CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-610
21-611

CHEMISTRY REVIEW(S)
NDA 21-610

OPANA™ ER
(Oxymorphone Hydrochloride) Extended-Release Tablets
5 mg, 10 mg, 20 mg, and 40 mg

Endo Pharmaceuticals

Jila H. Boal, Ph.D.
Division III, ONDQA
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1. NDA # 21-610

2. REVIEW # 2

3. REVIEW DATE: May 15, 2006

4. REVIEWER: Jila H. Boal, Ph.D

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<th>Previous Documents</th>
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<tr>
<td>IND 56,919</td>
<td>September 10, 1998</td>
</tr>
<tr>
<td>Original</td>
<td>December 19, 2002</td>
</tr>
<tr>
<td>Amendment</td>
<td>January 17, 2003</td>
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<td>General Correspondence</td>
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<td>February 13, 2003</td>
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<td>February 20, 2003</td>
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<td>April 15, 2003</td>
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<td>July 17, 2003</td>
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<td>August 20, 2003</td>
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</table>

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<tbody>
<tr>
<td>NDA Approvable Action Letter</td>
<td>October 15, 2003</td>
</tr>
<tr>
<td>CMC Teleconference</td>
<td>December 1, 2003</td>
</tr>
<tr>
<td>Post Action Letter</td>
<td>February 16, 2004</td>
</tr>
<tr>
<td>Meeting Minutes</td>
<td>March 16, 2004</td>
</tr>
<tr>
<td>Teleconference Meeting Minutes</td>
<td>May 7, 2004</td>
</tr>
<tr>
<td>Teleconference Meeting Minutes</td>
<td>July 16, 2004</td>
</tr>
<tr>
<td>Complete Response to the Approvable Action Letter</td>
<td>December 22, 2005</td>
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<tr>
<td>Amendment Proprietary Name Evaluation</td>
<td>February 20, 2006</td>
</tr>
<tr>
<td>Amendment In-vivo Study Results/ Oxymorphone</td>
<td>March 22, 2006</td>
</tr>
<tr>
<td>and Alcohol Co-administration</td>
<td>March 24, 2006</td>
</tr>
<tr>
<td>Amendment (color mock-ups of the labeling</td>
<td>March 24, 2006</td>
</tr>
<tr>
<td>Amendment Labeling</td>
<td></td>
</tr>
</tbody>
</table>
7. NAME & ADDRESS OF APPLICANT:

   Name: Endo Pharmaceuticals Inc.
   Address: 100 Painters Drive
             Chadds Ford, PA 19317
   Representative: Mary Alice Raudenbush
                   Vice President, Regulatory Affairs
   Telephone: (610) 558-9800 Ext 4204

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: OPANA™ ER (Oxymorphone Hydrochloride) Extended Release Tablets
   b) Non-Proprietary Name (USAN): Oxymorphone Hydrochloride
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b Application based on the following Listed Drugs:

   Numorphan Injection NDA # 11,707 and
   Numorphan Rectal Suppositories NDA # 11,738

10. PHARMACOL CATEGORY:
      Relief of moderate to severe pain in patients requiring continuous, around the clock opioid therapy for an extended period of time.

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 5, 10, 20, and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OTC
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

- [ ] SPOTS product – Form Completed
- X Not a SPOTS product

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Morphinan-6-one, 4,5—epoxy-3, 14-dihydroxy-17-methyl-, hydrochloride, (5α)- or, 4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride

C_{17}H_{19}NO_{4}·HCl

![Chemical Structure](image)

Molecular Weight: 337.80

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

<table>
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<tr>
<th>DMF #</th>
<th>Type</th>
<th>Holder</th>
<th>Item Referenced</th>
<th>CODE</th>
<th>STATUS</th>
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<th>Comments</th>
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<tr>
<td>14502</td>
<td>II</td>
<td>Mallinckrodt Inc.</td>
<td>Oxymorphone HCl, USP</td>
<td>1</td>
<td>Adequate</td>
<td>May 7, 2006</td>
<td>Review #2 by Jila Boal, Ph. D.</td>
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<tr>
<td>11868</td>
<td>IV</td>
<td>Penwest Pharmaceuticals Company</td>
<td>TIMERx®-N Controlled Release System</td>
<td>1</td>
<td>Adequate</td>
<td>April 24, 2006</td>
<td>Review #3 by Jila Boal, Ph. D.</td>
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<td></td>
<td>IV</td>
<td></td>
<td></td>
<td>1</td>
<td>Adequate</td>
<td>September 21, 2003</td>
<td>Review #3 by Jila Boal, Ph. D.</td>
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<td></td>
<td>III</td>
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<td>3</td>
<td>Adequate</td>
<td>September 15, 2000</td>
<td>DMF Strikeforce</td>
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</table>
Chemistry Review Data Sheet

| III | 1 | Adequate | September 12, 2003 | Dominic Chiapperino, Ph. D. |
| III | 3 | Adequate | March 22, 2001     | Pramoda Maturu, Ph. D. |
| III | 3 and 4 | Adequate | May 19, 2003       | Donald Klein, Ph. D. |
| III | 3  | Adequate | October 14, 2003   | DMF Strikeforce |
| III | 3  | Adequate | May 22, 2002       | DMF Strikeforce Rev. # 2, p. 22, 24 |
| III | 1  | Adequate | September 19, 2003 | Dominic Chiapperino, Ph. D. |

1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type I DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under “Comments”)

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

<table>
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<tr>
<th>Document</th>
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<th>Description</th>
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<tr>
<td>IND</td>
<td>56, 919</td>
<td>Numorphan (Oxymorphone HCl) C-R Tablets</td>
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<td>IND</td>
<td>58,602</td>
<td>Numorphan (Oxymorphone HCl) IR Tablets</td>
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<td>NDA</td>
<td>21-611</td>
<td>Oxymorphone HCl Immediate Release Tablets</td>
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<td>NDA</td>
<td>11-707</td>
<td>Numorphan Injection</td>
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<td>NDA</td>
<td>11-738</td>
<td>Numorphan Rectal Suppositories</td>
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18. STATUS:

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<th>Consults / CMC Related Reviews</th>
<th>Recommendation</th>
<th>Date</th>
<th>Reviewer</th>
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</thead>
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<tr>
<td>Biometrics</td>
<td>Not consulted. Real time stability data for up to 48 months was submitted for the three primary stability batches for</td>
<td></td>
<td></td>
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</table>

