

**B. ADVERSE EVENT REPORTING SYSTEM (AERS) AND DRUG QUALITY REPORTING SYSTEM (DQRS) DATABASE SEARCH:**

The steps in this investigation included various searches in the Adverse Event Reporting System (AERS) and the Drug Quality Reporting System (DQRS) for any reports with the Meddra terminology, "Drug Maladministration".

1. Medication Error Reports of Confusion Among Products With The Same Root Name "Rox"  
(The following narratives were transcribed from the medication error reports that were submitted. Furthermore, since all reports do not provide the date of events, other dates (such as the date that the report was written or when it was received by the MedWatch/USP/ISMP are listed below.)

**Roxicodone**

1. U# 016168 (Date of Report 12/29/92)

Roxane manufactures and packages two narcotics with extremely similar packaging, printing, and color of the tablets: Methadone and Roxicodone. Both products are in the same style package, same color package, same layout of print and same color tablet. The nurses meant to give oxycodone and mistakenly administered methadone due to similarities in packaging and the tablets. The reporter requests that the company change one of products packaging or tablets to a different color to prevent further medication administration errors. No patient outcome was reported.

2. M# 118023 (Date of Report 4/25/95)

The nursing department reviewed medication errors over the past two years. Nursing concluded that Roxane's products, morphine 15 mg, codeine 30 mg, Roxicodone 5 mg, and hydromorphone 4 mg, tablets were error prone due to similarities in the packaging and the tablet's color. No adverse events have been reported as a result, but errors have occurred.

3. U# 042215 (Date of Report 12/10/96)

Nursing staff ordered Roxanol oral solution, 20 mg/mL-30 mL bottle from pharmacy. Roxicodone Intensol, 20 mg/mL-30 ml bottle, was sent instead of Roxanol. The patient was incorrectly administered 60 mg of Roxicodone (instead of 60 mg of Roxanol). Since 30 mg of oral oxycodone is roughly equivalent to 60 mg of oral morphine, the patient received twice the intended morphine dose on each occasion. No patient outcome was reported.

4. U# 050360 (Date of Report 8/4/97)

The similarity of the names of OxyContin (controlled release oxycodone) and Roxicodone (oxycodone, immediate release), and the fact that the dosage form is rarely specified in an order and the drug is ordered by its generic name, creates a potential for medication error. The reporter has suggested using ancillary labels to warn that these two products are different with some successes. However, the reporter recommends changing the packaging for OxyContin to prevent the mix-up.

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<sup>3</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.<sup>1</sup>

5. U# 000039 (Date of Report 2/29/00)

Pharmacist dispensed Roxanol oral solution 20 mg/mL 30 mL for Roxicodone oral solution 20 mg/mL, 30 ml bottle. Both solutions are packaged similarly and were stored on the shelf adjacent to each other. No patient outcome was reported.

6. U# 000144 (Date of Report 3/15/00)

Roxicodone (oxycodone) was mixed up with methadone tablets in the Pyxis machine (stocked by a pharmacy technician). Nursing staff administered the medication to the patient. Patient received Roxicodone instead of methadone. No patient outcome was reported.

7. U# 000251 (Date of Report 4/20/00)

The pharmacy department is adding Roxicodone Intensol 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. Potential medication error can occur due to name confusion.

8. U# 000645 (Date of Report 5/2/00)

Report from Drug Information for Nurses: July/1998, Volume 27, No. 3.

There continues to be much confusion/misunderstanding about Roxicodone (oxycodone) products resulting in medication errors. All oxycodone products are not the same.

OxyContin (oxycodone) is the sustained release product. Roxicodone is the immediate release product. If the immediate release product is accidentally given for the sustained release product, the patient can receive too much oxycodone and subsequently experience respiratory depression, somnolence, bradycardia, and hypotension. Conversely, if the patient is given the sustained release for the immediate release product, patient might miss the benefit of bolus effect of immediate release dosage form. Adding to the confusion is the fact that Roxicodone is currently available in 5 mg tablet. It is often prescribed in higher doses (10-20 mg). OxyContin (sustained release oxycodone) is available as 10 mg, 20 mg, 40 mg and 80 mg tablets.

9. U# 647 (Date of Report 5/2/00)

There have been 3 medication errors where Roxicodone and Roxicet tablets were confused by the nursing staff. It is another instance of similar sounding name and packaging problem with Roxane's product. Pharmacy department had switched to Roxicet temporarily because Percocet had fallen off contract. No patient outcome was reported.

10. U# 000635 (Date of Report 5/2/00)

A pharmacist contacted the manufacturer about Roxanol and Roxicodone Intensol's look-alike packaging. The manufacturer made some changes, which have been minimal that the two products still look somewhat alike and the names still sounds very alike.

**Roxanol**

11. U# 040639 (Date of Report 7/15/93)

Physician ordered Roxicet liquid 1-2 tsp q4h prn pain. Roxicet is the combination of oxycodone and acetaminophen. At 6 am, nurse picked up Roxanol liquid (morphine solution 20 mg/mL) from pharmacy. Patient was given 10 mL of Roxanol (200 mg morphine).

Patient outcome was not reported.

12. U# 000787 (Date of Report 5/19/00)

Pharmacist dispensed Roxanol solution on a prescription written for Roxicet solution. The incorrect medication was administered to the patient who resulted in the hospitalization of the patient. This was a mail order pharmacy which was described by the pharmacist as a "volume-driven business". The pharmacist explained that the Rx volume made it impossible to provide quality patient care.

Roxicet

13. U# 040537 (Date of Report 3/16/93)

Roxiprin was dispensed instead of Roxicet. The potential for dispensing errors continued to be made due the similarity of packaging, labeling and tablet size and shape. The reporter recommended changing labeling and size of the bottles, and color code the products. No adverse patient outcome reported.

14. U# 017657 (Date of Report 8/6/93)

The names of the products are confusing to pharmacists and nurses. Roxicet 5/500 tablets and Roxilox capsules both contain oxycodone 5 mg and acetaminophen 500 mg, equivalent to Tylox. Roxicet contains oxycodone 5 mg and acetaminophen 325 mg, equivalent to Percocet. Reporter was concerned about mix up between these two products.

