CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40303

CHEMISTRY REVIEW(S)

1. **CHEMIST'S REVIEW NO. 3**

2. **ANDA** 40-303

3. **NAME AND ADDRESS OF APPLICANT**
Endo Pharmaceutical Inc.
500, Endo Blvd.
Garden City
N.Y. 11530

4. **LEGAL BASIS for ANDA SUBMISSION**
The RLD is Tylox capsules manufactured by McNeil Pharmaceuticals. Patent has expired and no exclusivities are pending.

5 **SUPPLEMENT(s)** None

6. **PROPRIETARY NAME** None

7 **NONPROPRIETARY NAME**

Oxycodone Hydrochloride/Acetaminophen

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** None

9. **AMENDMENTS AND OTHER DATES:**

March 12, 1998	Original submission
March 20, 1998	Acknowledgement letter
July 15, 1998	Bio review-waiver granted
August 26, 1998	Deficiency letter labeling
October 26, 1998	Labeling amendment
October 28, 1998	Labeling Approval
December 15, 1998	New correspondence
March 30, 1999	Deficiency letter
May 6, 1999	Amendment
October 21, 1999	Chemistry review
November 3, 1999	Facsimile deficiencies
November 11, 1999	Amendment

10. **PHARMACOLOGICAL CATEGORY**
Analgesic & Antipyretic

11 **Rx or OTC**

Rx

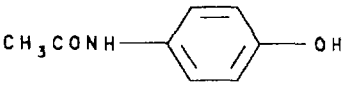
12. **RELATED IND/NDA/DMF(s)**

13. DOSAGE FORM
Capsule

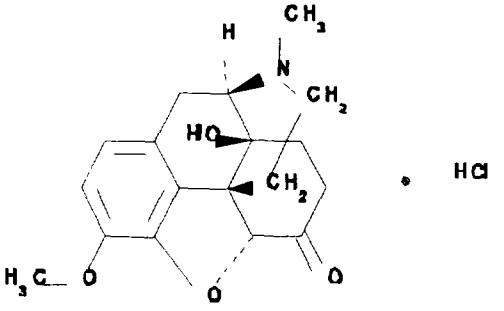
14. POTENCY
5 mg/500 mg

15. CHEMICAL NAME AND STRUCTURE
4,5a-Epoxy-14-hydroxy -3 methoxy-17 methylmorphinan-6-one-hydrochloride and 4 hydroxy-acetanilide

Acetaminophen
USP $C_8H_9NO_3$;
M.W. = 151.16



4'-Hydroxyacetanilide. CAS [103-90-2]
Oxycodone Hydrochloride. Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5*a*)-.
$C_{18}H_{21}NO_4 \bullet HCl$. 351.83. 124-90-3. Analgesic (narcotic).



16. **RECORDS AND REPORTS**
None

17. **COMMENTS**
The API and the finished drug product are compendial articles in USP 23. The proposed finished drug product tests and specifications are consistent with ANDAs 40-330 and 40-341, therefore, acceptable.

EER acceptable, dated 3/23/99.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Recommend approvable letter to issue.

19. **REVIEWER:** Edwin Ramos
/S/

DATE COMPLETED: November 29, 1999
11/1/99

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pages of trade

secret and/or

confidential

commercial

information

Chemistry Review #3

DIVISION REVIEW SUMMARY

ANDA: 40-303

DRUG PRODUCT: Oxycodone Hydrochloride and Acetaminophen

FIRM: Endo Pharmaceuticals
DOSAGE FORM: Capsules
STRENGTHS: 5 mg/500 mg
CONTAINERS:
Unit dose, 100's (150 cc) and 500's (950 cc)

CGMP STATEMENT/EIR UPDATE STATUS:
Acceptable dated 3/23/99.

BIO INFORMATION:
Acceptable dated 7/15/98.

VALIDATION
A method verification was performed and reported to be acceptable dated 6/2/98. Compendial product.

STABILITY
Lot no. LK483 was placed in accelerated (40°C/75%RH) and room temperature stability studies in the smallest and largest of the proposed marketing container configurations including the unit dose. The stability data appended are found to conform to the proposed stability specifications. Based upon the stability data submitted, the proposed 24 months expiration period should be granted.

The container/closure systems are described.

LABELING
Acceptable dated 10/28/98.

STERILIZATION VALIDATION
N/A

SIZE OF BIO/STABILITY BATCHES
Oxycodone Hydrochloride is manufactured by
DMF DMF was found to be adequate on ~~3/16/99~~. No relevant revisions since last review as of 11/29/99. 12/16/99

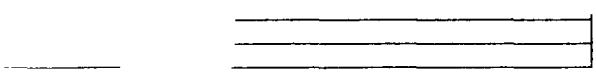
Acetaminophen is also manufactured by
DMF DMF was found to be adequate on 3/19/99. No relevant revisions since last review as of 11/29/99.

Oxycodone Hydrochloride and Acetaminophen Capsules, 5 mg/500 mg demonstration lot no. LK483/ kg capsules.

PROPOSED PRODUCTION BATCH

BBR for the intended production batch size of kg/ capsules is included.

SPECIFICATIONS TO BE APPROVED:



FINISHED DRUG PRODUCT:

Oxycodone HCl and Acetaminophen Capsules USP, 5/500 mg

Description--A reddish-orange, hard gelatin capsule with white print "E660" on cap and body
Identification
Dissolution for Oxycodone Hydrochloride - Meets USP (Q) % in 45 minutes
Content Uniformity - Meets USP
Dissolution for Acetaminophen - Meets USP requirements (Q) % in 45 minutes
Oxycodone Degradants Oxymorphone (hydrolisis) NMT % 10-ketooxycodone (oxidation) NMT % Individual unknown NMT % Total NMT %
APAP Degradants p-aminophenol (hydrolisis) NMT % Individual unknown NMT % Total NMT
Assay Oxycodone Hydrochloride % Assay Acetaminophen %

STABILITY:

Description	A red capsule with white print E660 on cap and body
Dissolution	Q % in 45 minutes for APAP and Oxycodone HCl
Assay	% APAP % Oxycodone HCl
Oxycodone degradants Oxymorphone HCl 10-Ketooxycodone HCl Single unknown Total	 NMT % NMT % NMT % NMT %
APAP degradants p-aminophenol Single unknown Total	 NMT % NMT % NMT %

RECOMMENDATION:

Recommend approbable letter to issue for Oxycodone and Acetaminophen Capsules, 5 mg/500 mg.

SIGNATURE: DATE: November 29, 1999

cc: ANDA # 40-303
DIVISION FILE
FIELD COPY

Endorsements:

HFD-640/E.Ramos/ /S/ 12/1/99

HFD-647/G.Smith/ /S/ 12/21/99

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APPROVAL