6/83
<table>
<thead>
<tr>
<th><strong>CHEMISTRY REVIEW</strong></th>
<th>Chemistry Review Data Sheet</th>
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<tbody>
<tr>
<td><strong>EES</strong></td>
<td>Except for one facility, all facilities are acceptable. However, after review of the updated information in DMF amendment for TIMERx®-N, it was determined that the facility (manufacturer of the TIMERx®-N excipient) does not need inspection. Requested for inspection of this facility was withdrawn from EES. An overall acceptable recommendation was then granted.</td>
</tr>
<tr>
<td><strong>Pharm/Tox</strong></td>
<td>Pharm/Tox do not have any concern regarding the excipients. The non-genotoxic impurity levels in the drug substance and drug product were reduced according to the relevant Guidances, and the genotoxic impurities are according to an interim acceptance criteria of 1.</td>
</tr>
<tr>
<td><strong>ClinicalPharm</strong></td>
<td>Not Consulted</td>
</tr>
<tr>
<td><strong>LNC</strong></td>
<td>Not consulted. Common dosage form and no issue with established naming</td>
</tr>
<tr>
<td><strong>Methods Validation</strong></td>
<td>Based on the ONDQA’s established criteria for NDA analytical method validation (1/5/2005), none of the test methods meet the criteria for further evaluation. Except the HPLC method for the level of genotoxic impurities, will be evaluated in future once the final acceptance criteria are established. The present values are accepted on an interim bases.</td>
</tr>
<tr>
<td><strong>DMETS and DDMAC</strong></td>
<td>DMETS has no objections to the use of the proprietary names, Opana and Opana ER provided that only one name Opana (NDA’s 21-610 and 21-611) is approved. DDMAC finds the proprietary names Opana and Opana ER acceptable from a promotional perspective.</td>
</tr>
<tr>
<td><strong>EA</strong></td>
<td>Not applicable. Categorical</td>
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**June 14, 2006** Office of Compliance Janine D. Ambrogio

**June 13, 2006** As per e-mail received from Mamata De, Ph.D. the Pharm / Tox primary reviewer.

**Jila Boal, Ph.D.**

**June 12, 2006** Felicia Duffy

**Jila Boal, Ph.D.**
<table>
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<tr>
<th>Exclusion claimed and granted.</th>
<th>Microbiology</th>
<th>N/A</th>
<th>Jila Boal, Ph.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable as this is solid oral dosage form and there are no apparent microbiological issues</td>
<td>Not applicable as this is solid oral dosage form and there are no apparent microbiological issues</td>
<td>N/A</td>
<td>Jila Boal, Ph.D.</td>
</tr>
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</table>
The Chemistry Review for NDA 21-610

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the standpoint of Product quality CMC, NDA 21-610 is recommended for approval. An expiration period of 36 months may be granted based on the assessment of the real time stability data.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
Oxymorphone HCl extended release tablets are formulated in four strengths 5, 10, 20, and 40 mg. They are all octagon-shaped, convex, film-coated tablets which are distinguished by their colors and imprint: the 5 mg is pink, the 10 mg is light orange, the 20 mg is light green, and the 40 mg is yellow.

In addition to oxymorphone HCl, the formulation contains hypromellose, iron oxide black, methylparaben, propylene glycol, silicified microcrystalline cellulose, sodium stearyl fumarate, TIMERx®-N, titanium dioxide, and triacetin. The 5, 10 and 20 mg tablets also contain macrogol, and polysorbate 80. In addition, the 5 mg tablets contain iron oxide red. The 10 mg tablets contain FD&C yellow No. 6. The 20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10. The 40 mg tablets contain FD&C yellow No. 6, D&C yellow No. 10, and lactose monohydrate. The manufacturing process consists of

The excipient TIMERx®-N is the primary means of controlling the drug release. It constitutes — of the tablet formulation. This hydrophilic matrix is a proprietary controlled-release drug delivery excipient developed by Penwest Pharmaceuticals. TIMERx® materials are composed of locust bean gum (LBG) and xanthan gum (XG), The CMC of TIMERx®-N is described in Penwest’s DMF 11868 which is deemed adequate to support this NDA.
Drug Release mechanism (TIMERx®-N Control Release):

Drug substance:
Oxymorphone HCl code 0881 is manufactured, quality controlled, and packaged by Mallinckrodt Inc. described in their DMF 14502.

Oxymorphone hydrochloride is readily soluble in aqueous alkalis; moderately soluble in _____ ethanol, sparingly soluble in ______. Freely soluble in water; sparingly soluble in alcohol and ether. The favorable solubility profile of the hydrochloride salt of oxymorphone in water makes it the preferred molecular form for extended release formulation when mixed with TIMERx-N. The drug substance exists in hydrated form.

B. Description of How the Drug Product is Intended to be Used
Oxymorphone hydrochloride is proposed for the management of moderate to severe pain where the use of an opioid is appropriate. The extended release dosage formulation of oxymorphone hydrochloride will be available as a 5 mg, 10 mg, 20 mg, and 40 mg tablet. In opioid naïve patients the recommended starting dose of the extended release dosage formulation is 5 mg taken orally every 12 hours.

These dosage formulations of oxymorphone hydrochloride have been classified as a Class II controlled substance.

Tablets are to be swallowed whole, and are not to be broken, chewed, crushed or dissolved. Taking broken, chewed, crushed or dissolved tablets leads to the rapid release and absorption of a potentially fatal dose of oxymorphone.

As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience.

The marketed drug product would be packaged in several different forms. Bottles of tablets with child-resistant closure. Bottles of 100 tablets with child-resistant closure. Bottles of— tablets with child-resistant closure. Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only).
C. Basis for Approvability or Not-Approval Recommendation

This submission is a complete response to the substantial CMC deficiencies identified in the original NDA submitted in 2002. Several post NDA Action meetings were held to streamline the approach for the resubmission of the NDA.

Since the formulation contains the drug substance in very small amounts (i.e. low dose formulations) the potential for API agglomeration or segregation within the ________

---

Also, significant differences in particle size could produce a heterogeneous mixture adversely impacting the ________ . Therefore, the following critical quality issues were resolved during this review, paving the way for approval recommendation.

Particle size specification ________ was established for the drug substance to better control ________ the tablets.

---

Since the data demonstrate that these parameters remained consistently within narrow ranges and did not impact the ________ final ________ , there was no need to specify them as ________ controls for routine ________ commercial manufacture. Also, better ________ controls have now been established for the particle size distribution of the drug substance and TIMERx-N.

The data submitted in the resubmission indicated that ________ process has been well developed and validated and it met Stage I testing acceptance criteria ________ .
Endo committed to performing drug release testing on core tablets with samples for the first three commercial batches of each strength before requesting to delete this test via a post-approval supplement. This should be reminded in the action letter.

In view of the recently identified safety concerns with dose dumping caused by alcohol, the in-vitro release of the product was assessed using hydroalcoholic media of various alcohol concentrations as the release media. The results indicated that the product was ruggedly designed as it did not dose dump. However, large quantities of ethanol consumed simultaneously with oxymorphone ER affected the pharmacokinetics of oxymorphone (i.e., increased Cmax). The mechanism by which this occurred (enhanced absorption, decreased metabolism, etc.) is being investigated by the firm. However, based on the in-vitro data, the mechanism of the increased plasma concentrations is likely not due to dose dumping. The firm should be asked to pursue mechanistic understanding of enhanced absorption of the drug following simultaneous alcohol consumption.