15. U# 019885 (Date of Report 7/28/94)

The packaging of Roxane Oramorph SR (sustained release of morphine) and Roxicet is so similar that medication errors have occurred. The medications are packaged in five, 5 by 5 strips covered with a brown wrap with a white design. Both tablets are white and round and look similar. No adverse patient outcome reported.

16. D# 117428 (Date of Report 3/1/95)

A reporter relayed her concern regarding the two products Roxicet and Roxiprin. They both have identical appearing packages. It is extremely easy to mix up the two products. Reporter is very concerned about giving the wrong medication to the wrong patient. An error has occurred with no adverse effect.

17. D# 119491 (Date of Report 8/15/95)

Between the two products (Roxiprin and Roxicet), they are packaged similarly causing nursing error when dispensing. Both tablets are white. Both packages are white with brown lettering. Reporter's main concern is that these two products should have different colored packaging. No adverse patient outcome was reported.

18. M# 122006 (Date of Report 5/22/96)

Poor labeling of Roxicet and Roxiprin. 1. Product names too similar. 2. Product identification too similar. 3. Same color ink on both products. 4. 2 medication errors reported. No adverse patient outcome reported. Reporter now separates these two products in the narcotic cupboard.

19. D# 123650 (Date of Report 1/21/97)

Reporter noted that there is a similarity between the 2 products (Roxicet and Roxane's brand acetaminophen w/codeine #3). The packages of these products are identical. There needs to be a change in either the packaging or labeling between these 2 products. No adverse patient outcome was reported.

2. Summary of Medication Errors Due To the Use of the Rootname "Rox".

EVENTS	# Of Reports	Outcome
<b>Roxicodone</b>		
Roxicodone dispensed instead of Roxane brand of morphine, codeine, and hydromorphone	1	Unknown
Roxicodone dispensed instead of Roxane methadone	2	Unknown
<b>Roxicodone/OxyContin</b>		
Roxicodone dispensed instead of Roxicet	3	Unknown
Roxanol soln dispensed instead of Roxicodone soln	1	Unknown
Roxicodone soln added to hospital formulary	1	Potential error
Roxicodone soln/Roxanol soln	1	Potential error
Roxicodone soln dispensed instead of Roxanol soln	1	Unknown
<b>Roxanol</b>		
Roxanol soln 10 mg ordered 10 ml dispensed (total 200mg morphine)	1	Death
Roxanol soln dispensed instead of Roxicet soln	1	Patient Hospitalized
Roxanol soln 10 ml dispensed instead of Roxicet soln	1	Unknown
Roxanol soln 20 mg ordered but 20 ml dispensed (400 mg morphine)	1	Unknown
Roxanol soln 15 mg ordered and 15 ml dispensed (300 mg morphine)	1	Death
Roxanol 2.5 mg ordered and 3 doses of 2.5 ml dispensed	1	Death
Roxanol soln dispensed instead of Demerol	1	Unknown
Roxanol soln direction 0.5-1ml q2-3 hr ordered with wrong direction as 1-2 teaspoonfuls q2-3hrs	1	Patient became disoriented and incoherent
<b>Roxicet</b>		
Roxicet dispensed instead of Roxiprin	3	Unknown
Roxicet and Roxane brand acetaminophen w/codeine #3	1	Potential error
Roxicet 5/500 and Roxicet	1	Potential error
Roxicet and Roxane Oramorph SR	1	Potential error
Roxiprin dispensed instead of Roxicet	1	Unknown

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## C. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

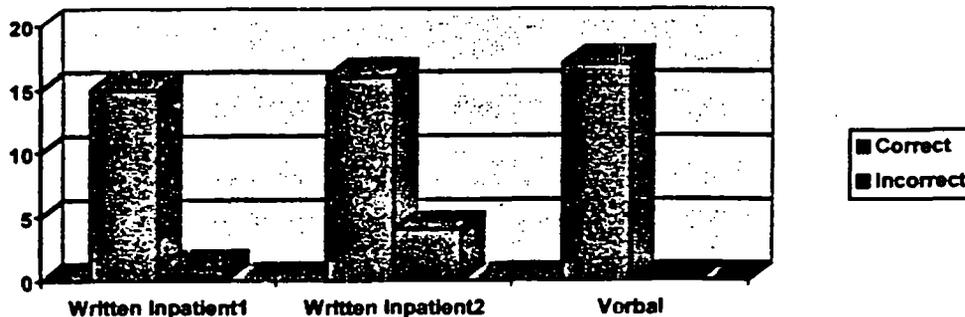
These studies were conducted by OPDRA and involved 94 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Roxicodone with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Roxicodone (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. We conducted two inpatient written studies to determine if a poorly written script (which is often seen in actual practice) could result in dramatically different results.

Hand Written Prescription	Verbal Prescription
<u>Inpatient Rx#1:</u> Roxicodone 30 mg q6h prn	Roxicodone 30 mg q6h prn
<u>Inpatient Rx#2:</u> Roxicodone 30 mg q6h prn	

### 2. Results:

The results are summarized in the following table.

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient #1	32	16(50%)	15	1
Written Inpatient #2	31	20(65%)	16	4
Verbal	31	17(55%)	17	0
Total	94	53(56%)	48(91%)	5(9%)



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Ninety-one percent of the participants responded with the correct name, Roxicodone. The incorrect written and verbal responses are in the following table.

	<u>Incorrectly Interpreted</u>
Written Inpatient#1	Roxiecodone
Written Inpatient#2	Roxnodone
	Roxpodone
	Roxisodone
	Roxudone

#### D. SAFETY EVALUATOR RISK ASSESSMENT

Results of the verbal and written analysis studies show 5 (9%) out of 53 participants interpreted the proprietary name, Roxicodone, incorrectly. We did not uncover any overlapping existing approved drug product names in our studies. However, a negative finding in a small sample size does not rule out the possibilities of name confusion among Roxicodone, Roxicet, Roxanol, Roxiprin and Roxilox. These names all share the root name, "Rox".

