

1ST Cycle Review
CSS

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 8, 2003

To: Bob A. Rappaport, M.D., Director
Division of Anesthetic, Critical Care
And Addiction Drug Products (HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

From: Silvia N. Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Subject: Consultation regarding proposed Abuse Liability Assessment, Label and proposed Risk Management Program (RMP)
NDA 21-610, Oxymorphone Extended Release (ER) Tablets and NDA 21-611, Oxymorphone Immediate Release (IR) Tablets
Sponsor: Endo Pharmaceuticals, Inc
Submissions reviewed in this consult: December 19, 2002 (NDA 21-610) and December 20, 2002 (NDA 21-611)
PDUFA date: October 17, 2003 (NDA 21-610) and October 20, 2003 (NDA 21-611)

BACKGROUND

This memorandum responds to the Division of Anesthetic, Critical Care, and Addiction Drug Products's request for CSS consultation on the abuse liability evaluation, drug labels and the proposed Risk Management Program (RMP) for Oxymorphone immediate release and extended release tablets. This consult will address the abuse liability of oxymorphone hydrochloride and specific aspects of each formulation. Comments regarding the label are being conveyed and discussed in team meetings held by the Division.

Oxymorphone extended release tablets in 5, 10, 20 and 40 mg doses are proposed for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time. Extended release tablets have been developed to provide analgesia for 12-hours.

Oxymorphone immediate release tablets in 5 mg and 10-mg doses are proposed for the management of moderate to severe pain where the use of an opiate is indicated.

Oxymorphone immediate release tablets (2 mg and 5 mg) were previously approved and marketed in the early 1960s but were voluntarily removed from the market for “commercial” reasons. The 2-mg and 5 mg tablets were available for approximately 7 years and the 10-mg tablets were available for approximately 11 years.

Currently oxymorphone is available as an injectable in 1mg/ml and 1.5 mg/ml strengths and as 5-mg suppositories.

Oxymorphone is a mu opioid agonist derived from thebaine controlled under Schedule II of the Controlled Substances Act. Chemically, it is considered to be the O-demethylated analog of oxycodone, and is a metabolite of oxycodone.

CONCLUSIONS AND RECOMMENDATIONS

1. Oxymorphone, like morphine, is a full opioid agonist that binds to mu, kappa and delta opioid receptors and is controlled under Schedule II (CII) of the Controlled Substances Act. Therefore, most of the typical physiological effects mediated through the activation of these opioid receptors should be expected.
2. A literature search reveals that no abuse liability study or comparative assessment of the subjective effects (e.g. euphoria, liking) of oxymorphone relative to other CII opioids could be found. Based upon the pharmacological profile the abuse liability of oxymorphone should be viewed as similar to that of morphine.
3. The proposed risk management plan needs to be described in more detail. Goals of the RMP overall and of each element need to be stated. Intervention plans should be discussed as appropriate. As indicated by the Sponsor several components such as the SOAP questionnaire are works in progress.
4. More information on the composition and function of the Safety Review Board needs to be provided.
5. The Sponsor should state its operational definitions of abuse and misuse.
6. The Sponsor lists the FDA Adverse Event Reporting System (AERS) as the source of information and signal detection of potential safety issues and it seems that this database will also be used to investigate cases of drug abuse, dependence and overdose. The Sponsor should send more information on how the data extracted from AERS will be analyzed. In addition to AERS, the Sponsor should monitor other databases such as DAWN and medical examiners reports, and Poison Control.
7. The Sponsor should also monitor sales, distribution, and prescription patterns in order to detect abnormal clusters. This will require appropriate methods to estimate the number of persons exposed.

8. The data collection, analysis plan, risk management evaluation plan, role of the Safety Review Board and frequency of summary reports are issues that need further clarification.
9. The Sponsor proposes to distribute a risk management kit for physicians with educational materials for both patients and physicians and a prototype patient-physician pain management contract. How will the kit be distributed?
10. The message that the product contains a potent drug that should be kept out of reach of children, pets and those to whom the drug has not been prescribed should be conveyed to the patient in every possible way.
11. Abuse, misuse and diversion cases should be reported to the Agency and also to the DEA as appropriate.

ABUSE LIABILITY

The Sponsor reviewed published literature on the abuse liability of oxymorphone. The most recent paper that addresses certain aspects of the abuse liability of oxymorphone was published in 1988. Abuse liability assessment of oxymorphone was addressed in the late 50s and early 60s and has not been revisited. Coblenz and Bierman (1956), concluded that the abuse potential of oxymorphone lies between that of morphine and hydromorphone based on observations in studies of dependence and withdrawal.

Keats and Telford (1960) evaluated the subjective effects of oxymorphone and morphine in patients who were free of pain, non-opioid tolerant, and who were awaiting elective surgical operations. In their study they used equianalgesic doses of morphine (10 mg/70 kg) and oxymorphone (1.05 mg/70kg) with both drugs administered intramuscularly on the afternoon prior to surgery. Under the conditions of the study, nausea, vomiting, sleepiness and dizziness occurred more frequently after oxymorphone administration than after morphine administration.

When compared to morphine administered to patients with neoplastic disease, the analgesic effect of oxymorphone subcutaneously was tenfold more potent, the onset of effect was more rapid and the duration of effect was slightly longer. Also, in these patients the investigators noted that doses of 1.33 mg and 2.0 mg of oxymorphone administered subcutaneously could be associated with respiratory depression (Eddy and Lee, 1959).

Binding studies conducted by the Sponsor show that like morphine, oxymorphone binds to mu, delta, and kappa opioid receptors. In contrast, oxycodone exhibited binding at the mu and delta 1 receptors, but not at the delta 2 or kappa opioid receptors under the conditions of the assay.

Oxymorphone's moderately high lipid solubility allows the molecule to effectively cross the blood brain barrier, and unlike fentanyl, once in the CNS oxymorphone tends to remain in the aqueous phase where receptors are concentrated, rather than redistributing into lipid membranes.

In a direct comparison of oxymorphone IR and ER tablets (Study EN3202-009), the mean oxymorphone elimination half-life was reported to be 10.29 ± 7.57 and 9.25 ± 2.72 hours following the administration of oxymorphone ER and IR dosage forms respectively. The median (range) T_{max} following oral administration of the IR formulation was 0.5 (0.25-1.0) hours and 5.0 (0.5-12 hours) following administration of the ER dosage form.

DRUG ABUSE, OVERDOSE, AND WITHDRAWAL IN CLINICAL TRIALS

The Sponsor reports that there were four AEs with the preferred term "drug interaction" that were more likely to be drug overdoses (CSR for EN 3202-012). One of the subjects received a single dose of 60 mg oxymorphone ER and, within 2 hours, received two rescue doses of 0.3 mg PCA oxymorphone due to insufficient pain relief. After the last PCA dose, the subject showed signs of CNS depression characterized by somnolence and confusion, which the investigator considered to be serious and treatment-related. Following this adverse event the oxymorphone 60-mg treatment arm was discontinued.

Drug withdrawal syndrome was reported for six (0.3%) of the 1764 subjects exposed to oxymorphone in all studies. All subjects reported to have had drug withdrawal syndrome received oxymorphone ER in Phase II/III studies. Two of the 382 subjects who received oxycodone ER (0.5%) in all studies were reported to have had withdrawal syndrome. Increased sweating, nausea, sedation and pruritus characterized the withdrawal syndrome.

DIVERSION OF INVESTIGATIONAL DRUG AT ONE OF THE STUDY SITES

On June 28, 2002, the Sponsor notified FDA of a possible diversion episode at a study site. ~~_____~~. Later it was determined that the study coordinator had taken the study drug. FDA inspected the site and reported that the Assistant State Attorney issued a letter on August 14, 2002 to the site stating that on August 9, 2002 the study coordinator pleaded guilty of possession of a Schedule II substance and grand theft.

DRUG ABUSE WARNING NETWORK (DAWN)

Oxymorphone appears in the DAWN 2002 Emergency Department Trends but the numbers are extremely low. There were three mentions in 2001 and two mentions in 2002.

In the mortality database, the numbers are also low. DAWN medical examiners reported 46 oxymorphone-related deaths for the 1994-2001 period. Most of these deaths involved other drugs in combination.

Oxymorphone injectable and suppositories are primarily used in institutional settings, and are not widely prescribed.

SUMMARY OF THE PROPOSED RISK MANAGEMENT PLAN (RMP)

The Sponsor proposed a RMP that will apply to both products, immediate and extended release oxymorphone. The goals of the RMP are not clear. The proposed RMP has an educational component and a postmarketing safety surveillance program. Also as part of the RMP the Sponsor is supporting the development of a questionnaire that will help to identify patients with a greater or lesser likelihood of encountering problems during opioid treatment. The classification will indicate to the physician if a patient needs extra monitoring while on pain medication, specifically opioid analgesics

Summaries of the information presented regarding each component follow.

Education

The Sponsor will develop and implement programs for physicians, pharmacists, nurses, other healthcare professionals, patients and their families on the appropriate use of opioid analgesics through:

- Sponsor's initiative on Pain Control, CME programs
- Satellite symposia and educational programs in conjunction with professional meetings
- Development of Clinical Guide to Opioid Analgesics
- Patient and Family Education
- Pharmacy education promoting pharmacy-physician interaction
- RMP kit for Physicians:
 - Educational materials for patients and physicians
 - Example of a patient-physician pain management contract
 - Other suggested materials

Appropriate Patient Selection

The Sponsor proposes a screening-risk reduction approach for use, in the future, as standard of practice treating chronic pain patients through:

- Development of a questionnaire for patients considered for opioid treatment. The questionnaire is known as **Screening for Opioid Addiction Potential tool (SOAP)**.
- Scale validation, testing and communication

A contractor under the auspices of a NIDA/NIH grant will develop the questionnaire.

The questionnaire will be tested using respondents who are chronic patients on opioid therapy and on patients who are not on opioid therapy, including patients with and without a history of abuse. Urine toxicology, spouse reports, physician responses, pain severity and independent psychological interviews will help to assess the predictive value of the questionnaire.