Acceptance criteria for degradation products were revised according to ICH Q3 B recommendations. Adequate finished product stability data was provided for up to . The analyses of stability data indicate that the assay, and total degradation products remained within current specifications well beyond 36 months for all packages at 25°C/60%RH. Based on the statistical analysis results and provided real time stability data, an expiration dating period of 36 months could be granted for Oxymorphone Hydrochloride ER Tablets, 5, 10, 20 and 40 mg. The requested expiration dating of 36 months could be granted.

The drug substance specifications have been revised as per ICH Q3A recommendations. The
which are present as process impurities from the synthesis of the drug substance are now controlled at the on an interim basis and will be tightened further based on the action taken by the DMF vendor. This should be reminded in the action letter. Karl Fischer analysis is incorporated with a justified acceptance criteria of

In summary, the specifications for impurities in the drug substance and drug product are adequately controlled based on ICH Q3A for the drug substance and ICH Q3B for the drug product. The applicant has provided adequate response to the deficiencies identified in the NDA action letter of October 15, 2003. The manufacturing process is shown to be well understood and robust so as not to result in over-potent tablets. Properly justified in-process controls are established. Stability data confirms an expiration dating of 36 months for this product. Thus, the NDA may be approved from CMC stand point.

III. Administrative

A. Reviewer’s Signature

*Electronically captured in DFS*

B. Endorsement Block

*Electronically captured in DFS*
Jila H. Boal, Ph. D, CMC Reviewer/ June 13, 2006
Ravi Harapanhalli, Ph. D, Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products) Division III, ONDQA
Lisa Bascham-Cruz, Project Manager

C. CC Block

*NDA 21-610*
HFD-170/LBascham-Cruz/ RHarapanhalli /JBoal
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-------------------
Jila Boal
6/14/2006 05:36:16 PM
CHEMIST

Ravi Harapanhalli
6/14/2006 05:44:58 PM
CHEMIST
NDA 21-610

Trademark® (Oxymorphone HCl) Extended-Release Tablets
5 mg, 10 mg, 20 mg, and 40 mg

Endo Pharmaceuticals

Jila H. Boal, Ph.D.
Division of Anesthetics, Critical Care, and Addiction Drug Products
(HFD-170)
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III. INVESTIGATIONAL FORMULATIONS ...................................................................... 102
Chemistry Review Data Sheet

1. NDA # 21-610

2. REVIEW # 1

3. REVIEW DATE: June 10, 2003

4. REVIEWER: Jila H. Boal, Ph.D

5. PREVIOUS DOCUMENTS:

   Previous Documents                      Document Date
   IND 56,919                               September 10, 1998

6. SUBMISSION(S) BEING REVIEWED:

   Submission(s) Reviewed                  Document Date
   Original                                December 19, 2002
   Amendment                               January 17, 2003
   General Correspondence                  January 24, 2003
   Amendment                               February 13, 2003
   Amendment                               February 20, 2003
   Amendment                               April 15, 2003
   Amendment                               July 17, 2003
   Amendment                               July 22, 2003
   Amendment                               August 20, 2003
   Amendment                               September 12, 2003

7. NAME & ADDRESS OF APPLICANT:

   Name:  Endo Pharmaceuticals Inc.
   Address:  100 Painters Drive
             Chadds Ford, PA 19317

   Representative:  Mary Alice Raudenbush
                    Vice President, Regulatory Affairs
8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To-be-determined (see the evaluation of the proprietary name by the Division of Medical Errors and Technical Support Office of Drug Safety, dated August 22, 2003).
b) Non-Proprietary Name (USAN): Oxymorphone HCl
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
   • Chem. Type: 3
   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505B2 Application based on the following Listed Drugs:
   Numorphan Injection NDA # 11,707 and
   Numorphan Rectal Suppositories NDA # 11,738

10. PHARMACOL. CATEGORY: Relief of moderate to severe pain in patients requiring continuous, around the clock opioid therapy for an extended period of time.

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 5, 10, 20, and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

   ____SPOTS product – Form Completed
   _X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Morphinan-6-one, 4,5-epoxy-3, 14-dihydroxy-17-methyl-, hydrochloride, (5α)-or,
4,5α-Epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
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<th>DMF #</th>
<th>Type</th>
<th>Holder</th>
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<td>September 24, 2003</td>
<td>Review #2 by Jila Boal, Ph. D.</td>
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<td>Dominic Chiapperino, Ph. D.</td>
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<td>May 19, 2003</td>
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<td>September 19, 2003</td>
<td>Dominic Chiapperino, Ph. D.</td>
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</table>
Chemistry Review Data Sheet

1. Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

2. Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

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<th>Document</th>
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<th>Description</th>
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<td>IND</td>
<td>56, 919</td>
<td>Numorphan (Oxymorphone HCl) C-R Tablets</td>
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<td>IND</td>
<td>58, 602</td>
<td>Numorphan (Oxymorphone HCl) IR Tablets</td>
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<td>NDA</td>
<td>21-611</td>
<td>Oxymorphone HCl Immediate Release Tablets</td>
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<tr>
<td>NDA</td>
<td>11-707</td>
<td>Numorphan Injection</td>
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<tr>
<td>NDA</td>
<td>11-738</td>
<td>Numorphan Rectal Suppositories</td>
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18. STATUS:

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<tr>
<th>Consults / CMC Related Reviews</th>
<th>Recommendation</th>
<th>Date</th>
<th>Reviewer</th>
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<tbody>
<tr>
<td>Biometrics</td>
<td>An expiration dating of may be granted. However, the data for the 5mg strength supports extrapolation to 24 months.</td>
<td>July 17, 2003</td>
<td>Dionne L. Price, Ph.D.</td>
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<tr>
<td>EES</td>
<td>Acceptable. However it was determined that facility (manufacturer of the TIMERx®-N excipient) needs inspection. Request for inspection of this facility will be submitted to the Office of Compliance.</td>
<td>February 26, 2003</td>
<td>Office of Compliance Janine D. Ambrogio</td>
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<td>Pharm/Tox</td>
<td>The impurities as well as any other (structural alerts for mutagenicity) which are identified as impurities, must be</td>
<td>Sep. 25, 2003</td>
<td>R. Daniel Mellon, Ph.D.</td>
</tr>
</tbody>
</table>
controlled to levels well below or be qualified. This qualification should include a minimal genetic toxicology screen (one in vitro mutagenicity assay and one in vitro chromosome aberrations assay) testing each compound at the limit dose for the assay. Should a genetic toxicology assay yield a positive result, the specification for the impurity should be lowered to NMT, or the impurity should be adequately qualified via a carcinogenicity assessment in a single species.

