

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number**      **40255**

**Trade Name**      **Oxycodone and Aspirin Tablets USP,**  
**4.5mg/0.38mg/325mg**

**Generic Name**      **Oxycodone and Aspirin Tablets USP,**  
**4.5mg/0.38mg/325mg**

**Sponsor**      **Watson Laboratories, Inc.**

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 40255**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number      40255**

**APPROVAL LETTER**



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and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

*Sporn*  
22-27-88

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER 40255**

**FINAL PRINTED LABELING**

**Royce**™ NDC 51875-0404-1

FEB 27

**OXYCODONE AND ASPIRIN TABLETS, USP**

**4.5 mg+/0.38 mg+/325 mg**

**\*WARNING: May be habit forming  
CAUTION: Federal law prohibits dispensing without prescription.**

**100 Tablets**

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:  
Exp. Date:



N 3 51875-0404-1 8

Each tablet contains:  
Oxycodone hydrochloride, USP ..... 4.5 mg+  
Aspirin, USP ..... 325 mg  
Oxycodone hydrochloride, USP may be habit forming.  
WARNING: May be habit forming.  
Oxycodone tartrate, USP ..... 0.38 mg+  
Oxycodone HCl is equivalent to 4.0337 mg of oxycodone tartrate.  
Oxycodone HCl is equivalent to 0.3008 mg of oxycodone.  
Usual Dosage: Full prescribing information see accompanying product literature.  
Store at controlled room temperature, 15°-30°C (59°-86°F).  
REPLACE CAP IMMEDIATELY.  
PROTECT FROM LIGHT AND MOISTURE.  
Dispense in a light, light-resistant container as defined in the USP.  
DEA ORDER FORM REQUIRED

**Royce**™ NDC 51875-0404-2

**OXYCODONE\* AND ASPIRIN TABLETS, USP**

**4.5 mg+/0.38 mg+/325 mg**

**\*WARNING: May be habit forming  
CAUTION: Federal law prohibits dispensing without prescription.**

**500 Tablets**

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:  
Exp. Date:



N 3 51875-0404-2 5

Each tablet contains:  
Oxycodone hydrochloride, USP ..... 4.5 mg+  
Aspirin, USP ..... 325 mg  
Oxycodone hydrochloride, USP may be habit forming.  
WARNING: May be habit forming.  
Oxycodone tartrate, USP ..... 0.38 mg+  
Oxycodone HCl is equivalent to 4.0337 mg of oxycodone tartrate.  
Oxycodone HCl is equivalent to 0.3008 mg of oxycodone.  
Usual Dosage: Full prescribing information see accompanying product literature.  
Store at controlled room temperature, 15°-30°C (59°-86°F).  
REPLACE CAP IMMEDIATELY.  
PROTECT FROM LIGHT AND MOISTURE.  
Dispense in a light, light-resistant container as defined in the USP.  
DEA ORDER FORM REQUIRED

**Royce**™ NDC 51875-0404-4

27

**OXYCODONE\* AND ASPIRIN TABLETS, USP**

**4.5 mg+/0.38 mg+/325 mg**

**\*WARNING: May be habit forming  
CAUTION: Federal law prohibits dispensing without prescription.**

**1000 Tablets**

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:  
Exp. Date:



N 3 51875-0404-4 9

Each tablet contains:  
Oxycodone hydrochloride, USP ..... 4.5 mg+  
Aspirin, USP ..... 325 mg  
Oxycodone hydrochloride, USP may be habit forming.  
WARNING: May be habit forming.  
Oxycodone tartrate, USP ..... 0.38 mg+  
Oxycodone HCl is equivalent to 4.0337 mg of oxycodone tartrate.  
Oxycodone HCl is equivalent to 0.3008 mg of oxycodone.  
Usual Dosage: Full prescribing information see accompanying product literature.  
Store at controlled room temperature, 15°-30°C (59°-86°F).  
REPLACE CAP IMMEDIATELY.  
PROTECT FROM LIGHT AND MOISTURE.  
Dispense in a light, light-resistant container as defined in the USP.  
DEA ORDER FORM REQUIRED



