negative outcomes. Products are now separated in the narcotic cupboard. USP DQRS 96-02147.
01758R	12/16/96	1375144	ROXANOL 30ML	Label Design Content	Patient in long term care unit was administered seven incorrect doses of Roxicodone (0054-3683-44) instead of Roxanol (0054-3751-44). The medical center believes the errors occurred because of the similar names, packages, concentration, labels and appearance of the products. USP 042215.
10158	8/8/97	1465725	ROXICODONE 5MG, #100	Label Design Content	The similarity of the names OxyContin and Roxicodone and the fact that the dosage form is rarely specified in an order and the drug is ordered by its generic name, create a potential for error. USP 50360.

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August 7, 2000

Roxane Laboratories, Inc.

Cynthia McCormick, M.D.
Director, Div. of Anesthetic, Critical Care & Addiction Drug Products
Center for Drug Evaluation and Research, HFD-170
Food and Drug Administration
Park Lawn Building, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

ATTENTION: Judit Milstein, Regulatory Project Manager

**SUBJECT: NDA #21-011 – Roxycodone™ Tablets, 15 mg and 30 mg
GENERAL CORRESPONDANCE – Response to Request
for Information**

Dear Dr. McCormick,

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

As your request in our 4-August-2000 teleconference, enclosed you will find color copies of the following Roxycodone™ Tablet container labeling:

- 100-count bottle label, 15 mg (8 copies)
- 100-count bottle label, 30 mg (8 copies)
- 25-count reverse-number card, 15 mg (8 copies)
- 25-count reverse-number card, 30 mg (8 copies)

Please note that the content of these labels is the same as those submitted in our February 28, 2000 Amendment 7.01 to the above pending application. However, color has been added to better distinguish the product from others in the Roxane family of palliative care pain medications.

Please do not hesitate to contact the undersigned if there are any additional questions or requests (phone: 614-241-4134; fax: 614-276-8061).

Sincerely,



Robert W. Pfeifer, M.S., R.Ph.
Associate Director, Drug Regulatory Affairs

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_____ Draft Labeling Page(s) Withheld

Milstein



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-011

Roxane Laboratories, Inc.
P. O. Box 16532
Columbus, Ohio 43216-6532

JUN 13 2000

Attention: Robert W. Pfeifer, M.S., R. Ph.
Manager, Drug Regulatory Affairs

Dear Mr. Pfeifer:

Please refer to the telecon between representatives of your firm and FDA on May 24, 2000.

The purpose of the telecon was to clarify the terms of the approvable letter dated September 23, 2000, with regard to the recommendation to monitor total related compounds in the stability protocol.

A copy of our minutes of that telecon is enclosed. These minutes are the official minutes of the telecon. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

[*/S/*]

Judit Milstein
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Center for Drug Evaluation and Research

Enclosure: Minutes of the telecon

APPEARS THIS WAY
ON ORIGINAL



Boehringer Ingelheim
Roxane Laboratories

Cynthia McCormick, M.D.
Director, Division of Anesthetics, Critical Care
and Addiction Drug Products (HFD-170)
Document Control Room #9B23
CDER/Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Roxane Laboratories, Inc.

28 February 2000

Re: NDA No. 21-011
Amendment No. 7.01
Roxicodone Tablets (Immediate Release)
Oxycodone HCl, 15 and 30 mg tablets
Complete Response to Approvable Letter

Re: 7.01

Sean Alan F.X. Reade, M.A.
Telephone 614-241-4131
Telefax 614-276-0321
E-Mail sreade@col.boehringer-
ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

Attn: Ms. Cathie Schumaker

Dear Dr. McCormick:

In accordance with 21 CFR 314.60, Roxane Laboratories, Inc. hereby amends NDA No. 21-011 for Roxicodone™ (oxycodone hydrochloride USP) 15 and 30 mg tablets. Enclosed in Amendment No. 7.01 are the archival copy and one review copy. This amendment is organized by the sections in the original NDA to facilitate review by different reviewers. The NDA is recategorized as a 505(b)(2) application.