OPDRA conducted prescription studies in an attempt to simulate the prescription ordering process. In this case, there was no confirmation that Roxicodone could be mistaken with Roxicet, Roxiprin, Roxilox nor Roxanol. However, the results of the DQRS and AERS searches conducted confirm that medication errors are occurring among products that share the root name, "Rox". These medication errors are mainly due to 1) name confusion, 2) look-alike packaging, 3) identical tablet color, 4) immediate release (Roxane products) vs sustained release (Purdue's OxyContin), and 5) overlapping strengths. Several of these medication errors resulted in serious patient outcome (i.e., death and hospitalization).

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

- A. Please be aware that the Director, Division of Labeling and Program Support in the Office of Generic Drugs (OGD), has requested the sponsor to revise their container labels and carton labeling to reduce confusion among the Roxane products. The sponsor has proposed to add differentiating colors to the background panel behind the product identification on the container label and carton labeling. A copy of the proposed changes are enclosed. Please note that this submission contains labels for Roxicodone 5 mg tablets, which are not approved. Discussions concerning the name of these products should be co-ordinated between OGD and the Division.
- B. OPDRA has focused the review on the packaging and the labeling of Roxicodone 15 and 30 mg tablets.

#### CONTAINER LABELS and CARTON LABELING

**IV. RECOMMENDATIONS:**

1. OPDRA does not recommend use of the name, Roxicodone.
2. OPDRA recommends the above label revisions.
3. The Office of Generic Drugs should be kept informed on the status of a possible name revision.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Peter Tam, RPh. at 301-827-3241.

[ /S/ ] 7/17/00

Peter Tam, RPh.  
Safety Evaluator  
Office of Postmarketing Drug Risk Assessment

Concur:

[ /S/ ] 7/17/2000

Jerry Phillips, RPh.  
Associate Director for Medication Error Prevention  
Office of Postmarketing Drug Risk Assessment

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CC: .

NDA - 21-011

Office Files

HFD-170; Judit Milstein, Project Manager, DACADP

HFD-170; Cynthia McCormick, M.D., Division Director, DACADP

HFD-610; Robert West, Director, Division of Labeling and Program Support, Office of Generic Drugs

HFD-042; Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)

HFD-440; Patrick Guinn, Project Manager, DDRE II, OPDRA (Electronic Only)

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Sammie Beams, Project Manager, OPDRA (Electronic Only)

HFD-400; Peter Honig, Director, OPDRA (Electronic only)

HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

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**MEMORANDUM OF TELECON**

**DATE:** May 24, 2000

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

**BETWEEN:**

Name: Robert W. Pfeifer, M.S., R.Ph., Manager, Drug Regulatory Affairs  
James Boersma, Ph.D., Manager, Analytical Development  
Michael Schobelock, Pharm.D., Associate Director, Medical Affairs  
Nahendra Dedhiya, Ph.D., Director, Product Development  
David Dunlevy, M.S., Manager, Quality Control, Analytical Design and Transfer  
Ann Kline, B.A., Clinical Research Manager  
Phone: (614) 276-4000 (Extension 2502)  
Representing: Roxane Laboratories

**AND**

Name: Cynthia G. McCormick, M.D., Director  
Albinus D'Sa, Chemistry Team Leader  
Pramoda Maturu, Chemistry Reviewer  
Judit Milstein, Regulatory Project Manager  
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170  
Steven Koepke, Deputy Division Director, DNDC2, ONDC

**SUBJECT:** Clarification of the terms of the approvable letter dated September 23, 2000, with the recommendation to include the monitoring of known, unknown and total impurities of the drug product.

**BACKGROUND:** On September 23, 2000, the Agency sent an approvable letter for Roxicodone® oxycodone hydrochloride). Listed as a comment and not a deficiency, was a recommendation that the "total related compounds be monitored as the stability protocol".

**DISCUSSION:** Dr. Koepke expressed that the sponsor will need to provide additional information on the drug product and it's impurities as follows.

1. Explain the origin of the "related impurities/related compounds", as to whether they are already present in the raw material or they are degradation products.
2. Provide the specifications of the raw materials. If the impurities originate during the stability protocol time-frame, quantify every degradation product present in excess of —, and provide analytical methods and individual specifications for the impurities.
3. The ICH guidelines should be followed for the requirements of a drug product.

Representatives of Roxane® Laboratories expressed that they will examine the stability data currently available, and will provide a response to the Agency in 4 weeks.

[ |S| ]

Judit Milstein, Regulatory Project Manager

[ |S| ] 6/6/00

Steven Koepke, Ph.D., Deputy Director, DNDC2/ONDC

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NDA 21-011  
Page 3

cc: Original NDA  
HFD-170/Div. File  
HFD-170/Judit Milstein/C. Schumaker  
HFD-170/P. Maturu/A.D'Sa/S.Koepke

Drafted by: JM 6-3-00  
Initialized by:  
Fianl:

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6/12/00

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TELECON

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## PRODUCT LABELING REVIEW

NDA 21-011  
ROXICODONE™ C II  
(Oxycodone Hydrochloride Tablets USP)  
Immediate Release 15 mg, 30 mg

The sections of the labeling dealing with drug abuse and overdose related warnings have been reviewed. The labeling is consistent with that of a similar product, PERCODAN (Oxycodone hydrochloride 4.5 mg, oxycodone terephthalate 0.38 mg, aspirin 325 mg).