**OXYCODONE AND ASPIRIN  
TABLETS, USP**



FEB 27 1995

**DESCRIPTION**

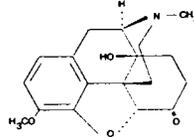
Oxycodone and Aspirin Tablets, for oral administration, contain:

- Oxycodone hydrochloride, USP 4.5 mg+
- Oxycodone terephthalate, USP 0.38 mg++
- Aspirin, USP 325 mg

+4.5 mg oxycodone HCl is equivalent to 4.0337 mg of oxycodone.  
++0.38 mg oxycodone terephthalate is equivalent to 0.3008 mg of oxycodone.

In addition, each tablet also contains the following inactive ingredients: corn starch, D&C Yellow #10 Aluminum-lake and microcrystalline cellulose.

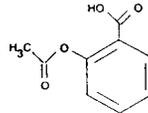
Oxycodone is chemically designated as 4,5 $\alpha$ -epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one. It is a white odorless crystalline powder which is derived from the opium alkaloid, thebaine, soluble in water and slightly soluble in alcohol. It may be represented by the following structural formula:



Molecular formula: C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>

Molecular weight: 315.37

Aspirin is chemically designated as salicylic acid acetate. It is a white crystalline powder, either odorless or with a faint odor. It is slightly soluble in water, freely soluble in alcohol, soluble in chloroform and in ether, and sparingly soluble in absolute ether. It may be represented by the following structural formula:



Molecular formula: C<sub>9</sub>H<sub>8</sub>O<sub>4</sub>

Molecular weight: 180.16

**CLINICAL PHARMACOLOGY**

The principle ingredient, oxycodone, is a semisynthetic narcotic analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principle actions of therapeutic value of the oxycodone in oxycodone and aspirin tablets are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Oxycodone and aspirin tablets also contain the non-narcotic antipyretic-analgesic, aspirin.

**INDICATIONS AND USAGE**

For the relief of moderate to moderately severe pain.

**CONTRAINDICATIONS**

Hypersensitivity to oxycodone or aspirin.

**WARNINGS**

**Drug Dependence:** Oxycodone 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 of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, oxycodone and aspirin tablets are subject to the Federal Controlled Substances Act.

**Usage in ambulatory patients:** Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using oxycodone and aspirin should be cautioned accordingly.

**Interactions with other central nervous system depressants:** Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone and aspirin may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

**Usage in pregnancy:** Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, oxycodone and aspirin should not be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

**Usage in children:** Oxycodone and aspirin should not be administered to children.

**Reye Syndrome** is a rare but serious disease which can follow flu or chicken pox in children and teenagers. While the cause of Reye Syndrome is unknown, some reports claim aspirin (or salicylates) may increase the risk of developing this disease.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

#### PRECAUTIONS

##### General

**Head injury and increased intracranial pressure:** The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

**Acute abdominal conditions:** The administration of oxycodone and aspirin or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

**Special risk patients:** Oxycodone and aspirin tablets should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

##### Drug Interactions

The CNS depressant effects of oxycodone and aspirin may be additive with that of other CNS depressants. (See **WARNINGS**)

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effects of uricosuric agents.

#### ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

#### DRUG ABUSE AND DEPENDENCE

Oxycodone and aspirin tablets are a Schedule II controlled substance. Oxycodone can produce drug dependence and has the potential for being abused. (See **WARNINGS**)

#### OVERDOSAGE

**Signs and Symptoms:** Serious overdose with oxycodone and aspirin is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of oxycodone and aspirin tablets may, in addition, result in acute salicylate intoxication.

**Treatment:** Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdose or unusual sensitivity to narcotics including oxycodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial adult dose 0.4 mg - 2 mg) preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

#### DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Oxycodone and aspirin tablets are given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

#### HOW SUPPLIED

Oxycodone and Aspirin Tablets, 4.5 mg+/0.38 mg+/325 mg are yellow, round biconvex tablets, debossed with product code number "404" above the score on one side and with the Royce logo on the other side.