Amendment No. 7.01 represents the complete response to the Approvable Letter dated 23 September 1999 and agreements achieved during the meeting with the Division of 15 December 1999 and the teleconference on 11 February 2000. The Approvable Letter identified six (6) deficiencies in the original NDA. Additional preclinical information was requested during the 15 December meeting with the Agency and Phase IV commitments for mutagenicity and carcinogenicity testing were confirmed during the 11 February teleconference.

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The following table links the cited deficiencies to the contents of this amendment. A more detailed description is located in the Overall Amendment Summary in Section 3 of the submission.

Category	Reference	Amendment Contents
Approvable Letter dated 23 September 1999	Deficiency 1 (Efficacy bridging study and efficacy data)	Section 6.0-Biolink study report Section 8.2-Efficacy rationale Section 8.7-ISE
	Deficiency 2 (Efficacy rationale)	Section 8.2-Efficacy rationale Section 8.7-ISE
	Deficiency 3 (Safety bridging study and safety data)	Section 6.0-Biolink study report Section 8.2-Safety rationale Section 8.8-ISS
	Deficiency 4 (Safety: ISS by total daily dose)	Section 8.8-ISS
	Deficiency 5 [505(b)(2) recategorization]	Revised: Form FDA-356h Section 13-Patent Information Section 14-Patent Certification Section 16-Debarment Certification Section 17-Field Copy Certification Section 18 User Fee Coversheet
	Deficiency 6 (Labeling)	Section 2-Labeling
15 December Meeting	Segment II Reproductive Studies	Section 5-Nonclinical reports Dose-Ranging (Final) Segment II (Draft)
CMC: Expiration dating extension	_____ stability update	Section 4-CMC

Proposed labeling is annotated and referenced appropriately.

Additionally, copies of the stability reports and revised product specifications containing new data on the _____ stability lots are provided in this amendment. These data support an extension of expiration dating from _____ months for Roxicodone™ Tablets, 15 and 30 mg, packaged in both unit dose blisters and _____ bottles, when stored at room temperature. The next time point, _____ is scheduled for testing in July 2000, during the current review cycle for this amendment, and we request at this time, the Agency's concurrence to accept the _____ stability data as it becomes available without initiating another review cycle.

Based on the teleconference with the Division on 11 February 2000, the following timelines for mutagenicity and carcinogenicity are proposed:

Mutagenicity – protocols for Salmonella typhimurium - E. coli /mammalian-microsome reverse mutation (with confirmatory assay), mouse lymphoma forward mutation, and *in vivo* mouse micronucleus assays will be issued to the Division in _____ and initiated following FDA approval.

Carcinogenicity – protocols will be issued to FDA for approval during the _____ with initiation projected _____

In accordance with the 23 September 1999 Approvable Letter, Amendment 7.01 provides appropriate revised documentation recategorizing the NDA as a 505(b)(2) application including 356h, Patent Information and Certification, and Debarment Certification.

We certify that a Field Copy of the Chemistry, Manufacturing and Control section of this application, prepared in accordance with the regulations set forth under 21 CFR 314.50(d)(1), along with a copy of Form FDA-356h and overall NDA Amendment Summary Volume have been provided to the Cincinnati, Ohio District Office under separate cover.

The User Fee Identification Number for NDA No. 21-011 is #3542. The User Fee for this NDA was previously issued to the FDA User Fee Lockbox Facility on 9 September 1998 and receipt was acknowledged by FDA-Regulatory Policy (Mr. Michael Jones, 301-594-2041) on 11 September 1998. A revised User Fee Cover Sheet recategorizing the NDA as a 505(b)(2) application is provided.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provision of 18 U.S.C., Section 1905 and/or U.S.C., Section 331(j).

Should you have any questions or need any additional information, please contact me by telephone at 614-241-4131 or by telefax at 614-276-0321. In my absence please contact my colleague, Jonathan Dohnalek at 614-241-4132.