Postmarketing Surveillance

- Safety Review Board will review cases of drug abuse, drug dependence and drug overdose to detect trends in demographics and concomitant use of other products.
- Contractor [redacted] will check safety data for various products (through FDA's Freedom of Information Act) and will report deviations in frequency of oxymorphone compared to other opioids. The database will generate quarterly reports. The proportion Analysis Engine [redacted] will be used to look for deviations in reaction frequency for oxymorphone ER/IR as compared to an expected value derived from a background set of drugs.

REFERENCES

Coblentz, A., Bierman, H.R. The analgesic properties of numorphan (14-Hydroxy-dihydromorphinone). *New Engl. J. Med.*, **1956**, 255 (15), 694-698.

Eddy, N.B., Lee, L.E. The analgesic equivalence to morphine and relative side action liability of oxymorphone (14-Hydroxydihydro-morphinone). *J. Pharmacol. & Exper. Therap.*, **1959**, 125, 116-121.

Keats, A.S., Telford, J. Studies of analgesic drugs V. The comparative subjective effects of oxymorphone and morphine. *Clin. Pharmacol. Therap.*, **1960**, 1(6), 703-707.

Sinatra, R.S., Hyde, N.H., Harrison, D.M. Oxymorphone Revisited. *Seminars in Anesthesia*, **1988**, VII (3), 208-215.

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1ST Cycle Review
DSRC'S + DDRE

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 6, 2003

TO: Bob A. Rappaport, M.D., Acting Director
 Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

THROUGH: Mark Avigan, M.D., Acting Director
 Office of Drug Safety, Division of Drug Risk Evaluation, HFD-430

 Toni Piazza-Hepp, Pharm.D., Acting Director
 Office of Drug Safety, Division of Surveillance, Research, and Communication
 Support, HFD-410

FROM: Mary Willy, Ph.D., M.P.H., Epidemiologist
 Office of Drug Safety, Division of Drug Risk Evaluation, HFD-430

 Gianna Rigoni, Pharm.D., M.S., Epidemiologist
 Office of Drug Safety, Division of Surveillance, Research and Communications
 Support, HFD-410

SUBJECT: Consult: Review of Oxymorphone HCL CR and IR Post-Marketing Surveillance
 PID#: D030594

I. EXECUTIVE SUMMARY

The Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) has requested ODS to review and comment on the elements of a proposed post-marketing surveillance plan from Endo Pharmaceuticals. The sponsor's RMP for oxymorphone requires additional information and development. A list of needed information has been identified in this document. It is recommended that the sponsor describe how this surveillance plan will meet the risk management goals (currently undefined) and what plan will be implemented to evaluate the program.

II. BACKGROUND

The sponsor submitted a risk management plan as part of the NDA documentation for immediate- and extended-release oxymorphone (14-hydroxydihydromorphinone), a semisynthetic opioid agonist that is intended for the relief of moderate to severe pain in patients requiring continuing pain relief for extended periods of time. An initial consult of the sponsor's risk management plan submitted by ODS to the division in June 2003 (1), identified the need for "a description of anticipated data sources for surveillance, the frequency with which updates from these sources will be obtained, types of analyses that will be performed on these data, and a rationale as to why

these particular data sources were chosen for surveillance." The sponsor was also asked to submit an intervention and evaluation plan.

III. SUMMARY of SURVEILLANCE

The sponsor describes several different sources for surveillance information including, post-marketing (spontaneous reports, scientific literature, clinical investigations, and post-marketing epidemiological surveillance studies), Toxic Exposure Surveillance System (TESS), and Drug Abuse Warning Network (DAWN). Adverse event information will be obtained for the sponsor by a contractor () and used to monitor for trends and/or signals. A "proportion analysis engine" will be used to look for deviations in reaction frequency for oxymorphone compared to a set of comparable drugs ("such as oxycodone, fentanyl, and morphine").

A safety review board (ESRB) is described in a second document. The ESRB is a multidisciplinary team of ENDO employees who will review potential cases of clinical significance, drug abuse, drug dependence and drug overdose to identify important trends. The group will meet quarterly.

When a problem of abuse, dependence, misuse, or overdose is identified, the sponsor plans to implement "targeted interventions." These interventions will include education to consumers and providers (physicians, nurses, and pharmacists) and "work " with DEA to minimize diversion and misuse.

IV. COMMENTS on SURVEILLANCE PLAN

Although the sponsor has described a multi-faceted surveillance program, we have the following concerns:

- 1) Post-marketing surveillance in section one is supposed to include post-marketing clinical investigations and epidemiological surveillance studies, but no further information is provided.
- 2) Given that many providers may not realize that abuse, dependence, misuse and diversion are reportable, the sponsor should develop some type of active education and surveillance system, perhaps using their sales force and/or a toll free number, to obtain cases.
- 3) In section 3, the ESRB members appear to be ENDO employees which may lead to a biased review of cases. The sponsor should include external experts in abuse and/or pain management on their board.
- 4) Two national databases have been identified as sources of data, TESS and DAWN. TESS is a telephone information database of calls received by poison control centers. The calls often concern children, are not verified, and are not timely. In addition, the sponsor intends on using the published annual report which provides very limited drug-specific information. The sponsor should arrange to obtain drug-specific information from TESS.
- 5) DAWN is an ongoing national survey of Emergency Departments and a non-random sample of medical examiners. The survey has undergone major changes beginning in 2003 and so studying trends that pre-date these changes is limited. The sponsor plans to "monitor the DAWN report, when it is released." The sponsor should investigate the

possibility of making a specific arrangement with the DAWN investigators to receive timely drug-specific information.

- 6) Other sources of nationalized surveillance data should be explored, including, but not limited to, the National Survey on Drug Use and Health (formerly the National Household Survey on Drug Abuse) and the Treatment Episode Dataset (TEDS) – both conducted by SAMHSA.
- 7) There may be value in monitoring drug utilization, particularly by geographic area and perhaps by provider specialty. It may be useful to estimate a denominator of how many people are actually exposed to this drug in the U.S. to calculate rates of abuse and misuse in the population. Although using drug utilization data is one way to estimate a denominator, other ways should be explored. Surveillance with drug utilization data may also identify specific geographic areas that have problems with diversion and physician specialties that may be mis-prescribing.
- 8) When analyzing surveillance data the sponsor plans to use oxymorphone-like comparators "such as" oxycodone, fentanyl, and morphine. Although it remains unclear what good comparators might be for any proposed surveillance program for abuse, we would suggest that hydromorphone and hydrocodone be included, as well as immediate- and extended-release dosage forms of all the above mentioned drugs.
- 9) The sponsor has not described their definition for abuse, dependence, misuse and diversion and also whether they plan to use numerators only in their analyses of trends or whether they plan to calculate rates. If rates are going to be used, the sponsor needs to describe the denominators that will be used.
- 10) More detailed information about the criteria for intervention and the intervention plan should be provided [i.e., how many "cases" have to be identified before Endo will intervene?].

V. CONCLUSIONS

The sponsor's RMP for oxymorphone requires additional information and development. A list of needed information has been identified in this document. The sponsor also needs to describe how this surveillance plan will meet their risk management goals (currently undefined) and provide an evaluation plan for the program.

REFERENCES

1. Willy, Mary and Rigoni, Gianna. June 19, 2003. Consult: Review of Oxymorphone HCL CR or IR Risk Management Plan. PID#: D030188

Judy Staffa, PhD, Lead Epi, DSRCS

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1ST Cycle Review
DSRCS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION



OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE, OFFICE OF DRUG SAFETY
DIVISION OF SURVEILLANCE, RESEARCH, AND COMMUNICATION SUPPORT

Memorandum

Date: October 3, 2003 HFD- 410

From: Leslie Wheelock, M.S., R.N. Voice: 301-827-7841
Associate Director Fax: 301-827-7241

Through: Toni Piazza-Hepp, Pharm.D.
Acting Director

Subject: Consult: Review of the Education Part of the Risk Management Plan for
Oxymorphone Extended Release Tablets, NDA 21-610 and Oxymorphone Immediate
Release Tablets, NDA 21-611

To: Bob A. Rappaport, M.D. Acting Director
Division of Anesthetic, Critical Care and Addition Drug Products, HFD 170

I. EXECUTIVE SUMMARY

This memorandum addresses the proposed educational parts of a risk management plan (RMP) for Oxymorphone Extended Release Tablets and Oxymorphone Immediate Release Tablets.

Currently, the proposal is lacking detail to allow a complete evaluation. This review provides recommendations for the sponsor regarding educational goal(s), objective(s), intervention(s), and evaluation components so that the educational part of the RMP can be evaluated.

II. GENERAL BACKGROUND:

On August 28, 2003, the Sponsor met with the Review Division who identified three key elements of Risk Management: a) risk of accidental exposure, b) risk of abuse and misuse, and c) risk of improper patient selection. The Sponsor was advised by the Review Division to submit a proposal for the education and prevention of abuse and misuse.

III. SUMMARY OF EDUCATIONAL PART OF THE RISK MANAGEMENT PLAN

The Educational part of the RMP identifies a large target audience consisting of physicians, pharmacists, nurses, other allied healthcare professionals, patients and their families.

The Educational Interventions consist of:

- CME programs as part of the Sponsor's National Initiative on Pain Control (NIPC)
- Satellite symposia and educational programs done in conjunction with professional organizations
- Reference book which the Sponsor has supported by an unrestricted grant
- Pharmacy education materials
- Risk management kit for physicians

The materials submitted for these interventions are:

- NIPC Volume 2 Neuropathic pain curriculum
- NIPC participant guide for Advances in Opioid Analgesia
- NIPC audioconference guide for Opioid Analgesia
- NIPC Pain Management Today newsletter
- PainEDU website and manual
- Pain in Oncologic and Aids Patients Handbook
- American Pain Society (APS) Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain Handbook
- American Academy of Pain Management and APS Consensus Statement on the use of Opioids for the Treatment of Chronic Pain
- Draft Outline for the McGraw Hill Practitioner's Guide to Prescribing Opioid Analgesics for Persistent Pain
- Proposal for a Decision Support Tool to Assist in Opioid Drug Rotation
- Draft Patient Brochure

The materials are not specific to Oxymorphone but are applicable to opioids in general.