### DRUG ABUSE AND DEPENDENCE

#### Controlled Substance:

ROXICODONE™ is a Schedule II narcotic under the U.S. Controlled Substances Act (CSA) (21 U.S.C. 801-886). ROXICODONE™ can produce drug dependence of the morphine type, and therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration. \_\_\_\_\_  
\_\_\_\_\_. ROXICODONE™ should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

#### Abuse:

Since ROXICODONE™ is a ~~mu~~-opioid agonist \_\_\_\_\_ it may be subject to misuse, abuse, and addiction. Addiction to opioids prescribed for pain management has not been estimated. \_\_\_\_\_ However, requests for opioids from patients addicted to opioids \_\_\_\_\_ occur. As such, \_\_\_\_\_ physicians should take appropriate care in prescribing ROXICODONE™ \_\_\_\_\_

#### Dependence:

Opioid analgesics may cause psychological and physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug after long term administration. Also, \_\_\_\_\_ symptoms of withdrawal may be precipitated through the administration of drugs with mu-opioid antagonist activity, e.g., naloxone or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine, dezocine). (See also OVERDOSAGE). Physical dependence usually does not occur to a clinically significant

degree, until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required to produce the same degree of analgesia, is initially manifested by a shortened duration of an analgesic effect and, subsequently, by decreases in the intensity of analgesia.

In chronic pain patients, and in opioid-tolerant cancer patients, the administration of ROXICODONE™ should be guided by the degree of tolerance manifested and the doses needed \_\_\_\_\_ to adequately relieve pain.

—The severity of the ROXICODONE™ \_\_\_\_\_ abstinence syndrome \_\_\_\_\_ may depend on the degree of physical dependence. Withdrawal — is characterized by rhinitis, myalgia, abdominal cramping, and occasional diarrhea. Most observable symptoms disappear in 5 to 14 days without treatment; however, there may be a phase of secondary or chronic abstinence which may last for 2 to 6 months characterized by insomnia, irritability, and muscular aches. —

The patient may be detoxified by gradual reduction of the dose. Gastrointestinal disturbances or dehydration should be treated with supportive care.

## OVERDOSAGE

### Signs and Symptoms:

Acute overdosage with ROXICODONE™ can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

### Treatment:

To treat ROXICODONE™ overdosage, primary attention should be given to the reestablishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The narcotic antagonists, naloxone or nalmefene, are specific antidotes for opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to ROXICODONE™ overdose. Opioid antagonists should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including oxycodone. —

\_\_\_\_\_ The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered.

Opioid-Tolerant Individuals: In an individual physically dependent on opioids, administration of usual dose of the antagonist will precipitate an acute withdrawal. The severity of the withdrawal produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist should be reserved for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

[ |S| ]

Michael Klein, Ph.D.  
Team Leader, Controlled Substance Evaluation  
September 9, 1999

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## Memorandum

**To:** Gary Buehler, Chair  
c/o - Khyati Roberts  
Medication Errors Subcommittee  
MPCC  
HFD-6, WOC II

**Subject:** OGD Control # 98-358  
Reference Control # 98-295

**Description:** Multiple medication error reports  
and concerns involving oxycodone  
containing drug products.

**From:** Adolph Vezza, R.Ph., M.H.S.  
Labeling Reviewer  
Labeling Review Branch - Division II  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**Through:** Douglas L. Sporn  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Robert L. West  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Rita Hassall  
Special Assistant  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Charlie Hoppes  
Team Leader  
Labeling Review Branch - Division II  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**Description:** Medication Errors - The errors involved the  
dispensing of Roxanol® (Morphine) Solution for  
Roxicet™ (Oxycodone Hydrochloride/Acetaminophen)



## Memorandum

Solution and the confusion of Roxicodone™ (Oxycodone) and Roxicet™ Tablets. Concern was also expressed of the possibility of confusing Roxicodone™, an immediate release oxycodone product and OxyContin®, an extended release oxycodone product. In addition, there is the possibility of confusing the two products, Roxanol™ and Roxicodone™ Intensol because of the similarity of the packaging and the names. All of the mentioned drug products are marketed by Roxane Labs except for OxyContin®, which is Purdue Pharma's product.

**History:** The medication error reports were reviewed and all of them involved carefully reading the prescription and the container label. Prescribing errors may occur if the providers are confused about which product they are ordering.

Two of the drug products in question are NDAs, Oxycontin® (Oxycodone Hydrochloride Extended-release Tablets) [NDA 20-553] and Roxicodone™ (Oxycodone Hydrochloride Immediate-release Tablets) [NDA 20-932]. Two of the drug products are ANDAs, Roxicet™ (Oxycodone Hydrochloride and Acetaminophen Oral Solution) [ANDA 89-351] and Roxicet™ (Oxycodone Hydrochloride and Acetaminophen Tablets) [ANDA 89-775]. Two of the drug products are not found in the Orange Book, Roxanol™ (Morphine Sulfate Oral Solution) and Roxicodone™ Intensol (Oxycodone Hydrochloride Oral Solution).

**Action:** A letter out will be sent to Roxane Laboratories informing them of the medication errors involving their drug products. Three suggestions were made: (1) revisit the company policies of having very similar dress for all their drug products; and (2) for having all of their trade names begin with "ROX"; and (3) the possibility of color coding the containers of the products in question.

See attached copy of letter to Roxane Labs, Inc.

If you have any questions, please call Adolph Vezza at (301) 827-5837.

**Attachment:** Letter Out for Roxane Laboratories



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug  
Administration

## Memorandum

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ANDA 89-351/R-17 (Oral Solution)  
89-775/R-15 (Tablet)

Roxane Laboratories, Inc.  
Attention: Ann M. Maloney  
P.O. Box 16532  
Columbus, Ohio 43216-65328

Dear Madam:

We acknowledge receipt on June 4, 1998 (ANDA 89-351) and September 8, 1998 (ANDA 89-775), of your annual reports dated June 3, 1998 and September 3, 1998, submitted pursuant to the provisions of 21 CFR 314.81(b)(2) and Section 505(k) of the Federal Food, Drug, and Cosmetic Act, for Roxicet™ Oral Solution (Oxycodone Hydrochloride and Acetaminophen Oral Solution), 5 mg/325 mg per 5 mL and Roxicet 5/500™ Caplets (Oxycodone Hydrochloride and Acetaminophen Tablets USP) 5 mg/500 mg.