Sincerely,



Sean Alan F.X. Reade, M.A.
Director, Drug Regulatory Affairs
New Drugs and Regulatory Services

*Done 2/10
ROR*

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

RE: NDA 21-011 (Amendment 7.0)

DATE OF SUBMISSION: February 28, 2000

In this NDA Amendment, the following studies were submitted for review.

- Study Report # XIRT0199: Oral Gavage Dosage-Range Developmental Toxicity Study Of Oxycodone In Rats. Final Pilot Report
- Study Report # XIRT0299: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of Oxycodone In Rabbits. Final Pilot Report
- Study Report # XIRT0399: Oral (gavage) Developmental Toxicity Study Of Oxycodone In Rats. Final Draft Report
- Study Report # XIRT0499: Oral (Stomach Tube) Developmental Toxicity Study of Oxycodone In Rabbits. Final Draft Report

The two definitive studies are drafts, the QA statements were not signed. The agency is requesting that the final report, including signed QA, be submitted for Study Reports XIRT0399 and XIRT0499 at the earliest convenience so that we can continue our review.

*Called B. Pfeifer @ 2/27/00 -
will ~~be~~ send final reports w/ D.A. Signatures today*

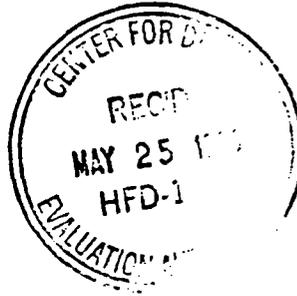
APPEARS THIS WAY
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Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Cynthia McCormick, M.D.
Division of Anesthetics, Critical Care
and Addition Drug Products
FDA - CDER, HFD-170
Parklawn Bldg: Doc. Control Rm. 95-23
5600 Fishers Lane
Rockville, Maryland 20857



May 24, 1999

NDA No. 21-011
Amendment No. 4.01

Roxicodone IR

Attention: Ms. Nancy Chamberlin

Sean Alan Reade, M.A.
Telephone 614-241-4131
Telefax 614-276-0321
E-Mail sreade@col.boehringer-
ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Dr. McCormick:

Based on our teleconferences with Ms. Nancy Chamberlin on 3 and 17 May 1999, Roxane Laboratories, Inc. (RLI) is submitting an Amendment to NDA No. 21-011 that addressed the following requests for additional information: labeling for NDA No. 21-011 (Roxicodone™IR) which matches the labeling in the approval letter for NDA No. 20-932 (Roxicodone™SR) and _____ stability reports updating drug product manufactured with _____ [15 mg (Lot Nos. 969032, 969083, and 969084) and 30 mg (Lot Nos. 959069, 969081, and 969082)] and _____ [15 mg (Lot No. 979023) and 30 mg (Lot no. 979024)] sourced oxycodone hydrochloride USP.

Amendment No. 4.01 addresses specific FDA requests for facilitation of labeling review as well as the _____ presented in the original NDA. Please recall that our teleconference of 17 May with Ms. Chamberlin and Drs. D'Sa and Maturu resulted in Divisional approval of the _____ for active raw material pending receipt of _____ stability data on the lots used in the NDA.

The following information is presented in this submission:

1.) Attachment I – electronic Zip files of

- Attachment II - [XSR-FDA-PI-1(fig)(rev2).doc]
- Attachment III - [XIR\PI-10 (structure)(sannot).doc]
- Attachment IV - [XIR\PI-10 (structure)(sannot)2nd version.doc]
- Attachment IV - [XIR\PI-10 (structure)(sannot)2nd version w tracking.doc]
- Attachment V - [TEMP\PI-10 (structure)(sannot) ver3.doc]
- Attachment V - [XIR\PI-10 (structure)(sannot) ver3wtracking.doc]