IV. COMMENTS ON EDUCATIONAL PART OF THE RISK MANAGEMENT PLAN

Design of RMP

Although the NIPC Educational Program identifies goals, the Sponsor's overall RMP does not provide terminal goal(s) or enabling sub-goals or objectives. We recommend that the Sponsor submit a design plan outlining goal(s), objective(s), interventions, and evaluation for the entire RMP (Willy and Rigoni, ODS Consult Memorandum, June 19, 2003) and how the component parts of the healthcare education and patient education fit into this overarching RMP.

Target Audience

The RMP identifies physicians, nurses, pharmacists, other allied healthcare professionals, patients and their families as the target audience. Since this audience is extremely broad, we recommend that the Sponsor identify narrower targeted audiences who need the education to change practice behaviors regarding abuse and misuse of opioids.

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Healthcare Provider Education

A listing of the Sponsor's NIPC CME programs and events with professional organizations as well as a mention of reference materials is provided. These following programs and events consist primarily of the following interventions, which facilitate knowledge acquisition and understanding:

- group instruction such as Dinner Dialogues, seminars, and professional conferences
- individual instruction such as audioconferences, Webcasts, Newsletters.

Regarding healthcare provider education, we have recommendations concerning the a) goal(s) and objective(s), b) interventions and c) evaluation.

Regarding, *goal(s) and objective(s)*, the CME activities focus on achieving knowledge and understanding. We recommend that the Sponsor develop objectives, which will address healthcare provider practice behaviors.

Regarding *interventions* used, we recommend that the Sponsor, in addition to the nationally renowned faculty, use local or community champions who serve as role models providing personal contact. This recommendation is based on evidence about role modeling as well as CME activities.

A champion who functions as a role model is a component of the Theory of Diffusion of Innovations (Rogers, 2002), which is being proposed to implement the SOAP delivery system by the Sponsor. The use of role models has been shown to be efficient and effective in educating health care professionals in the concepts of cancer pain management (Janjan, 1995) and in increasing knowledge and attitudes about pain management (Dooks, 2001).

While CME activities demonstrate acquisition of knowledge and understanding, CME delivery methods such as conferences have little direct impact on improving professional practice (Davis, 1995). Interactive CME sessions have been shown to enhance participant activity and provide the opportunity to practice skills thus effecting change in professional practice and on occasion, health care outcomes (Davis, 1998).

We also recommend the Sponsor add a reinforcing intervention, such as follow-up by the local champion, promoting integration of new behaviors after the educational intervention. CME activities using practice-enabling or reinforcing strategies improve physician performance (Davis, 1998; Davis, 2001; McPhee, 1991).

Regarding *evaluation*, which is based on the goal(s) and objective(s) of a program or plan, the Sponsor needs to submit a study design plan, which outlines how they intend to evaluate whether the goal(s) and objective(s) of the healthcare provider education part of the RMP are achieved. This plan needs to evaluate practice behaviors in addition to acquisition of knowledge and understanding, which are routinely evaluated with accredited continuing education.

We additionally recommend that the Sponsor pilot test the Decision Support Tool and Risk Management Kit as well as evaluate these interventions with regard to healthcare provider practice and patient outcomes.

Patient and Family Educational Interventions

The Sponsor has submitted a draft of a patient brochure on opioid analgesics as part of the RMP.

Regarding the Patient and Family Education part of the RMP, we have the following recommendations:

- a) identify goal(s) and objective(s) for patient and family education
- b) identify how the draft patient brochure will be used as an educational intervention
- c) include other evidence based interventions, which enhance patient outcomes regarding abuse and misuse of opioids
- d) submit a study design plan, which outlines how the Sponsor intends to evaluate whether the goal(s) and objective(s) of the patient and family education part of the RMP are achieved.

V. CONCLUSIONS

The Sponsor's educational part of the RMP for Oxymorphone requires additional information and development. Although, there is no Agency guidance to reference, the Sponsor may refer to the FDA Risk Management concept paper and standard principles of instructional design for educational programs and plans.

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VI. REFERENCES

- Davis, D.A. (1998). Does CME work? An analysis of the effect of educational activities on physician performance or health care outcomes. International Journal of Psychiatry in Medicine, 28(1), 21-39.
- Davis, D.A., O'Brien, M.A., Freemantle, N., Wolf, F.M., Mazmanian, P., Taylor-Vaisey, A. (1999). Impact of formal continuing medical education: Do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? JAMA, 282(9): 867-874.
- Davis, D.A., Thomson, M.A., Oxman, A.D., Haynes, R.B. (1995). Changing physician performance. A systematic review of the effect of continuing medical education strategies. JAMA, 274(9), 700-705.
- Davis, D.A., Thomson, M.A., Oxman, A.D., Haynes, R.B. (1992). Evidence for the effectiveness of CME. A review of 50 randomized controlled trials. JAMA, 268(9), 1111-1117.
- Dooks, P. (2001). Diffusion of pain management research into nursing practice. Cancer Nursing, 24(2), 99-103.
- Janjan, N.A, Martin, C.G., Payne, R., Dahl, J.L., Weissman, D.E., Hill, C.S. (1995). Teaching cancer pain management: Durability of educational effects of a role model program. Cancer 77(5), 996-1001.
- McPhee, J.A., Wilgosh, C.P., Roy, P.D., Miller, D.M. & Knox, M.G. (1991). Effect of pharmacy conducted education on prescribing of postoperative narcotics. American Journal of Hospital Pharmacy, 48(7), 1484-1487.
- Rogers, E.M. (2002). Diffusion of preventive innovations. Addictive Behaviors, 27, 989-993.
- Willy, M. & Rigoni, G. (June 19, 2003). Memorandum: ODS Consult: Review of Oxymorphone HCL CR and IR Risk Management Plan.

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Toni Piazza Hepp
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DRUG SAFETY OFFICE REVIEWER
Primary Reviewer: Leslie Wheelock

REQUEST FOR CONSULTATION

TO (Division/Office):
Controlled Substance Staff
Name: **Corinne Moody**
HFD-009

FROM: **Bob Rappaport, M.D.**
Division Director, Division of Anesthetic, Critical Care
and Addiction Drug Products

DATE 1/29/03	IND NO.	NDA NO. 21-611	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT December 20, 2003
NAME OF DRUG Oxymorphone HCL IR Tablets		PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG Opiate analgesic	DESIRED COMPLETION DATE October 20, 2003 (action)

NAME OF FIRM: **Endo Pharmaceuticals**

REASON FOR REQUEST

I. GENERAL

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| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER: |
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CSS specialty review for NDA

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS Review of Abuse Liability Pkg, labeling and devel. of RMP.
Attached is volume 1.1 and 1.2 for NDA 21-611 (oxymorphone HCL IR tablets). The entire document may be accessed through the EDR. The action date is October 20, 2003, but formal comments for the Sponsor may be required up to a month prior to that date for final letter sign off. Labeling negotiations are likely to occur up to the action date. Please contact Lisa E. Basham-Cruz, Regulatory Project Manager, with any questions at 301-827-7420. Please cc any formal response to Lisa Basham-Cruz (bashaml) and Pamela Hahn (hahnpl).
Please display our consult tracking number prominently on the cover of your response: 2003.170.A.00009
Thank you!

SIGNATURE OF REQUESTER Lisa E. Basham-Cruz	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND <input type="checkbox"/> DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 30, 2003

TO: Bob Rappaport, M.D., Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

VIA: Lisa Basham-Cruz, Regulatory Health Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Trademark
(oxymorphone HCL) Extended-Release Tablets, NDA 21-610.
(Consult 2003.170.A.00141)

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Trademark (oxymorphone HCL) Extended-Release Tablets, NDA 21-610. We have simplified the wording, made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Our proposed changes are based on the draft prescribing information submitted December 19, 2002. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

6 Page(s) Withheld

 Trade Secret / Confidential

2 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-_____

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
9/30/03 12:51:34 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
9/30/03 12:56:53 PM
DRUG SAFETY OFFICE REVIEWER



NDA 21-610
NDA 21-611

DISCIPLINE REVIEW LETTER

Endo Pharmaceuticals
100 Painters Drive
Chadds Ford, PA 19317

Attention: Mary Alice Raudenbush
Director, Regulatory Affairs

Dear Ms. Raudenbush:

Please refer to your December 19 and December 20, 2002, new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for oxymorphone HCl controlled-release 5, 10, 20, and 40 mg Tablets and oxymorphone HCl immediate-release 5 and 10 mg Tablets, respectively.

We also refer to your submissions dated February 11, 2003.

The Division of Medication Errors and Technical Support (DMETS) has completed the review of the tradename and carton and container labels section of your submission, and has identified the following deficiencies:

1. DMETS does not recommend the use of the proprietary name Opana. However, there are no objections to the use of the proprietary name '_____'. In addition, DMETS does not recommend use of the suffix "IR" or any suffix to identify the immediate release dosage formulation of oxymorphone hydrochloride tablets. The extended release dosage formulation of oxymorphone hydrochloride tablets should include an appropriate suffix to distinguish it from the immediate release dosage formulation.

- a. Review of the Proprietary Names, Opana and Opana IR

In reviewing the proprietary names, "Opana and Opana IR", the primary concern raised was related to the potential for name confusion with Opium.

Opium and Opana have the potential to look-alike when scripted. When scripted, Opium and Opana can look very similar, since the first two letters of each name are exactly the same and both names consist of 5 letters. All the letters of each name have a corresponding height characteristic when scripted. A handwriting sample is included for review.

Opium is available in two different dosage formulations, an oral solution and suppository. The oral solution of opium has been formulated into two different concentrations resulting in two products known as Opium Tincture, USP and Paregoric, USP. Although Opium Tincture, USP and Paregoric, USP are the official compendial names, other names have been associated with these products. Other names found in the literature refer to Opium Tincture, USP as Opium Tincture, deodorized; Opium Tincture (laudanum); deodorized tincture of opium; tincture of opium; DTO; and Opium. Therefore, any of these names, including "Opium" could be found on a prescription to indicate Opium Tincture, USP.