<table>
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<tr>
<th>Biopharm</th>
<th>The IVIVC studies do support the proposed acceptance criteria for the drug product dissolution.</th>
<th>September 23, 2003</th>
<th>David Lee, Ph.D.</th>
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<tr>
<td>LNC</td>
<td>NA</td>
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<td>Methods Validation</td>
<td>Not requested at this time since the specifications need to be revised.</td>
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<td>DDMAC</td>
<td>Recommends which should be followed with an appropriate suffix to distinguish the extended release dosage formulation of this product form the immediate release dosage formulation.</td>
<td>August 25, 2003</td>
<td>Scott Dallas, R.Ph.</td>
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<td>EA</td>
<td>Not applicable. Categorical exclusion claimed</td>
<td>N/A</td>
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<tr>
<td>Microbiology</td>
<td>Not applicable as this is solid oral dosage form and there are no apparent microbiological issues</td>
<td>N/A</td>
<td>N/A</td>
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</table>

Appears This Way
On Original
The Chemistry Review for NDA 21-610

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is approvable pending satisfactory resolution of CMC deficiencies and comments listed at the end of the review. The applicant should address all of the listed CMC deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None has been made.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product(s):
Background
Oxymorphone hydrochloride USP, has been used as an appropriate therapeutic choice for a variety of painful conditions since 1959. Oxymorphone has a significantly higher (10 times more potent if administered parentally and 2 to 3 times more potent if administered orally) analgesic potency compared to morphine. Currently Endo Pharmaceuticals Inc. markets oxymorphone hydrochloride USP, in two formulations.

- Numorphan® (oxymorphone HCl, USP) suppositories (5 mg) under NDA 11-738.
- Numorphan® (oxymorphone HCl, USP) Injection 1mg/ml (ampule) and 1.5 mg/ml (10 ml multiple dose vials) under NDA 11-707.

This NDA for which an IND was filed on September 10, 1997, is intended to control the release of oxymorphone HCl within the gastrointestinal tract, with the result that the drug is delivered at a specific predetermined rate suitable for a twice a day dosing. The drug release rate is dependent on the diffusion of the drug from the controlled release matrix. Mechanically, the rate of drug release is controlled by the rate of water penetration into the tablet matrix to form a tight gel with a slowly eroding core.

Dosage Strengths
The oxymorphone HCl extended release tablet is formulated in four strengths 5, 10, 20, and 40 mg. They are all octagon-shaped, convex, film-coated tablets which are
distinguished by their colors and imprint: the 5 mg is pink, the 10 mg is light orange, the 20 mg is light green, and the 40 mg is yellow.

**Formulation:**
Tablets contain the following inactive ingredients: hypromellose, iron oxide black, methylparaben, propylene glycol, silicified microcrystalline cellulose, sodium stearyl fumarate, TIMERx®-N, titanium dioxide, and triacetin. The 5, 10 and 20 mg tablets also contain macrogol, and polysorbate 80. In addition, the 5 mg tablets contain iron oxide red. The 10 mg tablets contain FD&C yellow No. 6. The 20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10. The 40 mg tablets contain FD&C yellow No. 6, D&C yellow No. 10, and lactose monohydrate.

The excipient TIMERx®-N is the primary means of controlling the drug release. It constitutes of the tablet formulation. This hydrophilic matrix is a proprietary controlled-release drug delivery excipient developed by Penwest Pharmaceuticals. TIMERx® materials are composed of locust bean gum and xanthan gum. The TIMERx®-N is a non-compendial active excipient, therefore the CMC information is contained in DMF 11868 which is supported by Penwest Pharmaceuticals. This DMF is reviewed by me and is deficient (see Review # 2 dated September 24, 2003). The following is the major deficiency of this DMF: the particle size distribution of the TIMERx®-N is not sufficiently specific to assure reproducible particle size distribution in all of the TIMERx®-N batches. Optimal particle size distribution of all of the components of the TIMERx®-N formulation is critical to uniformity of the powder blend in manufacturing of these tablets. Thus, the applicant will be asked to provide a tighter particle size distribution specification for the TIMERx®-N, e.g., distribution specification. Justification should be based on the batches used in the manufacturing of the NDA exhibit batches and biobatches.

**Manufacturer and Manufacturing Sites:**
Manufacturing process for Oxymorphone Hydrochloride Extended-Release Tablets is a
1) This site manufactured the initial clinical study tablets. Tablet strengths manufactured at this site were 10, 20, and 40 mg. The Clinical batches manufactured at are coated but unprinted tablets.

2) This site manufactured the following tablets:
- Tablets that were used in late phases of clinical trials. These were 5, 10, 20, and 40 mg tablets.
- manufactured the primary stability batches. Three primary stability (exhibit) batches tablets/scale of each strength were manufactured at this site. The primary stability or exhibit batches manufactured at are coated and printed tablets.
- site will be responsible for commercial production of all four tablet strengths. The commercial batches are \times the scale of the pilot batches which is consistent with the allowance of up to a increase in manufacturing scale (SUPAC-MR, scale-up, level -1).
- In addition, will be responsible for the packaging, labeling, and testing of all commercial batches.

Both used the same process to manufacture these tablets and the formulation of each respective strength is the same except for the tablet coating and imprinting. Both tablets were color film-coated, however for the tablets the coating solution contained and the tablets were imprinted with black ink.

To show that the drug products manufactured at the two sites are similar, Endo Pharmaceuticals Inc. has conducted an in-vitro drug release comparison and a bioequivalence study between the manufactured batches. The bioequivalence study was conducted on 40 mg tablets manufactured at the two sites. Results of the statistical analyses of bioequivalence study indicate that the products manufactured at both sites are bioequivalent (see the Clinical Pharmacology and Biopharmaceutics review of this NDA by Dr. David Lee dated September 23, 2003).

In vitro dissolution experiments were performed in 0.1N HCl and in pH 4.5 phosphate buffer. Dissolution study demonstrates the similarity of coated and printed tablets (primary stability or exhibit batches) manufactured at versus coated and unprinted tablets (Clinical batches) manufactured at .

The are critical parameters in manufacturing process, which is the manufacturing method used for these extended release tablets. In addition, the possibility for agglomeration and aggregation of the should be watched closely. Therefore we will ask the applicant to perform the following tests:
Executive Summary Section

The following ______ tests should be performed on routine bases in every commercial production batch of the extended release tablets:

a) Perform the following tests on the ______ and provide the acceptance criteria:

Packaging:
Each strength of the Oxymorphone HCl ER Tablet will be packaged in two different packaging configurations. Bottles and blisters, each bottle will contain ______ 100, ______ tablets with child-resistant closure. Each blister pack will contain 100 tablets (5 blister cards of 20 tablets).

- The bottle container/closure system consists of ______ bottles supplied by ______ and is composed of the ______ the child-resistant closures from ______ with ______

- The blister package consists of ________ and ______

Specifications:
The proposed regulatory specifications and analytical methods for quality control of Oxymorphone HCl Extended-Release Tablets, 5, 10, 20 and 40 mg, includes:
Description, Identification, Assay, Degradation Products, Uniformity of Dosage Units (Content Uniformity), and Drug Release (Dissolution).

Acceptance criteria for degradation products required revision. Specifically those degradation products with ______ moiety (structural alerts for mutagenicity) arising from the drug substance should be controlled to levels well below ______ (see the Draft Deficiency List at the end of this review).

As indicated before, due to the drug release mechanism of the drug product, the ______ of the drug product should be tested and controlled on stability.