- 2.) Attachment II – hard copy of the electronic Zip file [XSR-FDA-PI-1(fig)(rev2).doc] of the approved labeling for Roxicodone™SR (NDA No. 20-932)
- 3.) Attachment III – hard copy of the electronic Zip file [XIR\PI-10 (structure)(sannot).doc] of labeling originally submitted in NDA No. 21-011
- 4.) Attachment IV – hard copy of the electronic Zip file of “clean” [XIR\PI-10 (structure)(sannot)2nd version.doc] and “red-lined” [XIR\PI-10 (structure)(sannot)2nd version w tracking.doc] versions of Roxicodone™IR labeling edited to conform, where appropriate, to the approved labeling cited by NDA No. 20-932.
- 5.) Attachment V – hard copy of the electronic Zip file of “clean” [TEMP\PI-10 (structure)(sannot) ver3.doc] and “red-lined” [XIR\PI-10 (structure)(sannot) ver3wtracking.doc] versions of Roxicodone™IR labeling edited to conform, where appropriate, to the approved labeling cited by NDA No. 20-932 and reflect the changes requested by S-001, NDA No. 20-932 submitted 18 May 1999.
- 6.) Attachment VI – _____ stability reports for _____ [15 mg (Lot Nos. 969032, 969083, and 969084) and 30 mg (Lot Nos. 959069, 969081, and 969082)] and _____ [15 mg (Lot No. 979023) and 30 mg (Lot no. 979024)] sourced

Thank you for your prompt attention to this matter. I can be reached by telephone at 614-241-4131 and by telefax at 614-276-0321. In my absence do not hesitate to contact my colleague, Mr. Jonathan Dohnalek, Manager DRA New Drugs, at 614-241-4132.

Respectfully,



Sean Alan F.X. Reade
Director Drug Regulatory Affairs
New Drugs and Regulatory Services

Attachment V

Hard copies of the electronic Zip file of "clean" [TEMP\PI-10 (structure)(sannot) ver3.doc] and "red-lined" [XIR\PI-10 (structure)(sannot) ver3wtracking.doc] versions of Roxicodone™IR labeling edited to conform, where appropriate, to the approved labeling cited by NDA No. 20-932 and reflect the changes requested by S-001, NDA No. 20-932 submitted 18 May 1999. S-001 is currently under review by the Division.

Changes proposed for NDA No. 21-011 after harmonization, where appropriate, to the approved labeling for NDA No. 20-932 are:

Ambulatory Patient section in the _____ section of the package insert

After review of this version of the package insert, and other similar products in this therapeutic category (Oramorph SR, MS Contin and OxyContin), it appears that class labeling of the oral sustained opioids provides for this section to be placed, verbatim, in the Precautions section rather than the _____ section. We propose the movement of this section to the Precautions section of the package insert for ROXICODONE™IR.

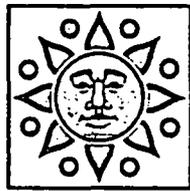
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DK

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

AUG 19 1998



Facsimile - Transmission Record

TO: [redacted]

[redacted]

[redacted]

FROM:

Bonnie McNeal
Food and Drug Administration
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
5600 Fishers Lane
Rockville, MD 20857
Phone#: 301-443-3741
Fax#: 310-443-7068

Date: August 19, 1998

Number of pages (including cover): 9

Telephone 301-443-4250 IMMEDIATELY if re-transmission is necessary.

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Dear —

Finally, here are the minutes from our May 1, 1998 meeting.

If you have any questions, please let me know.

Sincerely,

Bonnie

cc: orig END [redacted]
D.J. Fite
HFD-170/B.McNeal



DEPARTMENT OF HEALTH & HUMAN SERVICES

IND _____

Food and Drug Administration
Rockville MD 20857

AUG 19 1998

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, OH 43216-6532

Attention: Sean Allan Reade, M.S.
Director, Regulatory Affairs

Dear Mr. Reade:

Please refer to the meeting between representatives of your firm and FDA on May 1, 1998. The purpose of the meeting was to discuss the submission of an NDA.

As requested, a copy of our minutes of that meeting is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Bonnie McNeal, Project Manager, at (301) 443-3741.

During the meeting, the agency agreed to give you a response to your question about whether to submit a 505(b)(1) or a 505(b)(2) application and if there would be an impact on User Fees. Our answer is the following: **According to regulations, an NDA with new clinical data would be filed under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and User Fees would be required.**

Sincerely,

[/S/]
for Corinne Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III, HFD-170
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

Meeting Date: May 1, 1998

Time: 1:00 p.m.