If oxymorphone hydrochloride is formulated as an oral solution, then the products may possess many overlapping characteristics. Common product characteristics could include the prescription schedule (CII), indication for use (pain relief, although this is an unlabeled indication for opium), route of administration (oral) and dosage formulation (oral solution). The expression of strength is often omitted on products that are only available in one concentration; therefore this characteristic would only aid in differentiating Opium from Opana, if Opana were formulated as two different concentrations of an oral solution. Even though Opium Tincture should be administered as a fraction of a mL or in drops, medication errors have occurred in which Opium Tincture has been administered to patients as a teaspoonful(s) or in 5 to 10 mL's. Therefore the dose of Opana solution may not differentiate the products. Opium Tincture should only be dispensed in small quantities and in dropper bottles, but these characteristics do not always prevent errors with the interpretation of the product name. Therefore, there would be an increased risk of a medication error between the names Opium and Opana, if oxymorphone hydrochloride was formulated and marketed as an oral solution.

Opium is also available in a suppository dosage formulation. There are currently two different products on the market with the proprietary names of Opium and Belladonna Suppositories, and B&O suppositories. B&O suppositories are available in two different strengths, however the product known as Opium and Belladonna Suppositories is only available in one dosage strength. Therefore a prescription written for Opium suppositories would probably not be questioned by a pharmacist. If you decide to change the proprietary name "Numorphan" to "Opana," it will also be available as a suppository. Opium and Belladonna Suppositories are indicated for the relief of moderate to severe pain associated with rectal or bladder tenesmus that may occur in postoperative states and neoplastic situations. Oxymorphone hydrochloride suppositories are also indicated to relieve moderate to severe pain. Common product characteristics would include the prescription schedule (CII), indication for use (pain relief), route of administration (rectal) and dosage formulation (suppository). The product strength could possibly be omitted on both products, and therefore this characteristic would not aid in differentiating Opium from Opana. The look-alike similarities between the names, the similar product characteristics and indication for use would increase the risk of a medication error between the products.

If you decide to change the proprietary name "Numorphan" to "Opana," it will also be available as an injection. Although opium is not available as a parenteral dosage

formulation, the potential for confusion could still occur. An appropriate inpatient hospital order could be written as "Opana 1 ml IM q 6 hours as needed for pain". DMETS is concerned the Opana could be interpreted as Opium. Two characteristics that could aid in differentiating the medications Opium or Opana would be the dose and the route of administration. However, the 1mL dose may not raise any concern, even though the dose exceeds the recommended 0.6mL dose for Opium Tincture. Post-marketing medication error reports have shown Opium Tincture inappropriately dosed, and the commonality of the number 1 may not raise the attention of a healthcare practitioner. Also, the route of administration may not prevent an error if a healthcare practitioner has determined the medication to be Opium, since post-marketing medication error reports have shown oral dosage formulations have been administered parenterally by healthcare practitioners. Based on the common characteristics of the products and our knowledge of post-marketing medication errors there would be an increased risk of a medication error between the products.

If you strongly feel that medication errors will not occur with "Opana" and "Opium," provide justification with supporting data.

- b. A Review of Suffixes with respect to the Immediate-Release and Extended-Release Dosage Formulations

You have proposed to present the proprietary names for the immediate release and extended release dosage formulations as:

Tradename IR - Oxymorphone Hydrochloride Immediate-Release Tablets
Tradename - Oxymorphone Hydrochloride Extended-Release Tablets

DMETS has concern with the suffix "IR" to identify an immediate-release dosage formulation and no suffix to identify the extended-release dosage formulation.

The currently recognized and accepted practice of naming drug products with different formulations is to identify an immediate-release dosage formulation by a proprietary name without a modifier and an extended-release dosage formulation by a proprietary name followed by an appropriate suffix or modifier. DMETS is concerned that healthcare professionals and patients will assume that a proprietary name with a modifier or suffix will indicate the modified- or extended-release dosage formulation of the medication. This can be especially troublesome if one considers a mentally impaired cancer patient switching therapy from one opioid analgesic to another opioid analgesic. For example, the proprietary name, Oramorph SR identifies an extended-release dosage formulation of morphine sulfate. Therefore, the patient may assume that "Tradename IR" is the extended release medication and that "Tradename" is the immediate release medication. If these two dosage formulations were dosed incorrectly, it would greatly increase the potential for patient harm.

The suffix "IR" could cause also confusion among healthcare professionals. A search conducted of the electronic Orange Book indicates the suffix "IR" has not been associated with a tradename. Therefore, this would be a new modifier for healthcare

professionals and patients to learn and somehow prevent confusion with other existing modifiers. Existing modifiers that already identify extended-release dosage formulations include SR, ER, CR, XL, LA, CC, CD, XT, and XE. The suffix IR could be confused with existing modifiers.

Therefore, DMETS does not recommend use of the suffix "IR" or any suffix to identify the immediate-release dosage formulation of oxymorphone hydrochloride tablets. DMETS recommends that the extended-release dosage formulation of oxymorphone hydrochloride tablets include an appropriate suffix to distinguish it from the immediate-release dosage formulation.

c. Labeling, Packaging, and Safety Related Issues

DMETS has reviewed the draft blister and container labels, carton labeling and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. DMETS has identified the following areas of improvement, in the interest of minimizing user error and maximizing patient safety.

(1) Blister Labels

- (i) Increase the prominence of the product strength.
- (ii) The blister labels should be differentiated by contrasting color, boxing or some other means.

(2) Container Labels (100 tablets)

- (i) DMETS recommends that the appearance of the immediate-release and extended-release labels should be clearly differentiated.
- (ii) The 5 mg and 10 mg product strength on the immediate-release and extended-release labels should be clearly differentiated and should not use the same color scheme.

(3) Blister Carton Labeling (5 blister cards of 20 tablets)

- (i) Refer to comments (2)(i) and (2)(ii).
- (ii) The labeling for the 10 mg, 20 mg, and 40 mg extended-release tablets should declare the product contains FD&C Yellow No.6 per 21CFR 201.20.

(4) Package Insert Labeling

(i) General Comments

- (A) The proprietary name, established name and product strength should be more prominently displayed than the Endo® logo or the ENDO

PHARMACEUTICALS statement.

- (B) Replace the abbreviations “IR” and “ER” in the text of the labeling with the appropriate terminology, Immediate-Release or Extended-Release. The abbreviation “ER” should only be used as part of an approved proprietary name, for example: Depakote ER.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Parinda Jani
9/16/03 03:28:49 PM

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D030350

DATE: 9/12/03

TO: Robert Rappaport, M.D., Acting Director
Division of Anesthetics, Critical Care, and Addiction Drug Products
(DACCADP) (HFD-170)

THROUGH: Mark Avigan, M.D., Acting Director; 9/12/03
Division of Drug Risk Evaluation (DDRE)
Office of Drug Safety (ODS), HFD - 430

FROM: Martin Pollock, Pharm. D.
DDRE, ODS

SUBJECT: ODS POST MARKETING SAFETY REVIEW
Drug: Oxymorphone
Reaction: All events

*****Contains IMS Health and [REDACTED] data. Not to be shared outside of FDA
or with non-FDA staff without prior clearance from IMS Health and [REDACTED].***

EXECUTIVE SUMMARY

Oxymorphone (Numorphan, Endo Pharmaceuticals Inc.) is an opioid analgesic that has been marketed as an injection (NDA 11707, approved 4/2/59) and a suppository (NDA 11738, approved 5/31/60). The Division of Anesthetics, Critical Care, and Addiction Drug Products (DACCADP) has received NDAs from Endo for two new oxymorphone oral dosage forms: an immediate-release tablet (NDA 21611; FDA received date 12/20/02) and an extended-release tablet (NDA 21610; FDA received date 12/19/02). The Division has asked ODS to summarize all events in the Adverse Event Reporting System (AERS) for oxymorphone injection and suppositories in order to assist them in the evaluation of the safety labelling of the two oxymorphone oral dosage form NDAs.

AERS was searched for all events associated with oxymorphone. The time period was from marketing until 8/6/03. Oxymorphone utilization data was obtained from IMS Health and [REDACTED]. Thirty-seven unique cases were found ranging in dates of occurrence from 1973 to 2002 (FDA received date). Seventeen cases were excluded due to product defects (n=3) and fatal cases

(n=14) received from Purdue Pharma for active surveillance of Oxycontin™/oxycodone-related deaths that listed oxymorphone as a concomitant drug, without any evidence of oxymorphone administration (in 6 of the 14 cases, oxymorphone, a known metabolite of oxycodone, was determined from toxicological analysis).

Of the remaining 20 evaluable cases, there were five cases with a serious outcome (death, n=2; hospitalization, n=2; life-threatening, n =1). The oxymorphone dosage form used was injection (n=14), suppository (n=4), and unknown (n=2). There were two fatalities, both of which involved cancer patients. The 20 cases had 23 labelled events and 16 unlabelled events. Of the six cases with the 19 unlabelled events, all were limited by missing information (n=5) and contributing medical history (n=1).

This case series spans almost 30 years (1973 through 2002, FDA received dates), but drug utilization data was only available for the past 5 years (IMS Health) and 3 years , respectively. From the IMS Health data, it appears that oxymorphone use has been declining, especially for the suppositories (which had a small distribution compared to the injection to begin with). One author of a published review stated (without any further reason) that oxymorphone injection has been considered to have a limited use in pain treatment.¹ The decline in use could be the result of a switch in opioid preference, such that the use of other opioid(s) has been increasing. Additionally, there may have been less effort by the sponsor to promote the product. As a comparison, morphine, which is considered the standard in opioid pain treatment,^{2,3} has been on the market at least as long as oxymorphone and has 5244 reports (for any dosage form) in AERS.

The twenty oxymorphone reports received in AERS over the past three decades are insufficient to make any determination about particular trends or safety concerns.

BACKGROUND

Oxymorphan (Numorphan; Endo Pharmaceuticals Inc.) is an opioid analgesic that has been marketed as an injection (NDA 11707, approved 4/2/59) and a suppository (NDA 11738, approved 5/31/60). DACCADP has received NDAs from Endo for two new oxymorphone oral dosage forms: an immediate-release tablet (NDA 21611; FDA received date 12/20/02) and an extended-release tablet (NDA 21610; FDA received date 12/19/02). The Division has asked ODS to summarize all events in AERS for oxymorphone injection and suppositories in order to assist them in the evaluation of the safety labelling of the two oxymorphone oral dosage form NDAs. Because oxymorphone is a potent opioid, other databases other than AERS such as the Drug Abuse Warning Network⁴ and Toxic Exposure Surveillance System⁵ (both databases were not utilized for this consult) may also be useful to capture events (especially abuse-related).