SIZE	ROYCE NDC NUMBER
100	51875-0404-1
500	51875-0404-2
1000	51875-0404-4

Store at controlled room temperature: 15°-30°C (59°-86°F).

**REPLACE CAP IMMEDIATELY.**

**PROTECT FROM LIGHT AND MOISTURE.**

Dispense in a tight, light-resistant container as defined in the USP.

**DEA Order Form Required.**

**Rx only**

Royce Laboratories, Inc.  
16600 N.W. 54 Avenue  
Miami, FL 33014

Revised: Feb. 1998

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      40255**

**CHEMISTRY REVIEW(S)**



17. COMMENTS  
None

18. CONCLUSIONS AND RECOMMENDATIONS  
Recommend approval letter to issue.

19. REVIEWER:  
Edwin Ramos

DATE COMPLETED:  
January 9, 1998

2/19/98

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      40255**

**BIOEQUIVALENCE REVIEW(S)**

OCT - 3 1997

Oxycodone and Aspirin, USP  
Oxycodone HCl, Oxycodone Terephthalate, Aspirin  
4.5 mg/0.38 mg/325 mg Tablet  
ANDA #40-255  
Reviewer: James E. Chaney  
WP# 40255DW.597

Royce Laboratories Inc.  
Miami, Florida  
Submission Date:  
May 8, 1997

Review of Dissolution Data and a Waiver Request

The firm has submitted comparative *in vitro* dissolution data for its drug product, Oxycodone and Aspirin Tablet USP, (oxycodone HCl/oxycodone terephthalate/aspirin, 4.5 mg/0.38 mg/325 mg) comparing it to the reference, DuPont Merck's Percodan Tablets<sup>R</sup> (oxycodone HCl/oxycodone terephthalate/aspirin, 4.5 mg/0.38 mg/325 mg) in support of a request for a waiver of *in vivo* bioequivalence requirements.

Comments:

1. The test drug product contains active ingredients in the same strength and dosage form as the currently approved reference product, DuPont Merck's Percodan Tablet<sup>R</sup> (oxycodone HCl/oxycodone terephthalate/aspirin, 4.5 mg/0.38 mg/325 mg).
2. The dissolution method (USP) used was correct and satisfactory content uniformity data was submitted for the lot used in the dissolution testing. The amounts of oxycodone and aspirin were measured by both the USP analytical method and a validated in-house method. The results from the two methods are shown in Tables 1 and 2, respectively.
3. The dissolution testing data demonstrate that the test and reference products meet the USP dissolution specifications (Table 1). The specifications are that not less than of the labeled amount of oxycodone and not less than of the labelled amount of aspirin is dissolved in 30 minutes.
4. The reference product, DuPont Merck's Percodan Tablet<sup>R</sup>, (oxycodone HCl/oxycodone terephthalate/aspirin, 4.5 mg/0.38 mg/325 mg) is classified AA in "Approved Drug Products with Therapeutic Equivalence Evaluations". Therefore, since the dissolution testing is acceptable there would be no need to conduct an *in vivo* bioequivalence study.
5. The formulation of the test product is given in Table 3.

Recommendations:

1. The dissolution testing conducted by Royce Laboratories, Inc. on its drug product, oxycodone and aspirin tablets USP, 4.5 mg/0.38 mg/325 mg (oxycodone HCl/oxycodone terephthalate/aspirin), lot # NL-1901, has been found acceptable.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.05 M acetate buffer (pH 4.5) at 37°C using USP XXIII apparatus I (basket) at 50 rpm. The test product should meet the following specifications:

Not less than \_\_\_\_\_ of the labeled amount of oxycodone and NLT \_\_\_\_\_ of aspirin in the dosage form is dissolved in 30 minutes.

3. The Division of Bioequivalence agrees that the information submitted by Royce Laboratories, Inc. on its drug product, oxycodone and aspirin tablets USP, 4.5 mg/0.38 mg/325 mg falls under 21 CFR 320.22 of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the drug is granted. From the bioequivalence point of view, the Division of Bioequivalence deems oxycodone and aspirin tablets USP, 4.5 mg/0.38 mg/325 mg (oxycodone HCl/oxycodone terephthalate/aspirin) manufactured by Royce Laboratories, Inc. to be bioequivalent to the reference product, Percodan Tablets<sup>R</sup> 4.5 mg/0.38 mg/325 mg manufactured by DuPont Merck.