Drug release (dissolution) was studied in different dissolution media:
Stability:
Amendment of July 17, 2003 contained additional stability data, which extends the stability data for as long as 24 months for the primary stability batches and up to 48 months for supportive batches. Three lots of each tablet strength packaged in the commercial packaging configurations that are mentioned above were put on stability. The primary stability data includes six months data under ICH accelerated conditions (40°C/75% RH) and up to 24-months long-term room temperature (25°C/60% RH) data. Supportive stability data on clinical trial batches at both ICH accelerated and room temperature conditions are also provided in this NDA. An expiration dating period of 36 months is proposed by the applicant. However, analysis of dissolution data (18 months and 24 months data) indicates a possible increase in dissolution rate on stability and thus reveals the possibility of dose dumping at 36 months. Since this NDA is approvable the applicant will be asked to provide updated drug product stability data, with statistical analysis and the expiration dating for this product will be determined at that time.

Drug substance:
Background:
Oxymorphone (14-hydroxydihydromorphone) is a semi-synthetic opioid agonist derived from thebaine. It is a schedule II controlled substance.

Its structure is related to morphine, with the following differences:
- A ketone group substituted at the C-6 position of morphine.
- The 7-8 double bond saturation.
- Hydroxyl group substitution at C-14.

The hydrochloride salt form of Oxymorphone is a USP article. It is freely soluble in water (1 in 4).

Manufacturer and Manufacturing Sites:
Executive Summary Section

The drug substance manufacturer is Mallinckrodt Chemical Company. The CMC information supported by Mallinckrodt for oxymorphone HCl is contained in DMF # 14502. DMF 14502 is reviewed by me and was found deficient. Mallinckrodt will be informed on the deficiency of their DMF (see review of DMF 14502 by this reviewer).

The USP optical rotation test and acceptance criteria is broad and should be supported by an HPLC test. We will ask from the applicant to provide adequate information to support the stereochemical configuration and stereoisomeric purity of oxymorphone hydrochloride (i.e., the synthetically introduced chiral center).

Initial clinical trial materials were manufactured using drug substance from .

The long-term plan was to discontinue the manufacture of oxymorphone HCl drug substance. Therefore, was selected as the new drug substance supplier. All subsequent batches of drug product for clinical studies and for NDA submission were manufactured using the drug substance supplied by . The material from both companies exhibits comparable physical and chemical characteristics that are relevant to the manufacturing and performance of the drug product. These are, comparison of the , comparison of the particle size distribution, comparison of the intrinsic dissolution of the drug substance manufactured at the two sites, as well as the pH solubility profiles and the dissolution of the tablets manufactured using the drug substance from both suppliers.

Specifications:
Specifications include all USP compendial requirements, plus additional limits for related substances and residual solvents. . The validation of the HPLC assay and related substances method was performed by Mallinckrodt, and the data is contained in their DMF 14502. The applicant will be asked to submit the method validation for the HPLC drug substance assay and related substances in their NDA application and include this HPLC assay and related substances as the regulatory method rather than as an alternate test method. All the other methods are USP compendial and do not require validation.

The specifications for the drug substance should be modified and it will be requested from the applicant to include the followings in the drug substance specifications at release:

- Revise the specifications to establish the chromatographic method for assay and related substances as the “regulatory” methods for the NDA, replacing their designation as “alternate” methods.
Executive Summary Section

to provide a specification in the drug substance using an accurate and specific method (e.g., Karl Fischer titration).

- The impurities, as well as any other which are identified as impurities, must be controlled to levels well below (e.g., the current drug substance specification of NMT). The applicant will be asked to coordinate with the DMF holder Mallinckrodt to submit a tightened specification acceptable to the agency, or justify the current specification based on new carcinogenicity studies. Qualifications are based upon a maximum daily dose of 1 gram.

Packaging:
This is detailed in the DMF 14502 and is found adequate.

Stability:
Stability data for the drug substance supplied by Mallinckrodt is reported in the DMF. The stability data for lots of the drug substance manufactured by are reported in the NDA. Six months stability data at accelerated temperature conditions and up to 2 years data for long term storage conditions are provided. Note that the applicant is not using as the future supplier of the drug substance. Therefore the following comment will be sent to the applicant:
- Justify the proposed retest date for oxymorphone hydrochloride supplied by Mallinckrodt.

B. Description of How the Drug Product is Intended to be Used

Tablets are to be swallowed whole, and are not to be broken, chewed, crushed or dissolved. Taking broken, chewed, crushed or dissolved tablets leads to the rapid release and absorption of a potentially fatal dose of oxymorphone. As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of TRADEMARK, attention should be given to the following:
1. The total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
2. The relative potency estimate used to calculate the equivalent oxymorphone dose needed;
3. The patient's degree of opioid tolerance;
Executive Summary Section

4. The age, general condition, and medical status of the patient;
5. Concurrent non-opioid analgesic and other medications;
6. The type and severity of the patient's pain;
7. The balance between pain control and adverse experiences.

In clinical practice, it is suggested that opioid-naïve patients being initiated on chronic around-the-clock opioid therapy be started with the lowest available dose of the ER opioid. Therefore, it is recommended that opioid-naïve patients be started with 5 mg TRADEMARK q12h and patients receiving TRADEMARK (IR) may be converted to TRADEMARK (ER) by administering half the patient's total daily oral TRADEMARK (IR) dose as TRADEMARK (ER), q12 hours. For example, a patient receiving 60 mg/day TRADEMARK (IR) may require 30 mg TRADEMARK (ER) q12h. Supplemental TRADEMARK (IR) may be required for breakthrough pain until the response to the patient's daily TRADEMARK (ER) dosage has stabilized. In clinical practice, when rescue medication is warranted, it is recommended that the supplemental breakthrough dose be calculated at approximately 10-20% of the total daily TRADEMARK (ER) dose. For example, a patient on 30mg TRADEMARK (ER) q12h would receive 5-10mg of TRADEMARK (IR) as the supplemental breakthrough dose.

C. Basis for Approvability or Not-Approval Recommendation
The CMC deficiencies are listed at the end of this review. The applicant should adequately respond to these deficiencies before the Division approves this NDA.

III. Administrative

A. Reviewer’s Signature

_Electronically captured in DFS_

B. Endorsement Block

_Electronically captured in DFS_
Jila H. Boal, Ph. D, CMC Reviewer/ June 10, 2003
Dale Koble, Ph. D, Chemistry Team Leader/
Lisa Bascham-Cruz, Project Manager

C. CC Block

_NDA 21-610_
HFD-170/LBascham-Cruz/Dkoble/JBoal
Page(s) Withheld

Trade Secret / Confidential
Draft Labeling
Deliberative Process
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-------------------
Jila Boal
10/15/03 05:28:44 PM
CHEMIST

Dale Koble
10/15/03 05:32:53 PM
CHEMIST
NDA 21-611

OPANA™
(Oxymorphone Hydrochloride) Tablets
5 mg and 10 mg

Endo Pharmaceuticals

Jila H. Boal, Ph.D.
Division III, ONDQA
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Chemistry Review Data Sheet