Location: Parklawn Third Floor Conference Room "B"

IND Drug Name: IND 45,618 Roxicodone (oxycodone immediate release) Tablets,
15 mg and 30 mg

Type of Meeting: Pre-NDA Meeting with Sponsor

Meeting Chair: Dr. Cynthia McCormick

External Participant Lead: Sean Alan Reade

Meeting Recorder and Project Manager: Bonnie McNeal

FDA Attendees, Titles and Offices:

Cynthia McCormick, M.D., Div. Dir. DACCADP, HFD-170

Bob Rappaport, M.D., Medical Team Leader, HFD-170

Lucy Jean, Ph.D., Pharm/Tox Team Leader, HFD-170

Kathleen Haberny, Ph.D., Pharm/Tox Reviewer, HFD-170

John Hunt, Deputy Director, Biopharm Division, HFD-870

Ramana Uppoor, Ph.D., Biopharm Team Leader, HFD-870

Michael Klein, Ph.D., Team Leader, Controlled Substance Evaluation Team, HFD-170

Thomas Permutt, Ph.D., Team Leader, Mathematical Statistics, HFD-170

Juanita Ross, Chemistry Reviewer, HFD-170

Bonnie McNeal, Project Manager, HFD-170

Roxane Laboratories Inc. Attendees:

[_____]
Beverly Wynne, Ph.D., Medical Director, Roxane

Clinical Consultant to Roxane

Sean Alan Reade, M.S., Director, Regulatory Affairs, Roxane

Michael J. Schobelock, Pharm.D., Clinical Research Manager, Roxane

Douglas B. Ferriman, Pharm.D. student, Roxane

Objective: To review the proposed NDA submission for format and presentation of data and to answer questions posed in the submission.

Background:

Sponsor presented the product development history, proposed ISS, and preclinical and clinical sections of the NDA. Sponsor submits that it has established bioequivalency between the 15 and 30 mg tablets and the currently marketed products, documented dose proportionality between the 5, 15 and 30 mg tablets, and demonstrated safety of the dosage form in the target population. Sponsor will not seek exclusivity for the product. Agency reviewed the information in the meeting package prior to the meeting and had questions from each discipline.

Content of the NDA

- Chemistry requested that the sponsor submit to the file (see attached CMC Data Request for IND 46,618) as soon as possible and before the NDA is submitted.
- The Office of Clinical Pharmacology and Biopharmaceutics asked the Sponsor if the tablet used in the clinical trials is identical to the to-be-marketed product. Sponsor said it was.
- The Office of Clinical Pharmacology and Biopharmaceutics referred to a proposed multiple dose study in the March 1996 meeting minutes and asked if this study was complete. Sponsor responded that the study was not done because of safety concerns in giving the drug to healthy volunteers. This should be clearly explained in the NDA. Biopharmacology acknowledged that the population pharmacokinetics (PK) study may answer the question.
- The effects of food have been studied only on the oral solution and the sustained release tablets. The sponsor was instructed to follow the Agency's guidance to determine what would happen for the immediate release tablet formulation. The labeling will have to state specifically what the food effect is on the oral solution and also clearly state that this study was done on oral solution. No such data is available on the tablet formulation. However, some interpretation, by the reviewer, may be made based on all the data.
- Sponsor was asked to submit the dissolution information, the PK portion of the clinical studies, and the population PK analysis to the PK section of the NDA.
- Sponsor was asked to update the labeling with literature information on absorption, distribution, metabolism and excretion plus PK information for special populations and to associate the statements to be used in the label with specific literature references.
- The Pharmacology/Toxicology section of the NDA can be adequately supported by literature references. Agency suggested a revision of the Carcinogenesis, Mutagenesis and impairment of Fertility and Usage in Pregnancy section of the labeling. As the sponsor does not plan new studies, class labeling must be used.