James E. Chaney, Ph.D.  
Division of Bioequivalence  
Review Branch I

RD INITIALED YCHuang  
FT INITIALED YCHuang

Date 9/2/97

Concur: \_\_\_\_\_ Date: 10/3/97

Rabindra Patnaik, Ph.D.  
Acting Director, Division of Bioequivalence

cc: ANDA 40-255 (original, duplicate), HFD-652 (Huang, Chaney), HFD-650 (Director),  
Drug File, Division File

JEC/082697/WP #40255DW.597

**Table 1. In Vitro Dissolution Testing Using the USP Analytical Method**

Drug (Generic Name): Oxycodone and Aspirin Tablets

Dose Strength: 4.5 mg/0.38 mg/325 mg

ANDA No.: 40-255

Firm: Royce Laboratories, Inc.

Submission Date: May 8, 1997

File Name: 40255DW.597

**I. Conditions for Dissolution Testing:**

USP XXIII Basket: X Paddle: RPM: 50

No. Units Tested: 12

Medium: pH 4.5 Acetate Buffer Volume: 500 ml

Specifications: NLT of the oxycodone in 30 min and NLT of the aspirin in 30 min.

Reference Drug: DuPont Merck's Percodan Tablets<sup>R</sup> (oxycodone HCl/oxycodone terephthalate/aspirin, 4.5 mg/0.38 mg/325 mg)

Assay Methodology:

**II. Results of In Vitro Dissolution Testing:**

**Oxycodone**

Sampling Times (Minutes)	Test Product Lot #NL-1901 Strength(mg): 4.5 mg/0.38 mg HCl/Terephthalate salts			Reference Product Lot #EHL290A, Exp 9/97 Strength(mg): 4.5 mg/0.38 mg HCl/Terephthalate salts		
	Mean %	Range	%CV	Mean %	Range	%CV
10	100.5		2.0	96.5		4.9
20	100.6		4.1	99.4		1.8
30	101.8		2.1	98.2		3.1
45	101.6		1.9	99.1		0.9

**Aspirin**

Sampling Times (Minutes)	Test Product Lot # NL-1901 Strength (mg): 325			Reference Product Lot # EHL290A, Exp 9/97 Strength (mg): 325		
	Mean %	Range	%CV	Mean %	Range	%CV
10	62.0		7.7	34.9		15.6
20	92.9		1.8	66.4		10.3
30	94.6		3.2	84.1		5.7
45	95.8		2.4	93.1		3.6

**Table 2. In Vitro Dissolution Testing Using an In-House Analytical Method**

<b>Drug (Generic Name): Oxycodone and Aspirin Tablets</b> <b>Dose Strength: 4.5 mg/0.38 mg/325 mg</b> <b>ANDA No.: 40-255</b> <b>Firm: Royce Laboratories, Inc.</b> <b>Submission Date: May 8, 1997</b> <b>File Name: 40255DW.597</b>						
<b>I. Conditions for Dissolution Testing:</b> USP XXIII Basket: X Paddle: RPM: 50 No. Units Tested: 12 Medium: pH 4.5 Acetate Buffer Volume: 500 ml Specifications: NLT of the oxycodone in 30 min and NLT of the aspirin in 30 min. Reference Drug: DuPont Merck's Percodan Tablets <sup>R</sup> (oxycodone HCl/oxycodone terephthalate/aspirin, 4.5 mg/0.38 mg/325 mg) Assay Methodology:						
<b>II. Results of In Vitro Dissolution Testing:</b>						
<b>Oxycodone</b>						
<b>Sampling Times (Minutes)</b>	<b>Test Product</b> Lot #NL-1901 Strength(mg): 4.5 mg/0.38 mg HCl/Terephthalate salts			<b>Reference Product</b> Lot #EHL290A, Exp 9/97 Strength(mg): 4.5 mg/0.38 mg HCl/Terephthalate salts		
	Mean %	Range	%CV	Mean %	Range	%CV
10	104.0		2.1	99.0		4.0
20	106.8		2.2	103.0		1.3
30	106.6		2.0	100.4		1.3
45	104.9		2.3	102.5		1.1
<b>Aspirin</b>						
<b>Sampling Times (Minutes)</b>	<b>Test Product</b> Lot # NL-1901 Strength (mg): 325			<b>Reference Product</b> Lot # EHL290A, Exp 9/97 Strength (mg): 325		
	Mean %	Range	%CV	Mean %	Range	%CV
10	63.8		6.9	34.6		17.1
20	96.4		2.5	68.1		9.5
30	97.9		2.1	86.0		4.0
45	98.2		2.2	93.5		2.6