We have reviewed the labels and labeling submitted and have the following comments:

There have been medication errors reported with providers' confusing your products Roxanol™ (Morphine Sulfate Oral Solution) and Roxicet™ (Oxycodone Hydrochloride and Acetaminophen Oral Solution) and also Roxicodone™ (Oxycodone Hydrochloride Tablets) and Roxicet™ (Oxycodone Hydrochloride and Acetaminophen Tablets). In addition, the suggestion has been made that there exists the possibility of medication errors involving your two products Roxanol™ and Roxicodone™ Intensol (Oxycodone Hydrochloride Oral Solution) and also between Purdue Pharma's product Oxycontin® (Oxycodone Hydrochloride Extended-release Tablets) and Roxicodone™ (Oxycodone Hydrochloride Immediate-release Tablets).

Increase the prominence of the established name and strength. To increase label space for this revision and in accordance with the FDA Modernization Act, please revise your "CAUTION: Federal law ..." statement to read "Rx only".

Perhaps it is time to reevaluate your policies of having similar dress for all your drug products and for having trade names begin with "ROX". These two measures would decrease the likelihood of medication errors in the future. You might consider color coding the above products, e.g.,

Roxanol™ - morphine - red, Roxicodone™ - oxycodone - blue,  
Roxicet™ - oxycodone/acetaminophen - green.

The remainder of your report will be reviewed at a later date.

The material submitted is being retained as part of your application.

Sincerely yours,

Robert L. West, M.S., R.Ph.  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

cc: ANDA 89-351/R-17 (Oral Solution)  
89-775/R-15 (Tablet)  
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LETTER OUT

Endorsements:  
HFD-613/AVezza  
HFD-613/CHoppes

NDA 20-932 (Oxycodone sustained-release)  
NDA 21-011 (Oxycodone immediate release)  
Friday, February 11, 2000

IMTS #5515

FEB 11 2000

**Minutes of meeting**

**Representing FDA:**

Hal Blatt, Medical Reviewer  
Nancy Chamberlin, Project Manager  
Debra Fong, Project Manager  
Stella Grosser, Statistical Reviewer  
Sharon Hertz, Medical Reviewer  
Lucy Jean, Pharm/Tox Team Leader  
Cynthia McCormick, Director  
Tom Permutt, Statistical Team Leader  
Cathie Schumaker, Chief, Project Management Staff

**Representing Roxane Laboratories, Inc.**

J. Dohnalek

Ann Kline  
Mike Schobelock  
Beverley Wynne

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**NDA 20-932 Discussion:**

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[REDACTED]

**NDA 21-011 Discussion:**

See submission dated February 8, 2000, for background information.

FDA agrees that the mutagenicity and carcinogenicity studies can be conducted as Phase 4 commitments, although FDA would like to see them earlier. FDA does not see a significant difference in the interpretation of the initiation of the studies.

They don't want the mutagenicity studies to delay the response. This plan is acceptable to FDA.

FDA requested that Roxane provide a specific timeline for the carcinogenicity studies as it would be needed for the Phase 4 commitment.

[REDACTED]

Roxane will discuss further before making a final decision regarding the carcinogenicity program.

**BEST POSSIBLE COPY**

NDA 20-932 (Oxycodone sustained-release)  
NDA 21-011 (Oxycodone immediate release)  
Friday, February 11, 2000  
Page 3

Roxane expects to submit the response to the AE letter by the end of February 2000

Cathie Schumaker

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21-011 (Oxycodone immediate release)

Friday, February 11, 2000

Page 3

Roxane expects to submit the response to the AE letter by the end of February 2000

[ /S/ ]

Cathie Schumaker

Cc:

Orig NDA 20-932

NDA 21-011

IND 40,071

IND 46,618

HFD-170/Div (4)

HFD-170/Blatt/3-12-00

HFD-170/Grosser/3-16-00

HFD-170/Hertz/3-15-00

HFD-170/Jean/3-16-00

HFD-170/McCormick/3-17-00

HFD-170/Permutt/3-20-00

HFD-170/Rappaport

R/D:C.Schumaker/3-10-00

APPEARS THIS WAY  
ON ORIGINAL

1 Page(s) Withheld

..AY 6 1998

Div

## CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

### MEETING SUMMARY

IND 46,618 S.No. 017

Submission Date: February 20, 1998

Meeting Date: May 1, 1998

Drug Name and Formulation: Roxicodone IR (oxycodone) 15 and 30 mg tablets

Sponsor: ~~\_\_\_\_\_~~

Reviewer: Venkata Ramana S. Uppoor, Ph.D.

Type of Submission: Pre-NDA meeting

**BACKGROUND:** Roxicodone tablets contain oxycodone, a semisynthetic narcotic useful as an analgesic. Roxicodone is currently marketed by Roxane Laboratories, Inc. as a 5 mg immediate release tablet, a 5 mg/5 ml oral solution, and as a 20 mg/ml concentrated oral solution. These products have been marketed in US since early 1980s as "grandfathered" pre-1938 drug products. The present 15 and 30 mg tablet strengths are being developed for the relief of moderate to severe pain. These dosage strengths lie within the dosing range already approved for Roxicodone. Further, these dosage strengths (5, 15 and 30 mg) are compositionally proportional. Another SR formulation has been developed as well.

**PURPOSE OF THE MEETING:** This pre-NDA meeting was requested by the sponsor to discuss their planned presentation of the data in the NDA.

**STUDIES CONDUCTED:** Two clinical trials were conducted primarily with an intent to obtain adequate safety information. This NDA for the two new strengths, therefore, is primarily based on bioavailability/bioequivalence data. The following studies will be submitted in the NDA along with a reference to oxycodone SR NDA for supportive studies for basic pharmacokinetics:

- 1) A single dose study to compare the relative bioavailability of 5 mg IR tablet with 5 mg/5 ml oral solution.
- 2) A single dose study to compare the relative bioavailability of 30 mg IR tablet with 5 mg/5 ml oral solution.
- 3) A bioequivalence study between 3 x 5 mg IR tablets, 1 x 15 mg IR tablet and 0.75 ml of 20 mg/ml oral solution.
- 4) A bioequivalence study between 6 x 5 mg IR tablets and 1 x 30 mg tablet.
- 5) Two studies to provide steady state pharmacokinetics following administration of the oxycodone 5 mg/5 ml oral solution and SR formulation (no study on IR formulation).
- 6) Food effect study on oral solution and SR formulation (no study on IR formulation).
- 7) Dose proportionality study in the dosing range of 5 to 30 mg oxycodone using 1 x 5 mg

tablet, 3 x 5 mg tablets and 6 x 5 mg tablets.