- The sponsor was reminded that it will be necessary to submit an abuse liability section to the NDA following Code of Federal Regulations [21 CFR 314.50(5)(vii)] as well as proposed labeling.
- The general clinical plan was agreed upon as acceptable. There was discussion about the absence of pediatric information in the current label and the sponsor was provided the options either to make the necessary case to extrapolate adult efficacy data to the pediatric population drawing upon available supporting PK and safety data or to think about a phase 4 commitment. Sponsor was referred to the agency Pediatric Guidance.

Format of the NDA

- Sponsor reviewed the proposed format of sections of the NDA, the ISS, ISE and CRFs in particular. It was agreed that case report forms (CRFs) for deaths, withdrawals and serious adverse effects would be submitted and others will be available upon request.
- Electronic submission of portions of the NDA were discussed. The ISE and clinical summaries will be provided to the clinical reviewer in word processing format (Word). The PK section will be provided electronically: data sets in either ASCII or Excel (preferred) and summary study reports in processing format (Word).

Regulatory Aspects

- Timing of the submission was discussed. CMC presubmission was explored by the sponsor. The Agency stated that it could be accepted with the understanding that these materials may not be reviewed until the NDA was filed and that the NDA would not be considered filed until complete. Sponsor informed the agency that the NDA would be submitted during the third quarter of 1998 (July, August or September).
- The sponsor considered that this NDA may be a hybrid between a 505(b)(1) and a 505(b)(2) and asked how this would impact User Fees. FDA agreed to investigate this.

FDA Action Items: The agency will give a response to the sponsor on whether to submit a 505(b)(1) or a 505(b)(2) application and if there is an impact on User Fees.

**APPEARS THIS WAY
ON ORIGINAL**

Pre-NDA Meeting
IND 46,618
May 1, 1998

Page 4

[/S/] MD

Concurrence, Meeting Chair

[/S/] 8/10/98

Meeting Recorder and Project Manager, HFD-170

Enclosures handed to sponsor during the meeting:

- 1) CMC Data Request for IND 46,618
- 2) Clinical Pharmacology & Biopharmaceutics' Reviewer/Team Leader: Ramana Uppoor
Comments and Guidelines for preparation of the labeling (two pages)

APPEARS THIS WAY
ON ORIGINAL

May 1, 1998

CMC Data Request for IND 46,618

Please submit the following information to the IND file as soon as possible on clinical lots listed on pages 8 and 9 of the meeting package:

- 1. quantitative composition**
- 2. oxycodone source**
- 3. process description and process equipment**
- 4. release test results and test methods**
- 5. stability for the study duration in the clinical package**
- 6. proposed expiratory date**

The lot numbers for which information is needed are:

5 mg tablet - lots 951182, 951905, 960285, 960783, 961562, 961565, 962810.

15 mg tablet - lot 969032.

30 mg tablet - lot 959069.

**APPEARS THIS WAY
ON ORIGINAL**

IND 46,618 ROXICODONE IR 15 AND 30 MG TABLETS

Clinical Pharmacology & Biopharmaceutics' Reviewer/Team Leader: Ramana Uppoor

Comments:

- 1) The package does not include any multiple dose study on the IR tablet formulations. In the NDA, the sponsor should provide information on steady state pharmacokinetics (and accumulation) of oxycodone that can be obtained with this new formulation. This can be done by simulation of steady state pharmacokinetics based on the single dose data. This should be compared to the data obtained from the population pharmacokinetics.
- 2) No food effect study has been conducted on the IR tablet formulations. The sponsor should justify, in the NDA, whether a food effect is expected or not. The draft FDA guidance on Food effect studies can be utilized for this purpose. Further, it should also be clarified whether the products were administered in fasted state in the clinical studies. If the justification is based on the data from oral solution, the labeling, while describing the data, will also state that no food effect study was conducted on the IR formulation. If a specific claim for the IR product is needed, a food effect study on this formulation will be necessary.
- 3) In vitro dissolution data (on — units/lot) in multiple media for all the three strengths should be provided in the submission.
- 4) Is the clinical and to-be marketed formulation the same?
- 5) The sponsor should provide information to update the labeling regarding ADME (absorption, distribution, metabolism and excretion), pharmacokinetics in special populations such as elderly, pediatric subjects and also describe the effects of gender, race, renal insufficiency and hepatic insufficiency on the pharmacokinetics of the drug. Any information on drug-drug interactions should also be provided. An attachment for further guidelines on the labeling is provided as attachment I. Such information can be obtained from existing study data or from literature. In the NDA, The sponsor is requested to provide appropriate literature references along with summaries of each article and the labeling statement corresponding to that reference.
- 6) The study XIR0596 should also be submitted under Item 6, Human Pharmacokinetics and Bioavailability section of the NDA. This study, especially the population PK analysis, will be reviewed by this discipline. The population PK study report should specify the doses studied along with the dosage strengths used.
- 7) The control stream and data files associated with the population PK analysis should be submitted on a diskette in ASCII or EXCEL format.