1. NDA # 21-611

2. REVIEW # 2

3. REVIEW DATE: May 15, 2006

4. REVIEWER: Jila H. Boal, Ph.D.

5. PREVIOUS DOCUMENTS:

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<td>Dec. 20, 2002</td>
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<td>Feb. 13, 2003</td>
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<td>Jul. 17, 2003</td>
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<td>Aug. 6, 2003</td>
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<td>N 21-611-000-BL</td>
<td>Sep. 12, 2003</td>
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6. SUBMISSION(S) BEING REVIEWED:

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<td>October 15, 2003</td>
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<tr>
<td>CMC Teleconference</td>
<td>December 1, 2003</td>
</tr>
<tr>
<td>Post Action Letter</td>
<td>February 16, 2004</td>
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<tr>
<td>Meeting Minutes</td>
<td>March 16, 2004</td>
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<td>Teleconference Meeting Minutes</td>
<td>May 7, 2004</td>
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<td>Complete Response to the Approvable Action Letter Amendment (Proprietary Name Evaluation)</td>
<td>July 16, 2004</td>
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<tr>
<td>Amendment to a Complete Response–In-vivo Study Results/ Oxymorphone and Alcohol Co-administration</td>
<td>December 22, 2005</td>
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<td>February 20, 2006</td>
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<td>March 22, 2006</td>
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</table>
Amendment (color mock-ups of the labeling incorporating the proposed trade name for all three products) March 24, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Endo Pharmaceuticals
Address: 100 Painters Drive
         Chadds Ford, PA 19317
Representative: Mary Alice Raudenbush
               Vice President, Regulatory Affairs
Telephone: (610)-558-9800

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: OPANA™(Oxymorphone Hydrochloride) Tablets
b) Non-Proprietary Name (USAN): Oxymorphone Hydrochloride
c) Code Name/#: N/A
d) Chem. Type/Submission Priority :
   • Chem. Type: 3
   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

The application is filed as a 505B2 application based on the listed drugs:

   Numorphan Injection, NDA# 11-707
   Numorphan Rectal Suppositories, NDA# 11-738

10. PHARMACOL CATEGORY:
    Management of moderate to severe pain where the use of an oral opiate is appropriate

11. DOSAGE FORM:
    Immediate Release Tablet, Oral
12. STRENGTH/POTENCY:

5 and 10 mg per tablet

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED:  _X_ Rx  ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___ SPOTS product – Form Completed

_x_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Morphinan-6-one, 4,5—epoxy-3, 14-dihydroxy-17-methyl-, hydrochloride, (5α)-
or,
4,5α-Epoxy-3,14-dihydroxy-17-methylnorphinan-6-one hydrochloride

\[
\text{Mol. Formula: } C_{17}H_{19}NO_4 \cdot \text{HCl}
\]
\[
\text{Mol. Weight: } 337.80
\]

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

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<td>Oxymorphone HCl</td>
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<td>Review #2 by Jila Boal, May 7, 2006</td>
<td>Polymorph issues to be addressed</td>
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<td>3</td>
<td>Adequate</td>
<td>Oct. 14, 2003</td>
<td>Strikeforce</td>
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<td>Adequate</td>
<td>May 22, 2002</td>
<td>Strikeforce, Rev.#2, p. 22, 24</td>
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<td>Sep. 19, 2003, by Dominic Chiapperino</td>
<td></td>
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</table>

1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

<table>
<thead>
<tr>
<th>Document</th>
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<th>Description</th>
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<tr>
<td>IND</td>
<td>56,919</td>
<td>Numorphan (Oxymorphone HCl) C-R Tablets</td>
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<tr>
<td>IND</td>
<td>58,602</td>
<td>Numorphan (Oxymorphone HCl) IR Tablets</td>
</tr>
<tr>
<td>NDA</td>
<td>21-611</td>
<td>Oxymorphone HCl Immediate Release Tablets</td>
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### CHEMISTRY REVIEW

#### Executive Summary Section

<table>
<thead>
<tr>
<th>NDA</th>
<th>11-707</th>
<th>Numorphan Injection</th>
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<td>11-738</td>
<td>Numorphan Rectal Suppositories</td>
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<tr>
<td>NDA</td>
<td>21-610</td>
<td>Extended release formulation of oxymorphone hydrochloride tablets for oral administration.</td>
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#### 18. STATUS:

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<tr>
<th>CONSULTS/ CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
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<td>Biometrics</td>
<td>Not consulted. Real time stability data for up to 48 months was submitted for a proposed expiration dating of 30 months.</td>
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<td></td>
</tr>
<tr>
<td>EES</td>
<td>Facilities are acceptable</td>
<td>Feb. 13, 2006</td>
<td>Janine D. Ambrogio</td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>Pharm/Tox do not have any concern regarding the excipients. The non genotoxic impurity levels in the drug substance and drug product were reduced according to the relevant Guidances, and the genotoxic impurities are according to an interim acceptance criteria of .</td>
<td>June 13, 2006. As per e-mail received from Mamata De, Ph.D. the Pharm / Tox primary reviewer.</td>
<td>Daniel Mellon, Ph.D. Mamata De, Ph.D.</td>
</tr>
<tr>
<td>ClinicalPharm</td>
<td>Not Consulted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNC</td>
<td>Not consulted (simple dosage form)</td>
<td></td>
<td></td>
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<tr>
<td>Methods Validation</td>
<td>Based on the ONDQA's established criteria for NDA analytical method validation (1/5/2005), none of the test methods meet the criteria for further evaluation. Except the HPLC method for the level of genotoxic impurities, will be evaluated in future once the final acceptance criteria are established. The present</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Values are accepted on an interim bases.</td>
<td>DMETS has no objections to the use of the proprietary names, Opana and Opana ER provided that only one name Opana (NDA’s 21-610 and 21-611) is approved. DDMAC finds the proprietary names Opana and Opana ER acceptable from a promotional perspective.</td>
<td>June 12, 2006</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>---------------</td>
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<tr>
<td>DMETS and DDMAC</td>
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<tr>
<td>EA</td>
<td>Not applicable. Categorical exclusion claimed and granted.</td>
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<td>As per this review</td>
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<tr>
<td>Microbiology</td>
<td>N/A</td>
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</table>
The Chemistry Review for NDA 21-611

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   From the standpoint of Product quality CMC, NDA 21-611 is recommended for approval. An expiration period of 30 months may be granted based on the assessment of the stability data.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
   None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
This product is manufactured using PROCEDURE. Commercial batch will be manufactured at Lincoln, Nebraska, of Novartis Consumer Health, Inc. on a SCALE. The excipients in the drug product formulation are Lactose Monohydrate (NF), Pregelatinized Starch (NF), and Magnesium Stearate (NF). The 5 mg strength tablet contains a colorant, FD&C Blue #2 Aluminum Lake, which distinguishes it from the 10 mg strength tablet containing D&C Red #30 Aluminum Lake.

The 5 mg Tablets are blue, round, convex tablets debossed with E612 over 5 on one side and plain on the other. Bottles of — tablets with child-resistant closure. Bottles of 100 tablets with child-resistant closure. Bottles of — tablets with child-resistant closure. Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only).