Table 3.

**Formulation of Royce Laboratories' Oxycodone and Aspirin, 4.5 mg/0.38 mg/325 mg Tablets**

<b><u>Component</u></b>	<b><u>mg/Tablet</u></b>
Oxycodone Terephthalate, USP	0.38
Oxycodone HCl, USP	4.50
Microcrystalline Cellulose, NF	
D&C Yellow #10 Al-lake which is composed of D&C Yellow #10 and Aluminum hydroxide	
Aspirin which is composed of: Aspirin USP and	
<b>Total Weight</b>	<b>480.00</b>

# OFFICE OF GENERIC DRUGS

## DIVISION OF BIOEQUIVALENCE

**ANDA/AADA #** 40-255                      **SPONSOR:** Royce Laboratories, Inc.  
**DRUG & DOSAGE FORM:** Oxycodone and Aspirin Tablets, USP  
 (Oxycodone HCl; Oxycodone Terephthalate, Aspirin)

**STRENGTH (s):** 4.5 mg/0.38 mg/325 mg  
**TYPE OF STUDY:** Dissolution in support of requested waiver of *in vivo* bioequivalence study.  
**STUDY SITE:** Royce Laboratories, Inc.  
**STUDY SUMMARY:** Reference product is classified AA and comparative dissolution is acceptable. Waiver of BIO study is granted.

**DISSOLUTION:**

USP, Basket, 50 rpm, 12 Units, 500 mL pH 4.5 Acetate Buffer; Specifications: NL<sup>T</sup> of the oxycodone in 30 min and NL<sup>T</sup> of the aspirin in 30 min; Ref Drug: DuPont Merck's Percodan Tablet<sup>R</sup> (oxycodone HCl/oxycodone terephthalate/aspirin, 4.5 mg/0.38 mg/325 mg); Assay Methodology:

Time	Test Product			Reference Product		
	Mean	Range	%CV	Mean	Range	%CV
<b>Oxycodone</b>						
10	100.5		2.0	96.5		4.9
20	100.6		4.1	99.4		1.8
30	101.8		2.1	98.2		3.1
45	101.6		1.9	99.1		0.9
<b>Aspirin</b>						
10	62.0		7.7	34.9		15.6
20	92.9		1.8	66.4		10.3
30	94.6		3.2	84.1		5.7
45	95.8		2.4	93.1		3.6

**PRIMARY REVIEWER:** James E. Chaney, Ph.D.                      **BRANCH:** I  
**INITIAL:** \_\_\_\_\_ **DATE:** 1/14/98

**BRANCH CHIEF:** Yih Chain Huang, Ph.D.                      **BRANCH:** I  
**INITIAL:** \_\_\_\_\_ **DATE:** 1/14/98

**DIRECTOR, DIVISION OF BIOEQUIVALENCE:** Dale P. Conner, Pharm.D.  
**INITIAL:** \_\_\_\_\_ **DATE:** 1/14/98

**DIRECTOR, OFFICE OF GENERIC DRUGS:**  
**INITIAL:** \_\_\_\_\_ **DATE:** \_\_\_\_\_

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER            40255**

**ADMINISTRATIVE DOCUMENTS**

DIVISION REVIEW SUMMARY

ANDA: 40-255

DRUG PRODUCT: Oxycodone and Aspirin Tablets USP

FIRM: Watson Laboratories

DOSAGE FORM: Tablets

STRENGTH: 4.5 mg/0.38 mg/325 mg

CONTAINER: 120 cc/100's & 500 cc/500's & 950 cc/1,000's

CGMP STATEMENT/EIR UPDATE STATUS:

Acceptable dated 7/2/97.