ATTACHMENT I

GUIDELINES FOR THE PREPARATION OF THE PHARMACOKINETICS SECTION OF THE LABELING

Currently, the FDA is attempting to standardize the content and presentation of the information that is to be given in the *Pharmacokinetics* portion of the *Clinical Pharmacology* section of the package insert. The *Pharmacokinetics* portion should present information as appropriate under the subheadings of *Absorption, Distribution, Metabolism, and Excretion*. Following this, there should be a section with the heading of *Special Populations*, where pharmacokinetic information under the subheadings of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Insufficiency, and Drug-Drug Interactions* should be included. Where relevant information is lacking it should be so stated.

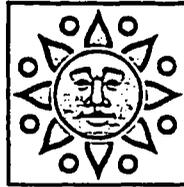
Lastly, a table(s) with mean (\pm SD) pharmacokinetic parameters determined under single and steady state conditions should be prepared. This table(s) should include bioavailability, peak concentration, time to peak, clearance, volume of distribution, half-life, and renal clearance for healthy subjects, and each special population including the drug's intended target population. Also, if appropriate a plot that illustrates drug plasma/serum concentration vs. time (i.e., different dosage strengths, comparison to a reference product, etc.) may be included.

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ON ORIGINAL

DF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

SEP 10 1997



Facsimile - Transmission Record

TO: [_____]
[_____]
[_____]
[_____]

FROM:
Bonnie McNeal
Food and Drug Administration
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
5600 Fishers Lane
Rockville, MD 20857
Phone#: 301-443-3741
Fax#: 301-443-3741

Date: September 10, 1997

Number of pages (including cover): 2

Telephone 301-443-4250 IMMEDIATELY if re-transmission is necessary.

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Dear Dr. _____

On the following page are some specific questions which came up during our agency meeting on your IND. Please include answers to these questions in a meeting package and submit it to us as soon as possible. We will then set up a meeting with you at the earliest date possible.

Sincerely,

Bonnie McNeal

Questions to the Sponsor regarding IND 46,618.

- 1. Please identify the formulation you wish to market.**
- 2. Have you done any pharmacokinetic studies with your to-be-marketed formulation?**
- 3. Please identify the formulations used in the bioavailability and dose proportionality studies.**
- 4. What are the indications which the sponsor is seeking for the drug product?**
- 5. Will the sponsor make clinical efficacy and safety claims based on the solution or on the tablet? If it is on the solution, then the to-be-marketed formulation needs to be better tied to the solution.**
- 6. What are the sponsor's plans for conducting efficacy trials and clinical studies?**
- 7. Please identify the batch numbers of drug product used for all clinical, pharmacokinetic and preclinical studies.**
- 8. We would like the sponsor to describe in detail their proposed clinical study.**
- 9. We would like to see preclinical data for the mutagenicity and pregnancy categories of the package insert. The agency suggests that the sponsor consider doing carcinogenicity, mutagenicity and reproductive toxicology studies. If no studies are done, the agency would like an extensive literature search on what is available for the pharmacology, toxicology and ADME (Absorption, Distribution, Metabolism, and Excretion); and the sponsor should write a drug class label for oxycodone.**
- 10. Does the sponsor plan to submit a 505(b)2 application?**

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ON ORIGINAL**