METHODS

AERS was searched for all events associated with oxymorphone. The time period was from marketing (of both injection and suppositories) until 8/6/03.

RESULTS

Thirty-seven unique cases were found. The cases were from the U.S. (n=36) and Canada (n=1). They were received in the following years: 1973 through 1978 (n=7), 1980 through 1988 (n=9), 1990 through 1995 (n=6), and 2000 through 2002 (n=15).

Seventeen cases were excluded as follows:

TABLE 1. EXCLUDED CASES

Exclusion reason	Number of cases	Comments
Product defect	3	All involved oxymorphone injection (discolored solution and precipitate formation, n=2; missing stopper retaining ring, n=1). No adverse events reported.
Purdue Pharma active surveillance for Oxycontin/oxycodone. No mention of oxymorphone administration.	14	Oxymorphone listed as suspect drug. Cases had many concomitant medications: 3 to 7 (n=4), 8 to 12 (n=9). Oxymorphone found in urine (n=6), blood (n=1), liver (n=1), and specimen source unknown (n=1). All cases were fatal. All received in 2001 through 2002.

The 14 Purdue cases were reported because the sponsor conducted an active surveillance program with select medical examiners across the country for oxycodone- and Oxycontin- associated fatalities.⁶ Many of these cases are in AERS and ODS has written a consult on them.⁷ The few oxycodone fatality cases that do mention oxymorphone offer no proof that oxymorphone was taken as a separate drug. The most likely dosage form for such ingestion would have been the injection which would be harder to obtain (mainly hospital/institutional item) in a recreational abuse environment. Oxymorphone is one of the metabolites of oxycodone; metabolism occurs via CYP2D6.⁸ A more likely scenario is that oxymorphone was listed on Purdue's reports due to its presence confirmed by toxicological evidence (specifically stated in 6 of the 14 cases). Regardless, the Purdue cases were heavily confounded by other multiple concomitant drugs (e.g., other opioids, benzodiazepines, and antidepressants); oxycodone and oxymorphone can also have a synergistic CNS depressant effect. In Purdue's large 1000-fatality-case analysis, oxymorphone was not mentioned among the twenty most frequently mentioned concomitant "contributory" drugs.⁶

Of the remaining 20 evaluable cases, there were six cases with serious outcome (death, n=2; hospitalization, n=2, and life-threatening, n=2). The oxymorphone dosage form used was injection (n=14), suppository (n=4), and unknown (n=2). The two fatalities, which involved cancer patients and did not mention specific events, are summarized in Appendix 1. The 20 evaluable cases were received in the following years: 1973 through 1978 (n=4), 1980 through 1988 (n=9), 1990 through 1995 (n=6), 2000 through 2002 (n=1). The country of origin was U.S. (n=19) and Canada (n=1).

As shown in Table 2, 16 cases were associated with a total of 23 labelled events that were mentioned in the Numorphan labelling and/or the new proposed oral-dosage form labelling (NDA 21610 and 21611). Of the 23 events, three (agitation, asthenia, and dermatitis) were not labelled for Numorphan, but were labelled in at least one of the NDAs for the proposed oral dosage forms. Table 2 also has four cases that had unlabelled events; unlabelled events are mentioned in Table 3.

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TABLE 2. LABELLED OXYMORPHONE-ASSOCIATED EVENTS

Event	# of instances	Product labelling			Comments
		Numorphan*	Immediate release ⁺	Extended release ⁺	
Pruritis	4	Yes	Yes	Yes	
Nausea	3	Yes	Yes	Yes	
Drug Ineffective*	3	Yes	Yes	Yes	
Nervousness	2	Yes	Yes	Yes	
Agitation	1	No	Yes	Yes	
Asthenia	1	No	Yes	Yes	Labelled as lethargy (IR), fatigue (ER)
Confusional state	1	Yes	Yes	Yes	
Dermatitis	1	No	No	Yes	
Drug dependence	1	Yes	Yes	Yes	
Erythematous lesion; maculopapular rash over whole body	1	Yes	No	No	Labelled (NU) as skin rash, hives
Hallucination	1	Yes	No	No	
Hypotension	1	Yes	No	No	
Sedation	1	Yes	Yes	Yes	Somnolence and Depressed level of consciousness (IR and ER)
Tachycardia	1	Yes	Yes	Yes	
Vomiting	1	Yes	Yes	Yes	

*Numorphan (NU) injection and suppositories.

⁺Immediate release (IR) oral, NDA 21611; extended release (ER) oral, NDA 21610.

*"Drug ineffective" is considered a labelled event for oxymorphone injection, suppositories, and tablets.

There were six cases that were associated with a total of 15 unlabelled events. Four of these cases also had labelled events and these cases are included in Table 2. These labelled events are shown in Table 3 in *italics*.

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TABLE 3. UNLABELLED OXYMORPHONE-ASSOCIATED EVENTS

Case #	Event	Received/ Event year; outcome	Concomitant medication	Medical history	Comments
1	Fecal abnormality, rectal disorder, chocolate-colored rectal discharge	1990/1989; Non-serious	Fiorinal, captopril, propranolol	Unknown	63-yr-old female addicted to Numorphan suppositories (10 mg/day) for unknown period. Had rectal events over the past two months.
2	Convulsions, generalized	1983/1982; Non-serious	Unknown	20-year history of migraine	63-yr-old female took suppository (unknown dosage) every 6 months for migraine for past 2 years; not fully recovered
3	Apnea	1973/ Unknown; Life-threatening	Unknown	"Strong and healthy"	4-yr-old-child received 2 mg suppository for pain post tonsillectomy and adenoidectomy. Physician-reporter had used suppositories in pediatrics in the past with no problem. Limited other information.
4	Hostility, <i>asthenia</i> , ⁺ <i>confusional state</i>	1992/1992; Non-serious	glycopyrrolate, midazolam, metoclopramide, APAP/codeine	Unknown	77-yr-old female; unknown dosage form; hard to read image.
5	Supraventricular arrhythmia, atrial fibrillation, hypertension, increased cardiac enzymes, anemia, hypoventilation, mental impairment, <i>tachycardia</i> , <i>lethargy</i> , <i>hypotension</i>	2000/2000; Life-threatening	Diphenhydramine, zolpidem, lisinopril, hydrochlorothiazide and atorvastatin.	Hypertension hyperlipidemia, irregular cardiac rhythm.	71-yr-old female enrolled in oxymorphone oral controlled release study.
6	Anorexia, tremor, <i>agitation</i> , <i>nervousness</i>	1986/1985; Hospitalization	Unknown	Seizures 3 yrs ago; no further occurrence.	15-yr-old female; intramuscular injection; rechallenge on second day, with only <i>agitation</i> appearing.

⁺Labelled events from Table 2 are shown in *italics*.

Of the six cases reporting unlabelled events, five cases (#1, 2, 3, 4, and 6) were limited by lack of information and one patient (#5) had a contributing medical history. The two cases with serious outcome (#5 and 6) from Table 3, along with one case with serious outcome from Table 2 are summarized in Appendix 2.

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DRUG UTILIZATION/SALES DATA

Sales of oxymorphone injection and suppositories to retail pharmacies and to other health care providers have dropped substantially over the past five years (Table 4).

TABLE 4. SALES (IN MILLIONS OF EXTENDED UNITS*) TO RETAIL AND HEALTH CARE PROVIDERS OF OXYMORPHONE BY DOSAGE FORM

Year	1998	1999	2000	2001	2002
Injection					
Suppositories					
Total					

*Extended units = number of individual tablets, capsules, etc., for solids, number of grams or milliliters for other forms. If the vial is dry or lyophilized, then extended units would not be in mls, it would always be 1.

†Numbers are rounded such that “zero” means — total projected units.

SOURCE: IMS HEALTH, National Sales Perspective™ Combined Data from Retail and Non-Retail, On-line

To examine use of these products within hospitals, we searched the — database.

The — database currently contains data from approximately 400 hospitals from January 1999 through the present with a lag time of 6 months. The data are periodically collected from participating hospitals, and include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every discharge during the time period. — main business is to assist healthcare institutions improve clinical and operating performance through group purchasing and other strategies. As part of this mission, the — group developed this database in part to analyze utilization of resources to improve clinical efficiency. The hospitals that contribute information to this database are a select sample of both — and U.S. institutions, and although they may not necessarily represent all hospitals in the U.S., estimates of use are weighted to provide estimates of national use.

— estimates are consistent with the sales data and suggest a substantial decline in the use of oxymorphone products over the last 3 years, as shown in Table 5. It is not known exactly why this change occurred. Reasons for this could have been a preference change to other opioids or a decreasing promotional effort by the sponsor.

TABLE 5. NATIONAL PROJECTION OF NUMBER OF HOSPITAL DISCHARGES IN U.S. IN WHICH OXYMORPHONE (INJECTION AND SUPPOSITORIES) WAS ADMINISTERED

Year	2000	2001	2002
Projected Cases/discharges			

Source. — Perspective On-line

****Contains proprietary data from IMS Health and — Not to be shared outside of FDA or with non-FDA staff without prior clearance from IMS Health and — ****

DISCUSSION/CONCLUSION

Of the two oxymorphone fatalities, one with advanced cerebral leukemia and the other with pancreatic cancer (see Appendix 1), the latter case appeared to have a rather large exposure to oxymorphone and this may have been contributory. However, with cancer, patients are known to build up opioid tolerance and consume high doses of the drugs.^{9,10} It is not known if this patient was already naïve to high dose opioids from prior cancer treatment. There was also no information of other concomitant medications that would be expected to be administered to such advanced stage cancer patients.¹¹

Referring to Table 2, the cardiac-(n=1) and respiratory-related (n=1) adverse events in two cases were the most serious. A 71-year-old female (Appendix 2) with arrhythmias received both the approved injection and the oral controlled-release study drug. Neither the injection nor oral oxymorphone is labelled for serious cardiac arrhythmias. The patient's prior cardiac condition could have been a contributing factor to the cardiac events. At normal doses, opioid effects on the cardiovascular system are limited to hypotension (including orthostatic; in part due to histamine release) and vasodilation.^{12,13} In the second case (4-year old-child receiving suppository; Appendix 2), the child experienced apnea (recovered), but the report did not state other information (e.g., concomitant medications) in order to allow attribution solely to one product. Suppository use in pediatrics is unlabelled.