BIO INFORMATION:

Acceptable dated October 10, 1997.

VALIDATION

Method verification was found acceptable.

STABILITY

Lot number NL-1901/ was placed in accelerated stability studies. Based upon the stability data submitted the proposed 24 months expiration period is granted.

The container/closure systems are described in the container section of the application.

LABELING

Satisfactory. See review dated 2/10/98.

STERILIZATION VALIDATION

N/A

SIZE OF BIO/STABILITY BATCHES

Oxycodone HCL & Oxycodone terephthalate are manufactured by \_\_\_\_\_ respectively. These DMF were found acceptable on 6/16/97 and 3/23/97, respectively. \_\_\_\_\_ is manufactured by \_\_\_\_\_ DMF was reviewed and found acceptable on 9/8/97.

The stability batches are the same as the bio batches.

PROPOSED PRODUCTION BATCH

Blank batch records for the intended production batch sizes of \_\_\_\_\_ units are appended.

RECOMMENDATION:

Recommend approval of generic drug product Oxycodone HCl/Oxycodone Terephthalate/Aspirin Tablets, USP 4.5 mg/0.38 mg/325 mg.

SIGNATURE:

DATE: January 9, 1998

Handwritten signature and date. The signature is a stylized cursive mark. The date is written as 2/19/98.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40255

CORRESPONDENCE



**WATSON**  
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

*PI (+ container labels) from 1-8-98 submission satisfactory for approval. - labeling, Miller 2/10/98*

February 6, 1998

**FACSIMILE AMENDMENT**

Office of Generic Drugs  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
ROCKVILLE MD 20855-2773

*EPL*  
**NDA ORIG AMENDMENT**  
*N/FA*

Reference: Oxycodone and Aspirin Tablets, 4.5 mg/0.38 mg/325 mg  
ANDA 40-255

Gentlemen:

This is in response to your facsimile amendment dated January 8, 1998 regarding our ANDA 40-255 for Oxycodone and Aspirin Tablets, 4.5 mg/0.38 mg/325 mg.

**LABELING DEFICIENCIES**

**COMMENT**

1. **GENERAL COMMENTS**

- a. The statement: "Warning: May be habit forming" is no longer required on container labeling. This change may be submitted in an annual report, provided that the change is described in full. A revision to delete this statement may be made for the package insert at this time.
- b. The FDA Modernization Act states that at the minimum the "Rx only" symbol will appear, it was the intent of the Agency to simplify the labeling requirements in that the "Rx only" symbol would replace the "Caution: Federal law requires..." statement. The label of the drug must bear the prescription only symbol ("Rx only"). This change may be submitted in the annual report, provided that the change is described in full. We encourage you to revise your carton and insert labeling in the same manner.

**RECEIVED**

FEB 09 1998

**GENERIC DRUGS**

RESPONSE

Watson has revised the package insert in accordance with the above comments. Please find enclosed 12 final printed package inserts in the original of the response and 12 final printed package inserts in the copy of the response sent to Rockville. All changes explained in a side-by-side comparison of our proposed package insert and our last submitted package insert.

Container labels will be revised in the future and samples of the revised labels will be submitted in the annual report with the changes described in full.

2. INSERT

a. Several comments

Numerous comments

RESPONSE

Watson has revised the package insert in accordance with the above comments. Please find enclosed 12 final printed package inserts in the original of the response and 12 final printed package inserts in the copy of the response sent to Rockville. All changes explained in a side-by-side comparison of our proposed package insert and our last submitted package insert.

If you have any questions or require any further information, please do not hesitate to contact us.

Sincerely,

WATSON LABORATORIES, INC.



