CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-011

CHEMISTRY REVIEW(S)

VISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG ODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #21-011 Roxicodone (Oxycodone HCl USP) Tablets, 15mg and 30mg

REVIEW# 3 revised **DATE REVIEWED:** 4 August 2000

SUBMISSION TYPE DATE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment #14.01	1 August 2000	2 August 2000	3 August 2000 (Request for ——— expiration date with up dated stability data for — NDA lots)
Amendment #13.01	17 July 2000	18 July 2000	20 July 2000 (Response to teleconference dated 11 July 2000)
Amendment #11.01	23 Jun 2000	26 June 2000	27 June 2000 (Response to teleconference dated 24 May 00)
Amendment #7.01	28 Feb.2000	29 Feb.2000	6.March 2000 (Response to AE letter dated 23 Sept 1999)

NAME & ADDRESS OF APPLICANT:
Roxane Laboratories,1809 Wilson Road, Columbus, Ohio 43228.
tention: Mr. Robert Pfeifer, Assoc.Dir. of RA, Tel 614-241-4134

UG PRODUCT NAME

Proprietary: ROXICODONE TABLETS
Established: (Oxycodone Hydrochloride USP) Tablets
Code Name/#: 124-90-3 for Oxycodone HCl
Chem.Type/Ther.Class: 3 S

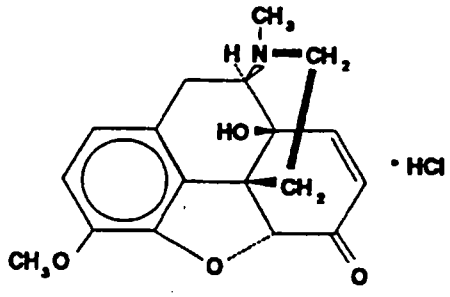
PHARMACOL. CATEGORY: for the management of moderate to severe pain.

DOSAGE FORM: 15 mg green tablets scored (identified 54 710) and 30 mg blue tablets (identified 54 199)
STRENGTHS: 15mg and 30mg Oxycodone HCl (equivalent to 13.5mg and 27mg Oxycodone free base)

DISPENSED: X **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and has the following structural formula:[4]



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

REMARKS:

Amendment dated 1 August 2000. Requested 3 year expiry date for oxicodone tablets by providing degradation products, potency, dissolution (average and mean) data for ——— NDA lots packaged in blisters and bottles and stored at 25C/60% RH. Controlled RH was added to the stability studies in June 1998, and prior to that ambient RH was used in the stability studies. Submitted a stability commitment to test the first three marketed batches and to report the results to FDA in annual reports (21 CFR 314.81 (b)(2)). Submitted a commitment to withdraw any lot which does not meet specifications (21 CFR 314.81(b)(1)(ii)).

Observed total unknown degradation products upon ———'s storage at 25C/60%RH in unit dose blisters and in bottles as 100s for the —NDA lots is shown below. All lots have met the acceptance criteria set at NMT —— w/w for total unknown degradation products based on the data given below

	Blisters	Bottles as 100s
15mg tablet lots		
969032 (used in MV, clinical and bio studies)		
969083	[———	———]
969084		
979023		
30mg tablet lots		
959069 (used in MV, clinical and bio studies)		
969081	[———	———]
969082		
979024		

drug related process impurities were excluded in the calculations, such as, [redacted] Oxycodone active drug has about [redacted] min retention time, and the chromatographic run time is about [redacted]

Amendment dated 28 Feb 2000: Submitted [redacted] stability update for the [redacted] NDA lots by reporting total unknown related compounds, single largest unknown related compound, oxycodone assay, dissolution, and appearance. Pending CMC review issue that total related substances (decomposition products) needs to be monitored, was not addressed in the amendment while responding to AE letter dated 23 Sept 1999. Roxane Labs has continued the regulatory posture that total unknown impurities are LT [redacted] individual unknown impurity is LT [redacted], and total related substances test is not a test in USP monograph for Oxycodone hydrochloride tablets USP. Total unknown related compounds and single largest unknown related compound were reported from area % values to weight % values by assuming a response factor of one. Excluded in the calculations of total unknown related compounds was unknown related compounds LT [redacted] (limit of detection) and known related compounds (process impurities) based on RRT.

