CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40303

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-303** Date of Submission: **March 12, 1998**

Applicant's Name: **Endo Pharmaceuticals Inc.**

Established Name: **Oxycodone and Acetaminophen Capsules USP, 5 mg/500 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require, at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: **http://www.fda.gov/cder/guidance/index.htm.** Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

   b. The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement and accompanying asterisk from your labels and labeling.

2. UNIT DOSE BLISTER

   a. See GENERAL COMMENT (b) above.

   b. Revise the established name and strength to read s "Oxycodone and Acetaminophen Capsule USP, 5 mg/500 mg".

   c. 21 CFR 201.1(h)(5) explains phrases that may qualify the distributor. The phrase may be

abbreviated.

d. We encourage you to consider reverse numbering your unit dose blister cards of 25 to facilitate the inventorying process.

3. CONTAINER 100s and 500s

a. See GENERAL COMMENTS above.

b. Increase the prominence of the controlled substance symbol.

c. To be consistent with the insert labeling replace the dagger (†) with an asterisk (*) as seen in the insert.

4. UNIT DOSE CARTON

See comments (a) through (c) under CONTAINER above.

5. INSERT

a. GENERAL COMMENTS

i. See GENERAL COMMENT (b) above.

ii. Replace the word ' with the word "narcotic(s)" throughout the text of the insert.

b. DESCRIPTION

i. Delete the period between "USP" and "5" in the second line.

ii. Acetaminophen is 4'-hydroxyacetanilide and occurs as a ... taste. The molecular formula for acetaminophen is ... and the molecular ... 151.17. It may be represented by the following structural formula [include structural formula here].

iii. ... a saline, bitter taste. The molecular formula for oxycodone ... and the molecular weight is 351.83.

c. CONTRAINDICATIONS

Oxycodone and acetaminophen capsules should not

... hypersensitivity to any component.

d. PRECAUTIONS

i. **"Pregnancy"** rather than **"Usage in Pregnancy"**.

ii. *Teratogenic Effects:* Pregnancy Category C

e. OVERDOSAGE

i. Acetaminophen, Signs and Symptoms - Combine and second and third paragraphs (... acetaminophen overdose. Despite this ...).

ii. Oxycodone, Treatment, Second sentence - Delete

f. HOW SUPPLIED

i. See GENERAL COMMENT (a) above.

ii. Oxycodone and Acetaminophen Capsules USP, 5 mg/500 mg reddish orange ... cap and body are supplied as follows:

Please revise your unit dose blister and container labels and unit dose carton and insert labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **40-303** Dates of Submission: **September 30 and October 26, 1998**

Applicant's Name: **Endo Pharmaceuticals Inc.**

Established Name: **Oxycodone and Acetaminophen Capsules USP, 5 mg/500 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s and 500s
Satisfactory as of September 30, 1998 submission.
Unit Dose Blister Label:
Satisfactory as of October 26, 1998 submission.
Unit Dose Carton Label:
Satisfactory as of September 30, 1998 submission.
Professional Package Insert Labeling:
Satisfactory as of September 30, 1998 submission.
Revisions needed post-approval: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: TYLOX®

ANDA Number: 88-790

ANDA Drug Name: TYLOX® (Oxycodone and Acetaminophen) Capsules

ANDA Firm: RW Johnson

Date of Approval of ANDA Insert and supplement #: 5-30-91 (S-008)

Has this been verified by the MIS system for the ANDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: labels on file

Basis of Approval for the Carton Labeling: labeling on file

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

	Yes	No	N.A.
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the modified labeling of Tylox®, revised April 1991, approved 5/30/91.

2. Dispensing

   USP: Preserve in tight, light-resistant containers.
   RLD: Dispense in a tight, light-resistant container as defined in the official compendium.
   ANDA: Dispense in a tight, light-resistant container as defined in the USP.
   Storage

   RLD: Store at CRT 15°-30°. Protect from moisture.
   ANDA: Same as innovator.

3. There are no patents or exclusivities for this drug product.

4. Components/composition

The inactives are accurately listed in the DESCRIPTION section (pp 76, 292, 295 vol 1.1)

5. Container/closure

The unit dose blister have foil backing (p 472 v 1.2). The 100s and 500s containers are made of HDPE and the 100s have CRC closures (pp 472, 475, 511, 554 and 588 v 1.2). The plastic portion of the blister is clear - upon discussion with C. Hoppes, it was felt that since the product is a capsule and a controlled substance (drug product would likely be locked up in dark place [med cart or safe] this is a non-issue.

6. The capsule description in the HOW SUPPLIED section is accurate (p 280 v 1.1).

7. Dupont Pharma is the manufacturer (p 298 v 1.1).

8. No bio study is required for this application since the drug is rated AA in the Orange Book. [505(j)(ii)a submission]

Date of Review: 10-8-98 Dates of Submission: 9-30-98 & 10-26-98

Primary Reviewer: Adolph Vezza Date: 10/28/98

/S/

Team Leader: Charlie Hoppes Date: 10/30/98

concur. /S/ 10/30/98

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cc:

ANDA: 40-303
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/10/28/98|X:\NEW\FIRMSAM\ENDO\LTRS&REV\40303APL Review

RECORD OF TELEPHONE CONVERSATION

I spoke to Carol Patterson on 10-22-98 about the 9-30-98 amendment to unapproved ANDA 40-303.
Specifically, the computer generated blister labels submitted were not of true size. I explained to Ms. Patterson that they needed to be before we could approve the application. The reason for this is that we need to see the true print size of all labels and labeling to ensure its legibility. Ms. Patterson agreed to submit blister labels of true size to this application.

Division of Labeling and Program Support

DATE
10-26-98

ANDA NUMBER
40-303

IND NUMBER

TELECON

INITIATED BY APPLICANT/ SPONSOR X **MADE BY TELE.**

X **FDA** _ **IN PERSON**

PRODUCT NAME
Oxycodone/APAP Capsules

FIRM NAME
ENDO

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Carol Patterson
Manager
Reg. Affairs

TELEPHONE NUMBER
(516) 522-3305

SIGNATURE
Adolph Vezza
/S/ 10/26/98