William Stahovec

Director of Regulatory Affairs and Quality Control



**WATSON**  
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

NEW LABEL RESP

NC

January 8, 1998

*Labeling revised  
drafted 1/27/98*

**FACSIMILE AMENDMENT**

Office of Generic Drugs  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
ROCKVILLE MD 20855-2773

Reference: Oxycodone and Aspirin Tablets, 4.5 mg/0.38 mg/325 mg  
ANDA 40-255

Gentlemen:

This is in response to your facsimile amendment dated December 22, 1997 regarding our ANDA 40-255 for Oxycodone and Aspirin Tablets, 4.5 mg/0.38 mg/325 mg.

CHEMISTRY DEFICIENCY

DEC 22 1997

Chemistry Comments to be Provided to the Applicant

NDA: 40-255      APPLICANT: Royce Labs.

DRUG PRODUCT: Oxycodone and Aspirin Tablets USP, 4.5 mg/0.38 mg/  
325 mg

The deficiencies presented below represent FACSIMILE deficiencies.

Deficiencies:

Sincerely yours,

*h*  
Frank O. Holcombe, Jr., Ph.D.  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research



**WATSON**  
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

December 18, 1997

ANDA #40-255

**TELEPHONE AMENDMENT**

Office of Generic Drugs  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
ROCKVILLE MD 20855-2773

**NEW CORRESP**  
N C

Gentlemen:

This is in response to a telephone call received today from Mr. Mark Anderson of your office regarding our October 30, 1997 submissions to change the ownership of all our ANDAs from Royce Laboratories to Watson Laboratories, Inc.

As requested, Watson Laboratories hereby commits and certifies that 1) we will keep all agreements, promises and conditions made by Royce and/or contained in the application, 2) the change of ownership was effective October 30, 1997, 3) Watson Laboratories, Inc. has a complete copy of each of Royce's applications that is maintained at the site of our Miami subsidiary, and 4) we will inform FDA about changes in the product labeling to reflect the new name of the manufacturer in our next Annual Report and about any other changes as required under §314.70.

Sincerely,

Loren Gelber, Ph.D.  
Vice President Regulatory Compliance  
Watson Laboratories, Inc.  
Miami (Royce) subsidiary

**RECEIVED**

DEC 19 1997

**GENERIC DRUGS**

# Royce Laboratories, Inc.

8, 1997

Office of Generic Drugs  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Regulatory Administration  
Regulatory Control Room  
1000 Park North II  
1000 Standish Place, Room 150  
BETHESDA, MARYLAND 20855-2773

505(j)(2)(a)(ok)  
Aurora Marie H. Weibel  
6/12/97

Gentlemen:

Royce Laboratories, Inc. is submitting an Abbreviated New Drug Application under section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Aspirin Tablets USP 4.5 mg/0.38 mg/325 mg.

In accordance with Section 306(k) of the Federal Food, Drug, and Cosmetic Act, Royce Laboratories, Inc. certifies that to the best of our knowledge we did not use any person debarred under subsections (a) or (b) of Section 306(k) in any capacity in connection with this application, nor will we use any such person in connection with this application in the future. Furthermore, we certify that to the best of our knowledge, neither Royce, nor any of its employees, affiliate companies or employees of such companies have been convicted within the last five years for acts described in subsections (a) and (b) of section 306.

This application is organized as suggested in Office of Generic Drugs Policy and Procedure Guide 0-91. The archival (blue) copy contains three volumes, The Chemistry Section (red) copy contains three volumes, and the Bioavailability Section (orange) copy contains one volume.

In addition, as required by the Federal Register Volume 58 No 172 published September 8, 1993, Royce Laboratories is submitting a copy of Sections I, II, III, IV, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, and XX to the FDA Orlando District, which is our home FDA District. Royce Laboratories, Inc. hereby certifies that the copy provided to the Orlando District is a true copy of the relevant sections submitted to the FDA Headquarters.

Sincerely,



ROYCE LABORATORIES, INC.  
Loren Gelber, Ph.D.  
Vice President Regulatory Compliance

RECEIVED

MAY 09 1997

GENERIC DRUGS