CONCLUSIONS & RECOMMENDATIONS:

Evaluation summary: If [redacted] degradation product peak for Roxicodone tablets is true then identification and qualification of degradation products is required because of dosing, 15mg dosing every 4 hrs for pain or 90 mg maximum daily dose, as per Q3B ICH guidance document dated November 1996. Additional MV work is needed at NRL and San Juan Labs so as to re-confirm [redacted] degradation product peak at about [redacted]

The acceptance criteria for Roxicodone Tablets for known degradation peaks by [redacted] are NMT [redacted] w/w. [redacted] degradation peaks at [redacted] in amounts grater than [redacted] are identified at [redacted] for [redacted] NDA lots by assuming a response factor of one. [redacted] stability up date for [redacted] NDA lots supports 3-year expiry date requested for Roxicodone tablets manufactured, packaged, and released at Roxane Labs. Stability up date has justified [redacted] as primary supplier and [redacted] as alternate supplier for Oxycodone HCL USP grade. All mfg. sites are acceptable, as per EES dated 13 April 1999. Quality control methods were verified by two FDA Labs, NRL and SJN, and found to be suitable for regulatory analysis. Description and how supplied section of the draft labeling submitted on 28 February 2000 was reviewed and found to be satisfactory.

Amendment dated 17 July 2000. To support that there are no degradation product peaks at about [redacted] for the Roxicodone tablets, Roxane Labs has submitted chromatograms for the [redacted] NDA lots stored for [redacted]. Chromatograms were requested in teleconference dated 11 July 2000 because [redacted] degradation product peak at about [redacted] was reported by FDA NRL Lab in MV recommendation dated 28 December 1999. FDA SJN Lab did not report similar finding in MV recommendation dated 22 November 1999 because the chromatogram runs were shortened to [redacted] degradation product peak for Roxicodone tablets given up to 15mg dosing every 4 hrs for pain (90 mg maximum daily dose) requires identification and qualification of degradation products for the regulatory approval of NDA 21-011, as per Q3B ICH guidance document dated November 1996. Chromatogram peaks in terms of area % were converted to weight % by assuming the response factor as one, as stated in this amendment.

Observed major unknown degradation products by RRT upon [redacted] storage at 25C/60%RH in blisters and in bottles is shown below for the [redacted] NDA lots. All lots have met the acceptance spec set at NMT [redacted] w/w for unknown degradation products at [redacted] based on the data given below. [redacted] is the limit of detection for the test method, and as such, unknown degradation products at [redacted] were excluded from evaluation. Some typical chromatograms were attached to this review along with the acceptance criteria for the drug product.

15mg tablet lots	Blisters	Bottles as 100s
969032 (used in MV, clinical and bio studies)	[redacted]	
969083		
969084		
979023		
30mg tablet lots		
959069 (used in MV, clinical and bio studies)	[redacted]	
969081		
969082	[redacted]	
979024		

Amendment dated 23 June 2000. The origin of drug related impurities (degradation products) in Roxicodone tablets, and whether they increase upon storage was not addressed in this amendment. In the stability report for the [redacted] NDA lots, the degradation products were reported as peak RRTs and proposed an acceptance criteria for total unknown impurities LT [redacted], individual unknown impurity LT [redacted] at RRTs [redacted] Known

The proposed specifications of —— for individual impurities and —— for total impurities for the drug product are justified by the submitted data and are considered acceptable.

Recommendations are to approve Roxicodone tablets 15 mg and 30 mg from CMC point of view. It is recommended the project manager have to include in the action letter the standard paragraph relating to pending MV work at FDA Labs.

Dr. P.Maturu, Review Chemist [/S/]

Dr. S.Koepke, Deputy Division Director DNDC2

[/S/] 8/17/00

cc:
NDA 21011
HFD-170/PMaturu, DKoble, SKoepke
HFD-170/JMilstein
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APPROVED

Seven enclosures:

1.Acceptance criteria for the drug product.
2.Stability data to support 3 year expiry date for the drug product.
3.Chromatograms submitted by the applicant for the drug product stored for —— to support that there are no degradation product peaks at about ——
4. Chromatograms submitted by NRL FDA Lab to support that there are degradation peaks at about ——
5. Chromatograms submitted by SJN FDA Lab with run time —— and the method call for run time of about ——
6. MV samples are from 15mg tablet lot 969032 and 30 mg tablet 959069. Same lots were used in clinical and bio studies (IND 46,618)
7. Chromatograms for Oxycodone HCl USP grade drug substance lots, supplied by ——————, for linkages to drug related process impurities.