8) Population PK analysis from the clinical safety study.

**DISCUSSION:** The following information was conveyed and provided in writing to the sponsor:

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 12 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.

In addition, the following information was discussed. The clinical and to-be marketed formulations, as per the sponsor, are identical. Further, the sponsor was requested to provide individual study summaries on a diskette in MICROSOFT WORD format.

[ /S/ ] 05/06/98

Venkata Ramana S. Uppoor, Ph.D.  
Division of Pharmaceutical Evaluation - II

FT Initialed by John Hunt [ /S/ ] 5/6/98

CC list: HFD-170: IND 46,618; Division file; CSO\Bonnie McNeal; MO/Cortinovis; HFD-870: Venkata Ramana S. Uppoor, Mei-Ling Chen, John Hunt; Lesko; CDR\Barbara Murphy.

APPEARS THIS WAY  
ON ORIGINAL

## 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.

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care and Addiction  
Drug Products

---

**Memorandum**

---

**Date:** September 10, 1999  
**From:** Nancy Chamberlin  
**Subject:** NDA 21-011 Summary of Safety  
**To:** File

---

Please refer to the Summary of Safety located in the 1.1 volume of the application.

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care and Addiction  
Drug Products

---

**Memorandum**

---

**Date:** September 10, 1999  
**From:** Nancy Chamberlin  
**Subject:** NDA 21-011 Summary of Efficacy  
**To:** File

---

Please refer to the Summary of Efficacy located in the 1.1 volume of the application.

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care and Addiction  
Drug Products

---

**Memorandum**

---

**Date:** September 10, 1999  
**From:** Nancy Chamberlin  
**Subject:** NDA 21-011 DSI Inspections  
**To:** File

---

There were no pivotal clinical trials to inspect.

It was discussed in January 1999 with the biopharm reviewer if they would need an inspection. The reply was that they were inspected recently for their NDA 20-932 application and they would not need an inspection for this one.

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care and Addiction  
Drug Products

---

**Memorandum**

---

**Date:** September 10, 1999  
**From:** Nancy Chamberlin  
**Subject:** NDA 21-011 Name  
**To:** File

---

Roxicodone (oxycodone) is the name that the sponsor plans to use for this product. This NDA was to provide for line extension of an already marketed product.

The name was not sent to the naming committee, because Roxicodone is the name that Roxane has used for the 5 mg tablet for many years.

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care and Addiction  
Drug Products

---

**Memorandum**

---

**Date:** September 10, 1999  
**From:** Nancy Chamberlin  
**Subject:** NDA 21-011 Advisory Committee  
**To:** File

---

There was no advisory committee meeting for this application.

APPEARS THIS WAY  
ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care and Addiction  
Drug Products

---

**Memorandum**

---

**Date:** September 10, 1999  
**From:** Nancy Chamberlin  
**Subject:** NDA 21-011 Pharmacology Phase IV commitments  
**To:** File

---

It was discussed during the September 9, 1999 telecon with Roxane that the Division would consider the carcinogenicity testing as phase IV commitments if that was agreeable with Pharmacology Team.

APPEARS THIS WAY  
ON ORIGINAL

## Electronic Mail Message

**Date:** 8/28/00 4:04:59 PM  
**From:** Sosa, Myriam M ( MSOSA@ORA.FDA.GOV )  
**To:** Milstein, Judit ( MILSTEINJ@A1 )  
**Cc:** Amador, Diana ( DAMADOR@ORA.FDA.GOV )  
**Subject:** Retest of NDA 21-011

Good Afternoon Mrs. Milstein:

We received the samples for the retest of NDA 21-011 on last Friday afternoon. Two of our analysts came on Saturday and performed the impurity test. According to the HPLC chromatograms there were no unknown peaks detected after

Myriam M. Sosa  
Supervisory Chemists  
SJN-DO  
(787) 729-6853 x 2177

APPEARS THIS WAY  
ON ORIGINAL

## Electronic Mail Message

**Date:** 8/25/00 2:18:29 PM  
**From:** King, Alfred C ( AKING1@ORA.FDA.GOV )  
**To:** Milstein, Judit ( MILSTEINJ@A1 )  
**To:** Wekell, Marleen M ( MWekell@ORA.FDA.GOV )  
**To:** Murphy, Elise A ( emurphy@ora.fda.gov )  
**To:** Amador, Diana ( DAMADOR@ORA.FDA.GOV )  
**Subject:** NDA 21-011, Roxicodone Tablets

The Northeast Regional Laboratory has reanalyzed the NDA for the related compounds/impurities. Analyzed was the 15mg finished dosage. The results of the analysis did not detect the presence of the unknown impurity. Our previous analysis had detected each of the known impurities cited in the NDA plus the one additional unknown "impurity" calculated to be at the \_\_\_\_\_ level. Since our analysis had detected exactly what had been expected for each of the known impurities, there was not any reason to suspect a problem with the analysis in general. Because we had reserve sample, I had the analyst reanalyze the sample. The nondetection of the additional "impurity" cannot be easily explained other to hypothesis that \_\_\_\_\_

Based upon the above reanalysis, I recommend that you proceed with the approval of the NDA, Roxicodone, if the impurity analysis is the only thing holding up its approval by CDER.