The 10 mg Tablets are Red, round, convex tablets debossed with E613 over 10 on one side and plain on the other. Bottles of — tablets with child-resistant closure. Bottles of 100 tablets with child-resistant closure. Bottles of — tablets with child-resistant closure. Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only).

B. Description of How the Drug Product is Intended to be Used
   Oxymorphine hydrochloride is proposed for the management of moderate to severe pain where the use of an opioid is appropriate. The immediate release dosage
formulation of oxycodone hydrochloride will be available as a 5 mg and 10 mg tablet. In opioid naïve patients the recommended starting dose of the immediate release dosage formulation is 5 mg taken orally every 6 hours as needed.

These dosage formulations of oxycodone hydrochloride have been classified as a Class II controlled substance.

C. Basis for Approvability or Not-Approval Recommendation

The NDA was submitted on December 20, 2002 under section 505(b) of the Federal Food, Drug and Cosmetic Act for Oxycodone Hydrochloride Immediate Release (IR) Tablets. An “approvable” action was taken on October 15, 2003 to which a complete response submitted on December 22, 2005. Since there were substantial CMC deficiencies in the original NDA, Endo and the Agency were engaged in several post-action meetings to formulate strategies to address them.

The active pharmaceutical ingredient (API), oxycodone as the hydrochloride salt, represents less than — of the overall components of the 5 mg tablet strength and less than — of the 10 mg tablet strength, as each tablet is formulated for a total weight of 220 mg. Since these are formulations in which the API is a relatively small portion of the overall formulation, and since the product are manufactured using

The data on the bulk and tap densities indicated that they remained unchanged in the exhibit and validation batches and were not indicative of—. Therefore, these will not be routinely monitored.
The firm had been asked to tighten acceptance criteria for dissolution but provided data indicating that a Q of _is achievable at 30 minutes and this is acceptable.

The impact of alcohol on dose dumping of oxymorphone from the formulation was assessed in-vitro using hydroalcoholic media of various alcohol concentrations as the release media. Based on the results the product was shown to be rugged and it did not dose dump in 40% alcohol. However, large quantities of ethanol consumed simultaneously with oxymorphone ER effect the pharmacokinetics of oxymorphone (i.e., increased Cmax). The mechanism by which this occurs (enhanced absorption, decreased metabolism, etc.) is unknown at present; however, based on the in-vitro data, the mechanism of the increased plasma concentrations is likely not due to dose dumping. This information has been captured appropriately in the package insert.

The analyses of stability data indicate that the assay, _and total degradation products would remain within current specifications through 30 months for all packages at 25°C/60%RH.

Drug substance specifications have been updated to include adequate acceptance criteria for the level of impurities and degradation products. These levels are revised based on the ICHQ 3A recommendations. The _which are present as process impurities from the synthesis of the drug substance are controlled at level on interim basis and this is consistent with the arrangements negotiated between the Agency and Mallinckrodt, the DMF holder of oxymorphone hydrochloride. The drug substance release specifications are also revised _Adequate justification for the acceptance criteria has been provided in DMF _.

In summary, the applicant has provided adequate response to the deficiencies identified in the NDA action letter of October 15, 2003. The manufacturing process seems to be robust. Properly justified _controls are established. Stability data confirms an expiration dating of 30 months for this product. Adequate finished product stability data was provided for up to 48 months. In addition, the supportive stability data confirmed the stability of this product through _months at long term conditions (25°C/60% RH). Hence, the requested expiration dating of 30 months could be granted.

III. Administrative

A. Reviewer’s Signature

_Electronically captured in DFS_
B. Endorsement Block

Electronically captured in DFS
Jila H. Boal, Ph. D, CMC Reviewer/June 13, 2006
Ravi Harapanhalli, Ph. D, Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology
Products) Division III, ONDQA
Lisa Bascham-Cruz, Project Manager

C. CC Block

NDA 21-611
HFD-170/LBascham-Cruz/ RHarapanhalli /JBoal
Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-______
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Jila Boal
6/13/2006 02:24:42 PM
CHEMIST

Ravi Harapanhalli
6/13/2006 03:32:50 PM
CHEMIST
NDA 21-611

Trademark® (Oxymorphone Hydrochloride) Tablets

Endo Pharmaceuticals

Dominic Chiapperino, Ph.D.
Division of Anesthetic, Critical Care and Addiction Drug Products
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Chemistry Review Data Sheet

1. NDA 21-611

2. REVIEW #1

3. REVIEW DATE: September 29, 2003

4. REVIEWER: Dominic Chiapperino, Ph.D.

5. PREVIOUS DOCUMENTS:

<table>
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<th>Previous Documents</th>
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<td>IND 58,602</td>
<td>July 7, 1999</td>
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6. SUBMISSION(S) BEING REVIEWED:

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<tr>
<td>N 21-611-000</td>
<td>Dec. 20, 2002</td>
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<td>N 21-611-000-BC</td>
<td>Feb. 13, 2003</td>
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<td>N 21-611-000-BC</td>
<td>Jul. 17, 2003</td>
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<td>N 21-611-000-BC</td>
<td>Aug. 6, 2003</td>
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<tr>
<td>N 21-611-000-BL</td>
<td>Sep. 12, 2003</td>
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</table>
7. NAME & ADDRESS OF APPLICANT:

Name: Endo Pharmaceuticals
Address: 100 Painters Drive
         Chadds Ford, PA 19317
Representative: Mary Alice Raudenbush
               Vice President, Regulatory Affairs
Telephone: (610)-558-9800

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TRADEMARK™ Tablets
b) Non-Proprietary Name (USAN): Oxymorphone Hydrochloride
c) Code Name/#:
d) Chem. Type/Submission Priority :
   • Chem. Type: 3
   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

   The application is filed as a 505B2 application based on the Listed drugs:

   Numorphan Injection, NDA# 11-707
   Numorphan Rectal Suppositories, NDA# 11-738

10. PHARMACOL. CATEGORY:

    Management of moderate to severe pain where the use of an oral opiate is appropriate

11. DOSAGE FORM:

    Immediate Release Tablet, Oral
12. STRENGTH/POTENCY:

5 or 10 mg per tablet

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED:  _X_Rx    ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

____SPOTS product – Form Completed

_X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride

\[
\text{Mol. Formula: C}_{17}\text{H}_{19}\text{NO}_4 \cdot \text{HCl}
\]

Mol. Weight: 337.80

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

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<td>14502</td>
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<td>Mallinckrodt</td>
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<td>Aug. 7, 2003, by Jila Boal</td>
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<td>Sep. 12, 2003, by Dominic Chiapperino</td>
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<td>Mar. 22, 2001, by Pramoda Maturu</td>
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<td>Adequate</td>
<td>May 19, 2003, By Donald Klein, Ph.D.</td>
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<td>Strikeforce</td>
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<td>May 22, 2002</td>
<td>Strikeforce, Rev.#2, p. 22, 24</td>
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<td>Sep. 19, 2003, by Dominic Chiapperino</td>
<td></td>
</tr>
</tbody>
</table>

¹ Action codes for DMF Table:
1 – DMFReviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