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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG ODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA# 21-011

REVIEW# 2 **DATE REVIEWED:** 7.30.99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	5-24-99	5-25-99	(Response to telecon of 5-17-99)
Amendment	6-10-99	6-11-99	(Response to 1st MV letter)
Amendment	6-23-99	6-24-99	(Response to telecon of 5-10-99)
Amendment	7-21-99	7-22-99	(Response to 2nd MV letter)

NAME & ADDRESS OF APPLICANT:
Roxane Laboratories, 1809 Wilson Road, Columbus, Ohio 43228, Sean Alan Reade, Director of RA, Tel 614-276-4000 ext. 2345.

DRUG PRODUCT NAME

Proprietary: ROXICODONE
Established: Oxycodone Hydrochloride Tablets USP
Code Name/#: 76-42-6, Oxycodone and 124-90-3,Oxycodone HCl
Chem.Type/Ther.Class: 3 S

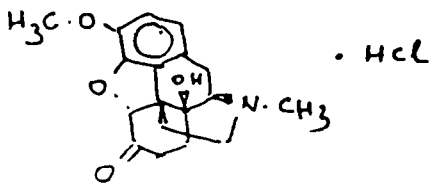
RMACOL. CATEGORY: for the management of moderate to severe pain.

DOSAGE FORM: 15 mg green tablets and 30 mg blue tablets

STRENGTHS: 15 and 30 mg

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
4,5 alpha-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. C18H21N04.HCl M.W.351.83. Crystalline powder freely soluble in water (1gm/10 ml) and n-octanol to water partition = 0.7, as per vol.1 p.84-85.



REMARKS:

Amendment dated 24 May 1999 with updated stability results and revised PPI was submitted as a response to telecon of 17 May 1999:

To justify ——— as alternate supplier for Oxycodone HCL active, satisfactory ———— analytical results were submitted for 15mg tablets lot 979023 and 30mg tablets lot 979024 in bottles as 100s and in —— blisters as — See enclosed pages 5-8. The up-dated stability report was submitted with ———— analytical results for the test parameters, assay, related compounds, dissolution, and appearance. Less than ——— % values were reported for total unknown related compounds for short term accelerated (40 C/75% RH) and long term room temperature (25 C) storage studies. ——— % values were reported for total unknown related compounds for the drug substance, ——— ——— and ———

To justify ———— as supplier for Oxycodone HCL active, satisfactory ———— analytical results were submitted for 15mg tablets lots 969032 and 30mg tablets lot 959069 in bottles and in blisters. See enclosed pages 9-12. The revised assay values were reported for ——— without any explanation for the revision from ——— ——— For example for bottle package, ———— in place of ——— for 15mg lot 969032, and ———— in place of ——— ——— for 30mg tablets lot 959069.

Satisfactory ——— RT analytical results were submitted for 15mg tablets lots 969083 and 969084 and 30mg tablets lots 969081 and 969082 in bottles ————.

Satisfactory ———— RT analytical results were submitted for 15mg tablets lots 969083 and 969084 and 30mg tablets lots 969081 and 969082 in blister ————

COMMENT: Total related compounds are not monitored in the stability report to assess the impact of storage on known related compounds. See enclosed pages 13-19. Submitted analytical results has excluded known related compounds, such as, ———— ———— etc. Satisfactory results were compiled for — long term storage for — lot per potency per supplier by not monitoring known related compounds.

Revised PPI dated 21 May 99 was submitted to show conformity with 21 CFR 201.56 for the content and format of labeling for human prescription drugs. Listed dyes in tablets are acceptable by reference to QC standards in 21 CFR 82.1710 for D&C Yellow #10 and 21 CFR 74.102 for FD&C Blue #2. Inactive ingredients in tablets are acceptable by reference to current standards in USP/NF. Active ingredient in Oxycodone hydrochloride tablets acceptable by reference to standards in current USP/NF. Oxycodone

hydrochloride tablets are acceptable by reference to current standards in USP/NF. Description section has listed proprietary name, established name, type of dosage form, route of administration, pharmacological class of the drug, chemical name, structural formula of the drug, appropriate physical constants, aqueous solubility 1gm in 7ml, octanol water partition 0.7. Dyes in tablets were listed as D&C Yellow #10 in 15mg tablets and FDC Blue #2 in 15mg and 30mg tablets.

Fluorescent light at about [redacted] and 75% relative humidity moisture had no impact on packaged oxycodone hydrochloride tablets during [redacted] stability testing (attachment VI in 5.24.99 amendment). However, as a routine practice dispensing in tight light resistant containers is cited in PPI. How supplied section has shown strength of the dosage form, color/shape/scoring, NDC code, storage conditions, etc.. Medication containing bottles and unit dose blisters are stored at controlled room temperature protected from moisture. Dosage and administration section of PPI/label, has shown the recommended daily dose, the intervals recommended between doses, the usual dose range, the method of titrating the dose, dosage equivalents and conversion factors to oral oxycodone, etc.