This case series spans almost 30 years (1973 through 2002, FDA received dates), but drug utilization data was only available for the past 5 years (IMS Health) and 3 years _____, respectively. From the IMS Health data, it appears that oxymorphone use has been declining, especially for the suppositories (which had small distribution compared to the injection to begin with). One author of a published review stated (without any further reason) that oxymorphone injection has been considered to have a limited use in pain treatment.¹ The decline in use could be the result of a switch in opioid preference, such that the use of other opioid(s) has been increasing. Also, there may have been less effort by the sponsor to promote oxymorphone injection and suppositories. As a comparison, morphine, which is considered the standard in opioid pain treatment,^{2,3} has been on the market at least as long as oxymorphone and has 5244 reports (for any dosage form) in AERS.

The twenty oxymorphone reports received in AERS over the past three decades are not enough to make any determination about particular trends or areas of safety concerns.

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APPENDIX 1. FATALITIES INVOLVING CANCER PATIENTS

ISR# 130625-30; Mfr control #: direct; Year received: 1980; Event date: unknown; Reporting country: foreign.

A female pediatric patient (unknown age) with history of advanced cerebral leukemia and septicemia received half (2.5 mg) of an oxymorphone suppository at 12:30 pm for severe headache and pain. She became drowsy and by 5:00 pm was in a coma. She died at 6:30 pm. The physician reporter felt the death was due to underlying disease. Concomitant medications were unknown.

ISR# 1890650-9; Mfr control #: NUM950006; Year received: 1995; Event date: _____ Reporting country: United States.

A 60-year-old female received oxymorphone injection for pancreatic cancer pain. On _____, the patient was started on 30 mg/hr with a bolus injection of 9 mg and a lockout time of 5 minutes (patient controlled analgesia [PCA]). There was no upper limit on the number of boluses per day. The total daily amount of oxymorphone used per day at this starting regimen was reported as 1.375 gm. The patient remained on oxymorphone injection until her death 51 days later. For the last two weeks of her life, she received 4.5 gm of oxymorphone per day. Over the 51 days of treatment, 550 vials (quantity per vial not specified) were used. Concomitant medications were unknown.

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APPENDIX 2. DETAILED SUMMARY OF SERIOUS, NON-FATAL CASES

ISR# 3508122-4; Mfr control #: Numorph2000-00072; Year received: 2000; Event date: _____
Reporting country: United States.

A 71-year-old male with history of anemia, hypertension, hyperlipidemia, irregular cardiac rhythm, and 50-years of alcohol consumption was enrolled in a double-blind study of Numorphan CR in post-knee arthroplasty. The patient underwent surgery and two doses of morphine sulfate i.v. were given, followed by morphine PCA. The patient complained of decreased sensation of the left toe and the following morning at 0500 hours, morphine PCA was discontinued and the study drug, Numorphan CR 20 mg, was given at 0645 hours; blood pressure was 162/76 mmHg and pulse rate was 78 beats/min. As a rescue medication, the patient received 7 doses (0.3 mg/dose) of oxymorphone PCA from 0745 to 1045 hours. Blood pressure had fallen to 81/52 mmHg and heart rate was 134 beats/min. At 1145 hours, blood pressure was 88/51 mmHg and heart rate was 150; the patient was very lethargic. At 1245 hours, blood pressure was 98/66 mmHg. The patient was in atrial fibrillation and supraventricular tachycardia and was transferred to the ICU. An electrocardiogram indicated undetermined rhythm, nonspecific intraventricular block, and marked ST and T wave abnormalities, suggestive of inferior and anterolateral ischemia. The patient's mental status also had deteriorated. It was determined that in addition to the patient administering PCA to himself, his wife also had administered an unknown amount of the PCA to the patient.

The cardiac enzymes were as follows:

Day	Time	Parameter and value
Same day that patient experienced atrial fibrillation and supraventricular tachycardia	1800 hrs	Creatinine kinase (295 U/L), CKMB (1.2 ng/mL), CPK Index (0.4 ng/mL), and Troponin 1 (0.8 ng/mL)
	2043 hrs	Troponin 1 (0.7 ng/mL)
Next day	0115 hrs	Troponin 1 (0.4 ng/mL)

The report stated that troponin and CPK isozymes did not support a myocardial infarction diagnosis.

The patient was treated with naloxone, digoxin, oxazepam, thiamine, and enoxaparin. By 1500 hours the patient was in normal sinus rhythm with blood pressure of 140/60 mmHg and heart rate of 115 bpm. The patient's pre-existing anemia had worsened and he was treated with a blood transfusion. The next day, the patient's mental status was back to baseline and the following day, the patient was transferred out of the ICU. The patient was discharged from the hospital six days after the events in stable condition.

Concomitant medications were diphenhydramine, zolpidem, acetaminophen, lisinopril, hydrochlorothiazide, and dolasetron. The reporter also stated that the "hypotension, hypoventilation, and tachycardia very likely resulted in the elevation of the troponins."

ISR# 385852-7; Mfr control #: M-850117A32; Year received: 1986; Event date: _____
Reporting country: United States.

A 15-year-old female with no known drug allergies and three-year history of seizures was admitted to the hospital for removal of a pilonidal cyst. The patient was given 1 mg of Numorphan (route not specified) for post-operative pain. Seventy-five minutes later the patient was upset, her hands were visibly shaking, and she was feeling "jittery all over." The patient was unable to eat supper, but did not complain of nausea and vomiting. Three hours later after

APPENDIX 2. DETAILED SUMMARY OF SERIOUS, NON-FATAL CASES CONTINUED

resting, the patient recovered. The next day, the patient received two doses of Numorphan (1 mg each, route not specified) and became agitated, tearful, and talkative. These events lasted "until the medication wore off." Before the patient received these latter two Numorphan doses, she felt "calm and pleasant." There was no information on concomitant medications.

ISR# 549942-8; Mfr control #: 093688; Year received: 1988; Event date: _____ ; Reporting country: United States.

A 38-year-old male with a history of alcohol abuse (but no delirium tremens) received morphine (epidural), Numorphan, meperidine, and hydromorphone (routes not specified) over a period of 4 to 5 days for post-operative pain from a spinal fusion. On the fourth or fifth day, the patient became uncooperative, combative, and developed hallucinations. The patient was known to abuse alcohol prior to the surgery. The patient did recover.

**ISR# 56727-8; Mfr control #: Direct Report; Year received: 1973; Event date: unknown
Reporting country: United States.**

4-year-old child (unknown sex) underwent a tonsillectomy and adenoidectomy. The child was then treated with one-half of a Numorphan 2 mg suppository. Soon after this, the nurse reported that the child was apneic. The child was intubated and given Narcan after which spontaneous respirations returned. The physician-reporter could not recall any of the pre-operative medications or the agents used for anesthesia. The physician-reporter stated that he routinely used the 2 mg suppositories in children less than 12 years over the past several years.

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9/5/03

Martin L. Pollock, Pharm. D.
Safety Evaluator

Concur:

9/5/03

Ann Corken-Mackey R.Ph., M.P.H.
Team Leader

-
- ¹ Intrussi CE. Clinical pharmacology of opioids for pain. *Clin. J. Pain.* 2002;18:S3-S13.
- ² Nicholson B. Responsible prescribing of opioids for the management of chronic pain. *Drugs* 2003;63:17-32
- ³ McQuay H. Opioids in pain management. *Lancet* 1999;353:2229-2232.
- ⁴ The DAWN Report: Trends in drug-related emergency department visits, 1994-2001 at a glance; *Office of Applied Studies*, SAMHSA June 2003.
- ⁵ Litovitz TL, Klein-Schwartz W, Rodgers GC, and Cobaugh DJ, Youniss J, Omslaer JC, May ME, Woolf AD, and Benson BE. 2001 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am. J. Emerg. Med.* 2002; 20(5):391-452.
- ⁶ Cone RV, Caplan TH, Ballina M. Oxycodone involvement in drug abuse deaths: a DAWN-based classification scheme applied to an oxycodone postmortem database containing over 1000 cases. *J. Anal. Tox.* 2003;27:57-67.
- ⁷ Pollock M, Green L, Bacsanyi J. Oxycotin-associated fatalities; PID #010503; 3/11/02. Consult written for Div. HHD 170.
- ⁸ Heiskanen TE, Ruismaki PM, Seppala TA, Kalso EA. Morphine or oxycodone in cancer pain? *Acta. Oncolog.* 2000;39:941-947.
- ⁹ Breivik H. Opioids in cancer and chronic non-cancer pain therapy—indications and controversies. *Acta. Anaesthesiol. Scand.* 2001;45:1056-1066.
- ¹⁰ Lo SL, Coleman RR. Exceptionally high narcotic analgesic requirements in a terminally ill cancer patient. *Clin. Pharm.* 1986;10:828-832.
- ¹¹ Sikora K, Advani S, Korolthouk V, Magrath I, Levy I, et al. Essential drugs for cancer therapy: a world health organization consultation. *Ann. Oncol.* 1999;10:385-390.
- ¹² Pugsley MK. The diverse molecular mechanisms responsible for the actions of opioids on the cardiovascular system. *Pharmacol and Therapeut.* 2002;93:51-75.
- ¹³ Reisine T, Pasternak G. Opioid analgesics and antagonists in Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed McGraw-Hill, N.Y.;521-565.

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/s/

Martin Pollock
9/15/03 03:43:23 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
9/16/03 05:47:29 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 28, 2003
TO: NDA file
FROM: Lisa Basham-Cruz
SUBJECT: August 6, 2003 teleconference with Endo Pharmaceuticals to discuss the Risk Management Plan for NDAs 21-610 and 21-611.

NDA 21-610, Oxymorphone Controlled-release Tablets
NDA 21-611, Oxymorphone Immediate-release Tablets

NOTE: This memo was emailed to MaryAlice Raudenbush and Bob Barto, of Endo Pharmaceuticals, on August 28, 2003.

