CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-351

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. #2

2. ANDA #75-351

3. NAME AND ADDRESS OF APPLICANT

Endo Pharmaceuticals Inc.
Attention: Jeanne Stelter
500 Endo Blvd.
Garden City, NY 11530

Phone: 516-522-3306
Fax: 516-832-2291

4. LEGAL BASIS FOR SUBMISSION

The firm certifies on page 10 that to the best of its knowledge, the patents for the listed drug product have expired (October 26, 1993) and no exclusivity data is listed in the "Orange Book".

Innovator: Sandoz - Fiorinal® with Codeine

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Butalbital, Aspirin, Caffeine and Codeine Phosphate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

8. AMENDMENTS AND OTHER DATES:

Original application: 3/31/98
FDA acknowledgment: 4/10/98
Amendment 12/23/98 to N/A letter (FACSIMILE) 12/1/98

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC

Treatment of tension headaches Rx

12. RELATED IND/NDA/DMF(s)

See under #37 DMF CHECKLIST

13. DOSAGE FORM

Capsules

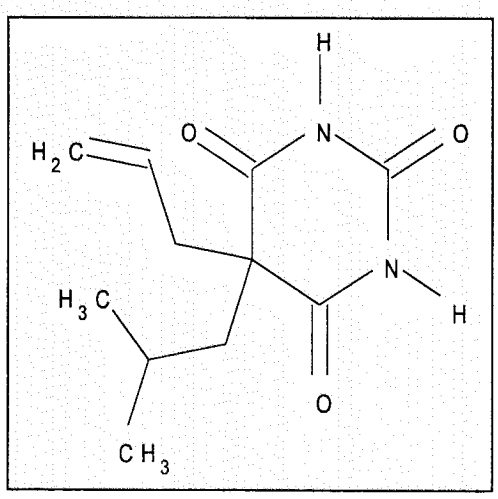
14. POTENCY

Butalbital, Aspirin, Caffeine and Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/30 mg.

15. CHEMICAL NAME AND STRUCTURE

Butalbital USP

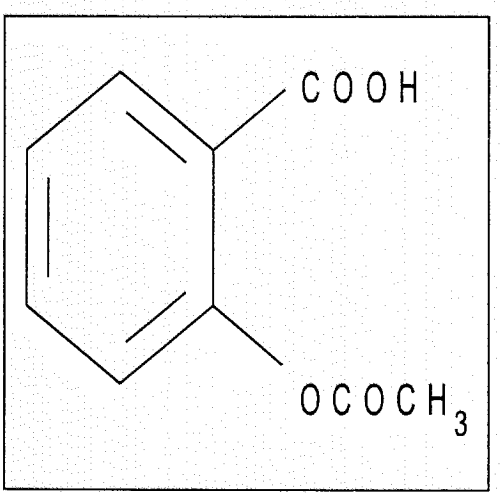
$C_{11}H_{16}N_2O_3$; M.W. = 224.26



5-Allyl-5-isobutylbarbituric acid. CAS [77-26-9]

Aspirin USP

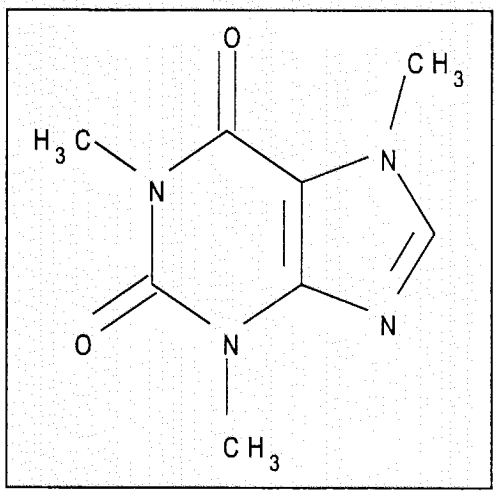
$C_9H_8O_4$; M.W. = 180.16



Salicylic acid acetate. CAS [50-78-2]

Caffeine USP

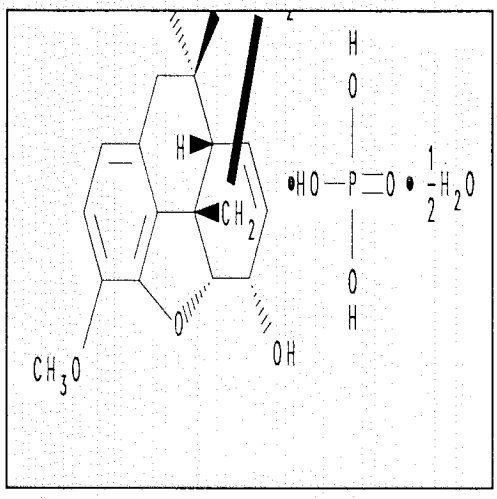
$C_8H_{10}N_4O_2$; M.W. = 194.19



1,3,7-Trimethylxanthine.
CAS [58-08-2]

Codeine Phosphate USP

$C_{18}H_{21}NO_3.H_3PO_4.\frac{1}{2}H_2O$; M.W. = 406.37



7,8-Didehydro-4-5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
In Amendment (FACSIMILE) 12/23/98 Firm answers our concerns in order: (all acceptable)

Q1. Gelatin capsules should be listed as part of the ingredients in the Components and Composition statement on page 115.

Q2. Please correct the misspelling of "Colloidal Silicon Dioxide, NF" on the same page.

A1 & A2. The revised statement provided is acceptable.

Regarding the active ingredients:
Q3a. Since all of your submitted Certificates of Analysis were performed in 1996, please update the specifications and submit the most recent ones if available.

A3a. Firm states that no additional batches have been manufactured, therefore, no additional testing of the active ingredients has been performed since the original filing. The specifications for the active ingredients have not changed with the exception of the addition of the method of potency and degradants assays of Caffeine.

Q3b. For Caffeine:
1) Tests for "Bulk Density" and "Sieve Test" are listed in your COA, but not listed in your specifications for Caffeine on page 172. Please clarify.

A1) Firm states that Tests for "Bulk Density" and "Sieve Test" were performed during early development work. When the manufacturing process using was chosen, both tests were deleted since they are not necessary for product manufactured using the process. One of the first steps in causes the drug substance to be physically bound to the other ingredients in the blend by nem together into a flake. This ep obviates the need for any particle size or density limitations for the individual ingredients.

2) Please adapt a HPLC method for assaying potency and degradants. There is an HPLC method proposed by 9th Supplement to USP on page 4522 (official 11/15/98).

A2) Per request, Firm has incorporated the USP HPLC method for assaying potency and degradants for Caffeine. The revised specifications and test results (with chromatograms) are provided.

Q3c. For Codeine Phosphate:
There is no specification listed for "Organic Volatile Impurities". Please clarify.

A3c. Firm states that OVI is not a USP requirement for Codeine Phosphate (unlike the other three active ingredients). The manufacturer, Inc, has certified that there is no potential for the presence of OVI as defined by the USP in their material, and, if tested, will comply with USP standards. A letter of certifications is enclosed.

Q4. The Post-approval Stability Commitment provided on page 760 should be signed and dated.

A4. The signed and dated Post-approval Stability Commitment provided is acceptable.

Status Summary:

Labeling:	Satisfactory (2/3/99)
Microbiology:	N/A
EER:	Acceptable (5/26/98)
Sample:	Satisfactory (6/25/98)
Bio:	Satisfactory (8/12/98)

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: Maria C. Shih

DATE COMPLETED: 1/14/99 7/6/99

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Chemistry