Amendment dated 10 June 99 was submitted in response to first IR from FDA Labs. Lab note book pages relating to assay, content uniformity, related compounds, dissolution at 45min, chromatograms, etc., were submitted in support of COA for 15mg Oxicodone tablets lot 969032. Test samples sent to FDA Labs were also identified. As per enclosed page 12, about [redacted] content was observed for the known related compound, [redacted] a significant increase from [redacted] % reported for the drug substance lot, [redacted] lot NE139393. These details are adequate for MV work at FDA Labs.

Amendment dated 23 June 1999 was submitted with a microbial limit test of not more than [redacted] per gram as an added test for the drug product release. See enclosed pages 18-19. Since the drug product has [redacted] lactose content, microbial limit test was suggested to the applicant on 10 May 1999.

Amendment dated 21 July 99 was submitted in response to 2nd IR from FDA Labs. Lab note book pages relating to assay, content uniformity, related compounds, dissolution at 45min, chromatograms, etc., were submitted in support of COA for 30mg Oxicodone tablets lot 959069. As per enclosed page 15, about [redacted] % content was reported for the known related compound, [redacted] on p.53, a significant increase from [redacted] % reported for the drug substance lot, [redacted] lot [redacted]139393. These details are adequate for MV work at FDA Labs.

MV work for alternate assay methods is in progress at Philadelphia and San Juan. By 19 July 99, test samples were shipped to FDA Labs.

CONCLUSIONS & RECOMMENDATIONS:

Evaluation summary: Adequate documentation is available for NDA 21011 registration batches, — lots of 15 mg and — lots of 30 mg IR Oxycodone HCl tablets, with —— long term stability to support ———— as primary supplier and ——— as alternate supplier. Microbial limit test is added for drug product release. Proposed QC methods are being verified by two FDA. All mfg sites are acceptable to OC.

Recommendations are to approve: (a) ———————— as suppliers for Oxycodone HCl USP; (b) ——— tablets batch sizes, and (c) .——— of expiry date for 15mg and 30mg Oxycodone tablets supplied as 100s in ——— bottles and as unit dose in—— blisters. My recommendation is that total related compounds be monitored as `stability protocol'.

Note to CSO; Please include standard MV paragraph in the letter to applicant.

[/S/] 7·30·99
Dr. P.Maturu, Review Chemist

[/S/] 7/30/99
Dr. A.D'Sa, Chemistry Team Leader

cc:
Orig NDA 21011
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HFD-820/JGibbs
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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA# 21-011

REVIEW# 1 **DATE REVIEWED:** Rev. 5.10.99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	29 Sept 98	30 Sept 98	13 Oct 98

NAME & ADDRESS OF APPLICANT:
Roxane Laboratories, 1809 Wilson Road, Columbus, Ohio 43228, Sean Alan Reade, Director of RA, Tel 614-276-4000 ext. 2345.

DRUG PRODUCT NAME

Proprietary:	ROXICODONE
Established:	Oxycodone Hydrochloride Tablets USP
Code Name/#:	76-42-6, Oxycodone and 124-90-3,Oxycodone HCl
Chem.Type/Ther.Class:	3 S

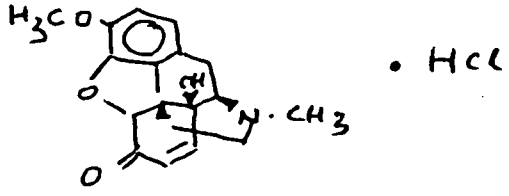
PHARMACOL. CATEGORY: for the management of moderate to severe pain.

DOSAGE FORM: 15 mg green tablets and 30 mg blue tablets

STRENGTHS: 15 and 30 mg

DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
4,5 alpha-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. C18H21N04.HCl M.W.351.83. Crystalline powder freely soluble in water (1gm/10 ml) and n-octanol to water partition = 0.7, as per vol.1 p.84-85.