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<th>DESCRIPTION</th>
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<td>Original NDA submission</td>
<td>N 21-610</td>
<td>Related NDA, extended release formulation of oxymorphone hydrochloride tablets for oral administration.</td>
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18. **STATUS:**

**ONDC:**

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<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
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<tr>
<td>Biometrics</td>
<td>Inadequate data to support expiry; 30-month expiry would be acceptable based on stability data analysis</td>
<td>Oct. 1, 2003</td>
<td>Dionne Price, Ph.D.</td>
</tr>
<tr>
<td>EES</td>
<td>Facilities are acceptable</td>
<td>Feb. 26, 2003</td>
<td>Janine D. Ambrogio</td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>Inadequate qualification of degradant impurities that have specified limits above ICH guidelines</td>
<td>Sep. 25, 2003</td>
<td>Daniel Mellon, Ph.D.</td>
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<td>Biopharm</td>
<td>Adequate on bioequivalency of clinical batches and exhibit batches made at different sites</td>
<td>Review filed in DFS Sep. 23, 2003</td>
<td>David Lee, Ph.D.</td>
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<td>LNC</td>
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<tr>
<td>Methods Validation</td>
<td>Will be initiated after firm response to action letter</td>
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<td></td>
</tr>
<tr>
<td>ODS</td>
<td>are best proprietary names considered for the immediate release (N 21-611) and extended release (N 21-610) oxymorphine hydrochloride drug products.</td>
<td>Review filed in DFS Aug. 25, 2003</td>
<td>Scott Dallas, R.Ph.</td>
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<td>EA</td>
<td>N/A</td>
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<tr>
<td>Microbiology</td>
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<td></td>
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</tr>
</tbody>
</table>
The Chemistry Review for NDA 21-611

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approveable, provided the applicant can address the deficiencies in manufacturing controls which are discussed below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 (Post-Marketing) commitments, agreements, and/or risk management steps currently being negotiated with the applicant which relate to chemistry, drug manufacture, or quality controls on the drug product.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product TRADEMARK™ Tablets, also known as Oxymorphone Hydrochloride Tablets, is an oral dosage form that is available in 5 or 10 mg strengths. The product will be marketed as a treatment for moderate to severe acute pain when the use of an oral opiate is appropriate.

The drug product is manufactured using . The excipients in the drug product formulation are Lactose Monohydrate (NF), Pregelatinized Starch (NF), and Magnesium Stearate (NF). The 5 mg strength tablet contains a colorant, FD&C Blue #2 Aluminum Lake, which distinguishes it from the 10 mg strength tablet containing D&C Red #30 Aluminum Lake. There is nothing objectionable about the quality of these excipients for use in the drug product other than a somewhat loose control over particle size, which may have an impact on the uniformity of the drug product.

The drug Product will be manufactured at the facility in Lincoln, Nebraska, of Novartis Consumer Health, Inc.. This site, proposed for the commercial batches to be made on a scale, was also the site where the exhibit batches were manufactured on a scale. The stability studies performed on these exhibit batches and on the primary clinical batches, some of which were manufactured by the contract firm , show the drug product to be stable over the 24 month
period, with minimal accumulation of degradant compounds related to the drug substance, oxymorphone.

The drug substance is the hydrochloride salt of oxymorphone, a potent analgesic in the opioid family of drug compounds. This salt is a white, or slightly off-white, odorless powder, easily soluble in water and acidic aqueous solution. The synthesis of the drug substance and much of the details of drug substance characterization and quality control are described by Mallinckrodt Chemical Company, Inc. under their DMF #14,502.

The marketed drug product would be packaged in several different forms. For both the 5 and 10 mg strength tablets, bottles in sizes, with child resistant caps, would be used for 100s respectively. Also planned for both strengths, blister packaging containing cards with 20 tablets would be used. All of the above packaging types have been utilized in stability studies with the exhibit batches made by NCH.

B. Description of How the Drug Product is Intended to be Used

The applicant proposes that these oxymorphone hydrochloride immediate release formulations for oral administration are intended to be used as follows:

These formulations broaden the range of therapeutic options available for the treatment of moderate to severe acute pain.

C. Basis for Approvability or Not-Approval Recommendation

There are several significant concerns, both with the drug substance and the drug product, which will need to be addressed by the applicant in order to obtain Agency approval of their NDA.

Drug Substance
With regard to the drug substance, oxymorphone hydrochloride, there are issues relating to potentially carcinogenic impurities. The improved control of these impurities by the DMF holder, Mallinckrodt Inc., or their qualification as safe by the applicant, will have to occur to alleviate concerns of the Agency on this issue. The compounds in question are present as process impurities from the synthesis of the drug substance. We have been in contact with both the applicant and the DMF holder of the drug substance to determine how they can work
toward a solution in limiting these impurities to an acceptably low level, or submitting
carcinogenicity study results that would qualify the compounds as safe at the current proposed
levels.

There is also the issue of inadequate characterization of the drug substance. The drug substance
release specifications include a specification of NMT __________. The data imply a
fairly consistent __________ of approximately __________ and the possibility of hydrate forms of the
drug substance, not determined or clarified by the applicant, should be addressed. Also, the
testing __________ should be specific __________, i.e. Karl Fischer analysis, where currently
it is measured by loss on drying at __________

Drug Product
The proposed commercial product, an orally administered immediate-release tablet containing
5 or 10 mg of oxymorphone hydrochloride, is intended for use in cases of severe or acute pain
where an opioid analgesic is appropriate. The broad concern of the Agency is that the controls
proposed to insure the consistent dosage amount of this drug product are inadequate.

The active pharmaceutical ingredient (API), oxymorphone as the hydrochloride salt, represents
less than __________ of the overall components of the 5 mg tablet strength and less than __________ of the 10
mg tablet strength, as each tablet is formulated for a total weight of 220 mg. Since these are
formulations in which the API is a relatively small portion of the overall formulation, and since
the manufacture of the tablet is performed __________ the potential for API concentration or segregation within the __________ drug
product is an immediate concern.

the applicant has not described in sufficient detail the
manufacturing procedures beyond batch records that would commit them to SOPs that the
Agency finds acceptable.

There is, however, a higher than usual
incidence of the need for “rescue” with naltrexone of patients in clinical studies that have been
reviewed by our Medical Officers. It is not clear as to whether this high incidence was caused
by inadvertent high doses attributable to heterogeneous blends of the drug product. Also, it
should be noted that the applicant’s proposed __________ scale-up in the manufacture of the
commercial batches is as yet untested with regard to __________ optimization of
parameters that may impact __________.

There are also degradant impurities controlled in the drug product which have specified limits
at levels that would require qualification. We do not believe that these impurities,
have been properly qualified based on the comments of our PharmTox reviewers.

In favor of the application, the drug product has shown to be quite stable, relatively free of impurities, and fairly uniform in dosage amounts based on the content uniformity testing performed. An “Approvable” action is expected to be taken in this first review cycle with respect to the CMC portion of the application.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block
Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-_____
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dominic Chiapperino
10/15/03 04:32:09 PM
CHEMIST

Dale Koble
10/15/03 04:47:15 PM
CHEMIST