ATTENDEES:

FDA:

Sharon Hertz, MD	Medical Team Leader, Analgesics and Neuropathy
Gerald DalPan, MD	Medical Reviewer
Shaun Comfort, MD	Medical Reviewer
Lisa Basham-Cruz, MS	Regulatory Project Manager

Endo Pharmaceuticals:

Bradley Galer, MD	Vice President, Scientific Affairs
MaryAlice Raudenbush	Vie President, Regulatory Affairs
Marie Pinizzotto, MD	Director, Clinical Drug Safety/Pharmacovigilance
Arnold Gammaitoni	Director, Medical Affairs
Jerry McLaughlin	Group marketing Director-Pain Products
Dan Carbery	Group Vice-President, Operations
Joe Ambrefe	Director, Endo Sales Force
Robert Barto	Manager, Regulatory Affairs

Following introductions, Dr. Hertz began by providing a general outline of what the Agency considers to be the primary components of a risk management plan (RMP). She stated that the current advice represents our most current understanding of risk management and is subject to change based on discussions during the ALSDAC meeting on RMPs scheduled for September 9 & 10, 2003.

Three Key Elements of Risk Management:

- Risk of accidental exposure
- Risk of abuse and misuse
- Risk of improper patient selection

These key elements may be addressed through a Risk Management Plan that includes:

1. Education & Prevention of Abuse & Misuse
 - a. Patient and caregiver information (PPI)
 - b. Physician/Health Care Provider information (PI)
 - c. Additional educational programs
 - (1) Avoidance of unintended exposure in household (pediatric)
 - (2) Awareness of safe prescribing practices
 - (3) Awareness of signs and symptoms of addiction
 - (4) Awareness of drug seeking behavior for nonmedical purposes (SOAP)
 - d. Prevention
2. Surveillance
 - a. Existing databases
 - (1) DAWN
 - (2) SAMHSA National Household Survey
 - b. Other
3. Intervention

The discussion addressed each of the key issues above. Regarding Education and Prevention of Abuse and Misuse, Endo stated that the PPI is drafted and undergoing internal review. Dr. Hertz advised the sponsor to submit it as soon as it is available. Dr. Hertz stated that the Agency needs more information on the educational proposal. By the time the application is approved, it is important to have as much of the program in place as possible so that deficiencies can be assessed and perhaps accepted post approval.

Dr. Hertz continued that, regarding the surveillance component of the risk management plan, much more information is needed about the databases utilized, how frequently they will be reviewed and how frequently data will be reported to the Agency. The sponsor responded that they plan to provide quarterly safety updates to the Agency, with details and follow-up on each case. Furthermore, they plan to obtain information through the Freedom of Information Office. Dr. Hertz suggested that the sponsor utilize databases such as DAWN and the National Household Survey. Dr. Hertz noted the limitations of Adverse Event reporting in terms of monitoring the incidence of abuse and misuse, and encouraged the sponsor to consider other databases as well as possibly consulting an individual expert on abuse and misuse. Dr. Hertz inquired about membership and function of the Safety Review Board. The sponsor responded that the board is made up of a variety of disciplines, including medical and regulatory, and meets quarterly. They will provide additional information on the Safety Review Board.

Dr. Hertz asked that the sponsor provide details of proposed intervention methods if signals are detected through surveillance. The sponsor had not fully explored their approach to intervention upon detection of a problem, e.g., detection of a high number of accidental overdoses. Dr. Hertz gave examples of activities such as focused educational campaigns, or contacting law enforcement. The sponsor stated that they will think about this and get back to the Agency with some proposals.

The sponsor inquired about the effect of the ALSDAC meeting on the action dates for their NDAs. Dr. Hertz responded that, if things go optimally, and the product is in all other areas appropriate for approval, the Division is not prepared to hold up approval based on an incomplete risk management plan. This has not been definitely decided, however, as the final decision will have to incorporate discussions made as a result of the ALSDAC discussions. If the application is not approved during the first cycle, these materials must be finalized and included in a resubmission. The sponsor was encouraged not to delay their response to our comments until after the ALSDAC, but to attempt to get as much of the plan in place as possible, as soon as possible.

- Lisa Basham-Cruz, MS
Regulatory Project Manager

Post Meeting Note: Additional guidance may be obtained from the Concept Paper: Risk Management Plans, dated March 3, 2003, and distributed for comment. This may be found at www.fda.gov/cder/meeting/riskManagement.htm, and is DRAFT ONLY.

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/s/

Lisa Basham-Cruz
8/28/03 05:34:37 PM
CSO

1st Cycle Review
DMETS

Office of Drug Safety

MEMO

To: Bob A. Rappaport, M.D.
Acting Director, Division of Anesthetic, Critical Care and Addiction Drug Products
HFD-170

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: Lisa Basham-Cruz,
Project Manager, Division of Anesthetic, Critical Care and Addiction Drug Products
HFD-170

Date: August 27, 2003

Re: ODS Consult 03-0105-1; Risk Management Plan
Oxymorphone Hydrochloride Immediate Release Tablets; NDA 21-611,
DACCADP Tracking Number 2003.170.A.00058, and
Oxymorphone Hydrochloride Extended Release Tablets; NDA 21-610,
DACCADP Tracking Number 2003.170.A.00057

This memorandum is in response to the March 24, 2003 requests from your Division for a review of a Risk Management Plan for oxymorphone hydrochloride immediate release and extended release tablets.

The Division of Medication Errors and Technical Support (DMETS) has reviewed the Risk Management Plan for the two dosage formulations of oxymorphone hydrochloride. The Risk Management Plan of the Abuse Liability Document did not provide a complete description of the goals, objectives, and program components for a complete evaluation. Therefore, DMETS has provided the following general concerns and comments.

1. Education

The information concerning the educational programs does not address how the programs will be evaluated for effectiveness, and what factors will determine if the program should be continued, altered or discontinued?

The sponsor has indicated the pharmacy education materials will stress the importance of the relationship between the pharmacy and the prescribing physician. Additional components to consider are to educate pharmacists on ways to access adherence and issues affecting adherence versus potential abuse or diversion of the medication.

Educational programs that address pain management, adherence, the potential for abuse, and diversion of the medication should emphasize that these issues require a team effort involving physicians, nurses, pharmacists, patients, and caregivers.

None of the educational materials were available for review. Therefore, when available please provide the Division of Surveillance, Research and Communication Support (DSRCS) with a copy of all educational materials to be provided to patients and caregivers. DSRCS and DMETS will provide a joint review on the educational materials for patients and their caregivers.

2. Post Marketing Safety Surveillance Program

The sponsor has established a Safety Review Board to review post-marketing data collected as part of the safety surveillance system. DMETS recommends all potential and actual medication errors identified by the sponsor be submitted to the Food and Drug Administration.

3. Labeling

DMETS has reviewed the proposed container labels, carton labeling, and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. These safety issues were addressed in ODS Consult 03-0105/03-0106. However, DMETS would like to stress the importance of differentiating the appearance of the labels and labeling for the immediate release dosage formulation from the extended release dosage formulation, and differentiating the appearance of the 5 mg and 10 mg overlapping dosage strengths on the labels and labeling of the immediate release and extended release dosage formulations.

If you have any questions or need clarification, please contact the Project Manager, Sammie Beam at 301-827-3242.

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/s/

Scott Dallas
8/29/03 07:49:02 AM
PHARMACIST

Denise Toyer
8/29/03 08:23:53 AM
PHARMACIST

Jerry Phillips
8/29/03 08:27:02 AM
DIRECTOR

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 21, 2003

TO: IND file

FROM: Lisa E. Basham-Cruz

SUBJECT: **carcinogenicity requirements for NDA submission**
IND 56,919, oxymorphone HCl extended-release tablets
IND 58,602, oxymorphone HCl immediate-release tablets

I contacted Mary Alice Raudenbush of Endo Pharmaceuticals on December 16, 2002, and informed her that the Division will accept carcinogenicity studies as a Phase 4 commitment, assuming the NDAs are approved in the first cycle. This decision was based on the following:

1. the carcinogenicity studies are underway,
2. there is extensive previous human experience with oxymorphone and opioids in general, and
3. the timing of the submission in light of the transition to current Divisional policy regarding the requirements for completion of carcinogenicity studies for older opioids at the time of NDA submission.

-Lisa E. Basham-Cruz, MS
Regulatory Project Manager

-R. Daniel Mellon, PhD/concurrence
Pharmacology Reviewer

-Tim McGovern, PhD/concurrence
Supervisory Pharmacologist

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EOP2 meeting
May 11, 2000
Oxymorphone CR

IND 56,919

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

Attention: Carol Patterson, M.S.
Manager, Regulatory Affairs

Dear Ms. Patterson:

Please refer to the End-of-Phase 2 meeting between representatives of your firm and FDA on May 11, 2000. The purpose of the meeting was to discuss the final phase of development of oxymorphone hydrochloride ~~tablets~~ tablets.

A copy of our minutes of the meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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INDUSTRY MEETING MINUTES

Meeting Date: May 11, 2000

IMTS# 5444

Time: 10:30 am – 12:00 pm

Location: Conference Room C

Drug: Numorphan® (oxymorphone HCl) ( Release Tablet

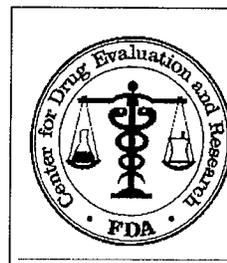
Sponsor: Roxane Laboratories

Indication: For relief of moderate to moderately severe pain

Type of Meeting: Type B Meeting, EOP2

Meeting Chair: Bob Rappaport, M.D., Deputy Director

Minutes Recorder: Laura Governale, Pharm.D., Regulatory Project Manager



FDA Attendees:

Titles:

Offices:

John Jenkins, M.D.	Office Director	HFD-102
Cynthia McCormick, M.D.	Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD-170
Harold Blatt, D.D.S.	Medical Reviewer	HFD-170
Kathleen Haberny, Ph.D.	Pharmacology Reviewer	HFD-170
Albinus D'Sa, Ph.D.	Chemistry Team Leader	HFD-170
Steve Koepke, Ph.D.	Chemistry Supervisor	HFD-170
Michael Theodorakis, Ph.D.	Chemistry Reviewer	HFD-170
Ramana Uppoor, Ph.D.	Biopharmaceutics Team Leader	HFD-870
Albert Chen, Ph.D.	Biopharmaceutics Reviewer	HFD-870
Tom Permutt, Ph.D.	Biostatistics Team Leader	HFD-170
Laura Governale, Pharm. D.	Regulatory Project Manager	HFD-170

Participants:

Titles:

David Lee, M.D., Ph.D.	Senior Vice President, R&D and Regulatory Affairs
Charles Laudadio, MBA, M.D.	Director, Clinical Research
Danny Kao, Ph.D.	Manager, Pharmaceuticals Development
Carol Patterson, M.S.	Manager, Regulatory Affairs
Ken Utecht, MBA	Project Manager
Troy McCall, Ph.D.	Senior Director, Research & Development Penwest Pharmaceuticals Inc.