RELATED DOCUMENTS:
IND 46618 dated 9 Oct 98.
DMF — for _____ by _____
DMF — for _____ by _____

REMARKS:

IND 46618, a predecessor for NDA 21011, was filed in Nov 94 to compare the bioavailability of 30 mg IR oxycodone tablets with [redacted] tablet weight, early formulation, to the marketed 5 mg IR oxycodone tablets with 100 mg tablet weight. This formulation was subsequently reformulated to [redacted] tablet weights, and filed as NDA 21011. 26 subjects were given the early formulation and 19 subjects were given the reformulated formulation to collect the safety data. Safety data from these 45 subjects was included in the integrated summary of safety. Early formulation was reviewed by Dr. Bhavnagri, in Nov 94, with an information request. A re-request was made in May 98 at pre-NDA meeting with the sponsor. Re-request has included, items such as, quantitative composition, oxycodone source, process equipment, process description, release test methods, stability for the clinical study duration, for different oxycodone strengths. The 5, 15 and 30 mg oxycodone tablets were identified with their respective lot nos. Roxane has responded satisfactorily to the information request as amendment to IND 46618 on 9 Oct 98.

USP grade Oxycodone HCl, a total of [redacted] lots from [redacted] were used in the clinical Development program for NDA 21011. These sites were acceptable to OC, as per EES dated 13 April 99. [redacted] lot T03115 was formulated as 15 mg/lot969032 and 30 mg/lot 959069 IR tablets, and [redacted] stability data on these lots were given in NDA to support of [redacted] expiry for bottles and blisters. [redacted] suppliers of Oxycodone HCl have supplied an acceptable USP quality active, and the applicant was able to produce acceptable quality drug product.

For the NDA filing, 15 mg green tablet and 30 mg blue tablet, were [redacted] tablet weight using [redacted] batch size at site with CFN# [redacted] This site is acceptable to OC, as per EES dated 13 April 99. The inactive ingredients were, lactose NF, microcrystalline cellulose NF [redacted] sodium starch glycolate NF [redacted] stearic acid NF, DC yellow no.10 [redacted] (15mg tablet), and FDC Blue no. 2 [redacted] (15mg and 30mg tablets). Roxane's 15 mg and 30mg Oxycodone hydrochloride tablets meet USP monograph standards. Lot release tests were positive description and identity, dissolution Q of NLT [redacted] in 45 min, uniformity of dosage units, [redacted] assay, NMT [redacted] total related compounds and NMT [redacted] single related compounds. Individual tablet dissolution was recorded for ten tablets on the COA at the time of lot release. Alternate QC methods were employed in place of USP methods, and these methods were submitted to 2 FDA labs, on 5.6.99.

Unit operations and process equipment were as follows for the [redacted] NDA registration batches: [redacted]

[ ]

The drug products were supplied as 100s in bottles and as unit dose blisters in 25s per card for NDA registration. The drug products were dispensed in tight light resistant containers, protected from moisture, and stored at controlled room temperature. Up to ——— satisfactory stability at 25 C was submitted for — lot per potency compounded from ——————— lot T03115, 15 mg/lot 969032 and 30 mg/lot 959069. Up to ——— satisfactory accelerated stability was also submitted for bottles and blisters stored at either 40 C/75% RH or 25 C/about ——— light storage conditions. The proposed stability protocol in vol. 3 p.463, was acceptable. Container labels for the drug products have no US patents, and there are no US patents for single entity IR Oxycodone HCL for the treatment of moderate to severe pain, as per patent certification to NDA.

CONCLUSIONS & RECOMMENDATIONS:

All mfg. sites are acceptable to OC. Adequate documentation was submitted for the NDA registration batches, — lots of 15 mg and — lots of 30 mg IR Oxycodone HCl tablets, with a request for 3 years of exclusivity. Up to ——— stability date was submitted for — lot per potency formulated from ——————— lot T03115. Alternate QC methods for release and stability testing were employed and these methods were submitted to two FDA labs on 5.6.99 for methods verification.

My recommendations are to approve, (a) ——————— Oxycodone HCl USP as a supplier; (b) ——— tablets batch sizes, and (c) ——— of expiry date for the drug product supplied as 100s in ——— bottles and as unit dose in ——— blisters.

It is unclear from the submission, that drug products made from — sources were used in clinical trials. Post-approval, ——— source may be approved upon completion of ——— stability testing of lots 979023 and 979024. Microbial limit tests, USP (61) general test, are not specified for Oxycodone HCl tablets USP. However, given ——— % w/w lactose content of the tablets, the applicant be advised to include a microbial limit tests for the release of Oxycodone tablets.

Note to CSO; Please include standard MV paragraph in the letter to applicant.

[/S/] 5.10.99
Dr. P.Maturu, Review Chemist

[/S/] 5/10/99
Dr. A.D'Sa, Chemistry Team Leader

cc:
Orig. NDA 21011
HFD-170/PMaturu,AD'Sa
HFD-820/JGibbs

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ADEQUATE

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