CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER _____

ADMINISTRATIVE DOCUMENTS

Addendum to Application

Establishment Information

Chemical/Biochemical Name

5-allyl-5-isobutylbarbituric acid/benzoic acid, 2-(acetyloxy) - / 1,3,7-y-trimethylxanthine/morphine-3-methylether phosphate (1:1) (salt) hemihydrate

Active Drug Substance:

The manufacturing, packaging and control site for the drug substances are as follows:

[redacted]

Finished Dosage Form:

The manufacturing, packaging and control site of the drug product is:

DuPont Pharmaceuticals Company

[redacted]

Drug Establishment Registration Number: 2419829

[redacted]

The manufacturing site is ready for inspection.

The sponsor of this ANDA is:

Endo Pharmaceuticals Inc.
500 Endo Blvd.
Garden City, NY 11530

Packaging Components:

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

ANDA Number: **75-351** Date of Submission: **March 31, 1998**

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

Established Name: **Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/ 30 mg**

Labeling Deficiencies:

1. GENERAL COMMENT:

   Revise your storage temperature recommendations throughout your labels and labeling as follows:

   Store below 25°C (77°F).

2. CONTAINER 100s and 500s

   a. See GENERAL COMMENT above.

   b. Usual Adult Dosage: 1 or 2 capsules every four hours. Total daily dose should not exceed 6 capsules.

3. INSERT

   a. DESCRIPTION

      i. Revise the second paragraph as follows:

      Codeine phosphate [7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate, $C_{18}H_{24}NO_7P$, anhydrous mw 397.37], occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. It is an opioid analgesic and antitussive.

      ii. Revise the third paragraph as follows:

      ...224.26), a white odorless crystalline powder, is a short ...

iii. Revise the fifth paragraph to read as follows:

Aspirin [benzoic ... -(acetyloxy)-, $C_9H_8O_4$, mw 180.16] is ...

iv. "structural formulas" rather than "chemical structures".

v. Improve the print quality of the double bonds found in the structural formula of butalbital.

b. CLINICAL PHARMACOLOGY

i. Aspirin, Penultimate paragraph, last sentence

A). "mcg" rather than "µg".

B). In a reported bioavailability study a peak concentration ...

ii. Codeine

A). First paragraph, last sentence - ...breast milk. Codeine is not bound to ... (delete "The plasma ... however,").

B). Penultimate paragraph, last sentence - In a reported bioavailability study peak concentrations of ...

iii. Butalbital

A). Third paragraph, last sentence - In a reported bioavailability study a peak concentration ...

B). Delete the penultimate paragraph (The *in vitro* ... blood cells.).

iv. Caffeine

A). Second paragraph, third sentence - ... 1-methyluric acid. (delete the second hyphen).

B). Penultimate paragraph, last sentence - In a reported bioavailability study a peak concentration of ...

c. INDICATIONS AND USAGE

Revise the section title as seen above.

d. PRECAUTIONS

i. General -- First paragraph - ... or head injuries. (delete elevated intracranial ... peptic ulcer.")

ii. Drug/Laboratory Test Interactions -- Aspirin - ... 5-hydroxyindoeacetic acid ... (delete the second hyphen).

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

e. ADVERSE REACTIONS

Other Adverse Events Reported During Controlled Clinical Trials - We encourage you to revise the sub-subsection headings as shown below:

i. ***Central Nervous System:***

ii. ***Autonomic Nervous System:***

f. DRUG ABUSE AND DEPENDENCE

i. Delete "**Controlled Substance**" and "**Abuse and Dependence**".

ii. First sentence - ... Administration and are classified ...

iii. "**Codeine**" and "**Butalbital**" should not be in italic print.

g. OVERDOSAGE

i. Signs and Symptoms, First sentence - delete "hypovolemic".

ii. Treatment

A). Third paragraph - delete the second and third sentences (The value of ... pressure monitoring.).

B). Penultimate paragraph

1). The word "(NARCAN®*)" can be

deleted.

2). Delete the terminal zero (i.e.; 2 mg).

C). Delete the last paragraph.

iii. Toxic and Lethal Doses - Delete the terminal zeroes.

h. HOW SUPPLIED

i. ... Capsules USP, 50 mg/325 mg/40 mg/30 mg are supplied as follows:

- yellow capsule ...

ii. See GENERAL COMMENT above.

iii. We encourage you to relocate the symbol "**Rx only**" to be beneath the title of the insert.

iv. You may delete the statement:

*NARCAN® is a registered trademark of Endo Pharmaceuticals Inc.

Please revise your container labels 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.

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