Alfred C. King  
Director, Drug Chemistry Branch  
Northeast Regional Laboratory  
(718)340-7000, ext. 7126

43 Page(s) Withheld



## FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS  
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel:(301)827-7410

### NDA Safety Update

#### Application Information

NDA Number: 21-011

Sponsor: Roxane Laboratories

#### Drug Name

Generic Name: Oxycodone Hydrochloride (Immediate Release)

Trade Name: Roxicodone

Proposed Indication: Moderate to Severe Pain

Dosage Forms: 15 and 30 mg tablets

Route: Oral

#### Reviewer Information

Clinical Reviewer: Chang Q. Lee, MD, M.S.H.A., Dr.PH

Peer Medical reviewer: Bob Rappaport, MD, Deputy Division Director

Original Receipt Date: September 30, 1998

Completion Date: August 26, 1999

The sponsor filed a safety update report dated 2/11/99. However, no new safety information was submitted. The sponsor stated that there were no clinical or pre-clinical studies initiated or ongoing for Roxicodone tablets from the time of NDA submission to the report date.

**Regulatory Action: NAI**

[ \_\_\_\_\_ ] 8/26/99

Chang Q. Lee, M.D., MSHA, Dr.PH

Division of Anesthetic, Critical Care and Addiction Drug Products

August 26, 1999

# REQUEST FOR CONSULTATION

TO (Division/Office): Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm 15B03

FROM: HFD-170/ Dr. Cynthia McCormick

DATE 04-03-00	IND NO.	NDA NO. 21-011	TYPE OF DOCUMENT	DATE OF DOCUMENT 02-28-00
NAME OF DRUG Roxicodone Tablets (immediate release)		PRIORITY CONSIDERATION Medium	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE 5-8-00

NAME OF FIRM: Roxane Laboratories

## 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 II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                                |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                     |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                           |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                    |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Review of Tradename |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <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 IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV 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 RICK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

### V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
-----------------------------------	--------------------------------------

COMMENTS/SPECIAL INSTRUCTIONS:  
Please review the brand name for this product, oxycodone HCl. The previously approved name is Roxicodone. The 6-month due date is 8/29/00. Your expeditious review on this matter is greatly appreciated.

If you have any written comments, please provide a copy for Susmita Samanta, Regulatory Project Manager, HFD-170 and Joan Fuschetto, HFD-170.

SIGNATURE OF REQUESTER [ /S/ ] 4/3/00	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

**BEST POSSIBLE COPY**

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-11</u> / SE _____ - _____		
Drug <u>Roxicodone (oxycodone hydrochloride)</u> Applicant <u>Roxane Laboratories</u>		
RPM <u>Judit Milstein</u> Phone <u>(301) 827-7440</u>		
<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Reference listed drug <u>ANDA 7337 (Percodan)</u>		
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review	Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P
Pivotal IND(s) <u>46,618 and NDA 20,932</u>		
Application classifications:		PDUFA Goal Dates:
Chem Class _____		Primary _____
Other (e.g., orphan, OTC) _____		Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:  User Fee Paid  
 User Fee Waiver (attach waiver notification letter)  
 User Fee Exemption
  
- ◆ Action Letter.....  AP  AE  NA
  
- ◆ Labeling & Labels
 

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert) .....	X
Other labeling in class (most recent 3) or class labeling.....	_____
Has DDMAC reviewed the labeling? .....	<input checked="" type="checkbox"/> Yes (include review) <input type="checkbox"/> No
Immediate container and carton labels .....	X
Nomenclature review .....	X
  
- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application  is  is not on the AIP.  
 Exception for review (Center Director's memo)..... \_\_\_\_\_  
 OC Clearance for approval..... \_\_\_\_\_

- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review) ■ Materials requested in AP letter
  
- ◆ Post-marketing Commitments
  - Agency request for Phase 4 Commitments.....   X
  - Copy of Applicant's commitments .....
  
- ◆ Was Press Office notified of action (for approval action only)?.....  Yes  No
  - Copy of Press Release or Talk Paper.....
  
- ◆ Patent
  - Information [505(b)(1)] .....
  - Patent Certification [505(b)(2)].....   X
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
  
- ◆ Exclusivity Summary .....
  
- ◆ Debarment Statement .....
  
- ◆ Financial Disclosure
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....
  
- ◆ Correspondence/Memoranda/Faxes .....
  
- ◆ Minutes of Meetings .....

  - Date of EOP2 Meeting \_\_\_\_\_
  - Date of pre NDA Meeting   May 1, 1998
  - Date of pre-AP Safety Conference \_\_\_\_\_

  
- ◆ Advisory Committee Meeting .....

  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

  
- ◆ Federal Register Notices, DESI documents .....

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....
  
- ◆ Clinical review(s) and memoranda .....

- ◆ Safety Update review(s) ..... X
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred  
Pediatric Page..... \_\_\_\_\_
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable
- ◆ Statistical review(s) and memoranda ..... X
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) ..... X  
Recommendation for scheduling ..... \_\_\_\_\_
- ◆ Microbiology (efficacy) review(s) and memoranda ..... N/A
- ◆ DSI Audits ..... N/A  
 Clinical studies  bioequivalence studies ..... \_\_\_\_\_

**CMC INFORMATION:**

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

- ◆ CMC review(s) and memoranda ..... X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ◆ DMF review(s) ..... N/A
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... X
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... X
- ◆ Facilities Inspection (include EES report) ..... X  
Date completed \_\_\_\_\_  Acceptable  Not Acceptable
- ◆ Methods Validation .....  Completed  Not Completed

**PRECLINICAL PHARM/TOX INFORMATION:**

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

- ◆ Pharm/Tox review(s) and memoranda ..... X
- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/A

- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... N/A

**APPEARS THIS WAY  
ON ORIGINAL**

**18.0 User Fee Cover Sheet**

A completed User Fee Cover Sheet (Form FDA-3397) is provided.

**APPEARS THIS WAY  
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS  Mailing Address: Roxane Laboratories P.O. Box 16532 Columbus, OH 43216-6532  Facility Address: 1809 Wilson Road Columbus, OH 43228	3. PRODUCT NAME Roxicodone Tablets 15 mg and 30 mg (Oxycodone HCl Tablets USP)
2. TELEPHONE NUMBER (Include Area Code)  (614) 241-4131	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:  <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER 3542	6. LICENSE NUMBER / NDA NUMBER 21-011

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input checked="" type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, on reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO  
(See reverse side if answered YES)

**A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.**

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer  
Paperwork Reduction Project (0910-0297)  
Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

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

Please DO NOT RETURN this form to this address.

NATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Director, Drug Regulatory Affairs New Drugs and Regulatory Services	DATE 10 February 2000
--	---	--------------------------

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: November 30, 1996

USER FEE COVER SHEET

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden to:

Report's Clearance Officer, PHS  
Robert H. Mansbury Building, Room 721-6  
330 Independence Avenue, S.W.  
Washington, DC 20201  
ADU: PRA

and to:

Office of Management and Budget  
Paperwork Reduction Project (0910-0297)  
Washington, DC 20503

Please DO NOT RETURN this form to either of these addresses.

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

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

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Roxane Laboratories, Inc.  
P.O. Box 16532  
Columbus, OH 43216  
Attn: Sean Alan Reade

3. TELEPHONE NUMBER (Include Area Code)

(614) 276-4000 ext. 2345

4. PRODUCT NAME

TOXICODONE<sup>TM</sup> (15 and 30 mg)

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?

YES  NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

# 3542

7. LICENSE NUMBER/ NDA NUMBER

NDA No. 21-011

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92
- AN INSULIN PRODUCT SUBMITTED UNDER 506

- THE APPLICATION IS SUBMITTED UNDER 505(b)(2)  
(See reverse before checking box.)

FOR BIOLOGICAL PRODUCTS ONLY

- WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- EQUINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 5/1/92

- A CRUDE ALLERGENIC EXTRACT PRODUCT
- AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?

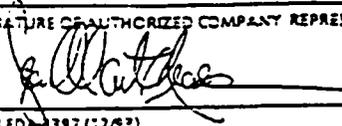
YES  NO  
(See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO  
(See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Director Regulatory Affairs

DATE

9 September 1998

BEST POSSIBLE COPY



P.O. Box 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Fax 614.274-0974

9 September 1998

FDA User Fee Lockbox Facility  
Mellon Bank  
Three Mellon Bank Center  
27<sup>th</sup> Floor (FDA 360909)  
Pittsburgh, PA 15259-0001

Subject: NDA No. 21-011  
Roxicodone™ (15 and 30 mg)  
User Fee Identification No. 3542

Payment of User Fee

Under the provisions of the "Prescription Drug User Fee Act of 1992," we are submitting a check for \$256,846.00. This payment reflects the fee rate for FY 1998 for original NDA submissions requiring clinical data cited in the Federal Register (Vol. 62, No. 236, 9 December 1997, p. 64849). The enclosed check represents 100% of the scheduled User Fee for NDA No. 21-011.

Regulatory correspondence concerning this NDA should be directed to Sean Alan F.X. Reade, Director of Regulatory Affairs, Roxane Laboratories, Inc. P.O. Box 16532, Columbus, Ohio 43216. I can be contacted by telephone at 800-848-0120, ext. 2345 and by telefax at 614-276-0321.

Please issue a receipt of payment following the deposit of our User Fee for NDA No. 21-011 User Fee ID No. 3542).

Respectfully,

Sean Alan F.X. Reade, M.A.  
Director Regulatory Affairs

**BEST POSSIBLE COPY**

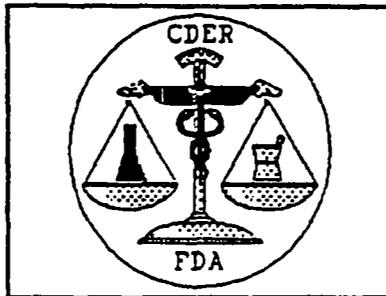
ROXANE • PAIN • INSTITUTE



1 • 8 0 0 • 3 3 3 • 9 1 0 0

U.S. FOOD AND DRUG ADMINISTRATION

**FAX CONTROL  
SHEET**



To: TO WHOM IT MAY CONCERN  
Title:  
Dept:  
Company: ROYANE LABORATORIES INC  
FAX: 916142760321

Date: Thursday, August 20, 1998

Our Ref:  
Subject: USER FXES

Message No. 12606

From: U.S. Food and Drug Administration  
FDA/CDER  
5600 Fishers Lane  
Rockville, MD 20857 U.S.A.

FAX: Phone:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone at the above number and return it to us at the above address by mail. Thank you.

Page 1, document continues...

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\*\*\*\*\*  
= THE FOOD AND DRUG ADMINISTRATION =  
= USER FEE ID ASSIGNMENT SYSTEM =  
\*\*\*\*\*

\*\*\*\*\* SUBMISSION INFORMATION \*\*\*\*\*

APPLICATION: NO21011  
ORIGINAL OR SUPPLEMENT: N  
RESUBMISSION?:  
FAX NUMBER: 6142760321  
COMPANY: ROXANE LABORATORIES INC  
REQUEST DATE: 20-AUG-1998

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>> USER FEE ID#: 3542

The assigned User Fee ID number must be noted on the submission sent into the FDA for review and also noted on the submitted payment.

This FAX will be the only notification you will receive of this User Fee ID Assignment.

APPEARS THIS WAY  
ON ORIGINAL

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DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration

SEP 21 1998

September 17, 1998

Sean Alan F.X. Reade, M.A.  
Director, Regulatory Affairs  
Roxane Laboratories  
P.O. Box 16532  
Columbus, OH 43216-6532

Dear Mr. Sean Alan Reade:

FDA received payment information on 09/11/98, concerning your check \_\_\_\_\_ dated 09/04/98 in the amount of \$256,846.00 for NDA 21-011. The check was deposited at Mellon Bank on 09/10/98. If I can be of further assistance please feel free to call me on (301) 827-5042. Thank you.

Sincerely,

[ /S/ ]

Donna Simms

FDA-Accounts Receivable Branch

APPEARS THIS WAY  
ON ORIGINAL

204 Draft Labeling Page(s) Withheld