Meeting Objective: The primary objective of this meeting was to discuss the final phase of development for oxymorphone hydrochloride controlled-release tablets.

General Discussion: Following introductions, the sponsor highlighted the regulatory history for oxymorphone tablets. The immediate-release formulation of oxymorphone HCl was approved in 1959 for 2 mg and 5 mg strengths, and in 1960 for the 10 mg strength under NDA 11-737. The parenteral and the rectal use formulations were approved in 1959 under NDA 11-707 and NDA 11-738, respectively. In 1979, Endo Laboratories withdrew the oral tablet formulations under NDA 11-737. The DESI process was not completed for the oral tablets.

Dr. McCormick inquired what conditions were placed on the tablet formulations by the Agency. The sponsor replied that the Agency requested bioequivalency to the parental product. The DESI process was completed for the parenteral and the rectal formulations; however, the sponsor was not currently familiar with the DESI approval process for these products. The sponsor stated that they will have to look into their files for the DESI approval letters for the parenteral and the rectal formulations.

Dr. Rappaport led the discussion toward answering the sponsor's questions which were included in the April 6, 2000, meeting package. The sponsor's questions are listed in italics.

1. *Regulatory*

Is the Agency accepting electronic submissions for IND and NDA filings?

Dr. Rappaport replied that the Center policy on electronic submissions is available on the FDA web site. The persons to contact regarding electronic submissions are Randy Levin and the project manager. Specific questions may be directed to the project manager.

Due to a scheduling conflict, Dr. Haberny will discuss the pharm/tox issues first, then the division will address the other questions in the sponsor's meeting package. Dr. Rappaport added that the requirements for pharm/tox data have changed since the last meeting with the sponsor. The Agency has been formulating a set of requirements for reprotox, genotox, and mutagenicity studies which may be different from previous requirements.

2. *Pharmacology/Toxicology*

Endo believes that together with the general body of knowledge on related opioids, oxymorphone has undergone sufficient toxicological evaluation to support the proposed indication. Does the Agency concur?

Dr. Haberny outlined the following non-clinical recommendations to the sponsor.

- a. Chronic oral oxymorphone dosing has not been adequately studied by today's standards for drug evaluation. A 13-week GLP toxicology study in an appropriate animal species is needed. The evaluation should include evaluation of toxicokinetics, clinical signs, mortality, body weights, food consumption, ophthalmologic examination, clinical pathology (hematology, clinical chemistry and urinalysis), organ weights, and gross and histopathology examination at necropsy.

- b. Studies to evaluate the mutagenic potential of oxymorphone will be needed with the NDA submission to update the label.
- c. The study on embryo-fetal development (Segment II reproductive toxicity) reported in the current label showed that Numorphan® was teratogenic in hamsters. As that study was not performed using currently acceptable standards based on the ICH guidelines, additional studies to evaluate embryo-fetal development in two species using the current ICH guidelines are necessary to update the label. Studies on fertility (Segment I) and pre- and post-natal development (Segment III) are also required. These studies should be submitted with or before your NDA.

Dr. Rappaport urged the sponsor to submit their protocols for the reproductive toxicity studies for Agency review prior to initiating those studies.

- d. Studies to evaluate the carcinogenic potential of oxymorphone will be needed and can be conducted as a Phase 4 commitment. These studies should be conducted in 2 species.
- e. For the NDA, toxicological assessment will be recommended for any excipient that is not approved.

Dr. Lee of Endo Pharmaceuticals expressed his concern regarding the dosage selection for the carcinogenicity studies. Due to the development of tolerance, the maximum tolerated dose for these carcinogenicity studies are not fixed. Dr. Lee stated that he would like concurrence from the Agency on the design of the carcinogenicity studies for the appropriate dosage selection and the development of tolerance.

Dr. Jenkins stated that depending on the review of the genotox studies, the carcinogenicity studies may be conducted as a Phase 4 commitment. If the genotox study results are positive, then this may raise other issues which must be factored into the Phase 4 commitment. Dr. Lee stated that a false positive may result depending on the choice of the mutagenicity study. Dr. Jenkins replied that a battery of tests should help establish true positives and false positives. Dr. Rappaport stated that the Agency is willing to examine the protocol and come to an agreement on the study design. Dr. Jenkins added that if the results of the battery of tests are positive, the carcinogenicity studies should be conducted before approval of the NDA; otherwise, the studies may be conducted as a Phase 4 commitment. Dr. Lee replied that oxymorphone is very similar to codeine and therefore not likely to produce positive results.

3. *Clinical*

The proposed indication for Oxymorphone Hydrochloride () -Release Tablets is: "For the management of moderate to severe pain where the use of an opioid is appropriate." Endo believes that the clinical package (assuming that it meets its objective) is adequate to support the above indication. Does the Agency concur?

Dr. Rappaport replied that the Agency would have to review the data in order to make this assessment. Starting with the efficacy data, the preliminary results of Study 015 have been submitted to the Agency and the study is still in progress. The Agency has not yet received Study 016. Dr. Rappaport inquired whether the blind had been broken in Study 015 in reference to the notification amendment submitted to the Agency on April 25, 2000. The sponsor replied that the study blind was maintained and that the last patient enrolled has completed the study. Dr. Rappaport stated that the basic design of the study appears to be appropriate and that if the design of the other studies is similar, then they should be appropriate as well. However, in the dose escalation portion of Study 015(?), there may be difficulties in achieving a level of significance with the current number of patients at the 40 mg dose level. The sponsor replied that the goal of that study was to reach an indication of the dose-response; however, there was an increase in the drop-out rate at the higher dose. He added that this result does not appear to be any more significant than other drugs in the same class. The anticipated drop-out rate is approximately 50% and the objective was to have at least 240 patients complete the study with 60 patients per group.

Dr. Permutt indicated that the description of the statistical analysis was not as specific as it should be for a Phase 3 pivotal study. The sponsor should file a data analysis plan before they unblind, specifying the primary analysis in order to remove concerns about multiplicity. The sponsor stated that the data cleaning up process is already taking place and that they will share their plan of analysis before proceeding. Dr. Lee stated that the objectives of Study 012 were to determine onset and duration of action. A protocol for Study 017 will also be filed to the Agency.

Dr. Rappaport requested that the sponsor clarify the number of patients for safety evaluation. The sponsor replied that 854 patients are expected to enroll in the efficacy studies and 631 patients are projected to complete the study. The long-term one-year open-label extension study is currently enrolling well. 159 patients have enrolled since December 1999, and 105 remain active. A 17-month follow-up will be included at the time of NDA filing. Approximately 600 patients will be eligible to enter the extension and every effort will be made to enter as many as possible.

Dr. McCormick stated that the Agency would prefer a more robust safety database. The sponsor may consider including the parenteral and the rectal formulations to supplement the safety database. Also, the immediate release (IR) program running in parallel should provide additional data for this NDA. Dr. Lee replied that the above numbers do not include the patients from the IR program. The IR program will have approximately 300 patients from the single-dose study. Dr. McCormick encouraged the sponsor to obtain as much knowledge on the safety of this drug as possible. The post-marketing exposure from the rectal and the parenteral products should not comprise the primary safety database; however, the Agency will consider it as supportive data. Dr. Lee stated that he does not expect oxymorphone to be significantly different from other opioids in regard to safety. He inquired how many patients would be required to demonstrate safety. Dr. McCormick replied that information from the IR

studies may be included to comprise total exposure. For the IR studies, a minimum of 1000 patients are required to demonstrate safety for single exposure. The target for long-term exposure is 100 patients per one year. The sponsor stated that approximately 600 patients are eligible for entry into the long-term exposure study from the chronic studies. Of that, 200 patients may enter into the long-term exposure study. Dr. McCormick stated that the pediatric studies for the controlled-release formulation may also be used to enrich the safety database. Ideally, the pediatric studies should be conducted before NDA approval. The sponsor stated that the youngest patient studied thus far is 18 years old. Dr. Rappaport added that if the current dosage is not appropriate for pediatric patients, the sponsor should formulate an alternative dosage for this population. Similarly, the sponsor should consider studying the geriatric population.

Dr. Albert Chen remarked on the biopharmaceutic concerns regarding this drug.

1. On CMC (page 12), regarding the demonstration of "equivalency" of the finished product for both manufactures, the following clarification is needed: are both manufactures proposed for making commercial product or is one site for manufacturing clinically tested batch (pivotal PK and/or clinical trials) and the other for commercial batch?

The sponsor stated that the original batches were manufactured at ~~_____~~ and a new manufacturer will be used for the commercial batch. Dr. Chen replied that a bioequivalence (BE) study will be needed in this case. Dr. Upoor added that if both sites are manufacturing for the Phase 3 studies, information must be submitted for both sites to demonstrate identical methods of manufacturing. When there is a change in the manufacturer, a BE study is required only for the highest strength. The sponsor was referred to the SUPAC Guidelines for additional information.

2. On CMC (page 12), regarding tablets being coated and printed (commercial) and being coated only (current exhibit batch)
 - a. Need *in vitro* dissolution data to demonstrate similarity in 3 dissolution media.
 - b. Additionally, at least 3 dissolution media and different methods (e.g., agitation speeds) should be chosen for testing tablets (for stability or commercial manufacture) in order to select optimal dissolution method. The selected optimal method should be used for pivotal stability testing.
 - c. In the NDA submission, dissolution data from biobatch(es) (~~_____~~) and stability (and/or commercial) batches using the selected optimal dissolution method need to be provided in order to set the dissolution specifications.

The sponsor should discuss the optimal dissolution method to be proposed for pivotal stability testing with the Agency.

Dr. Chen added that 3 batches per strength are needed for dissolution data.

3. Regarding the proposed pharmacokinetic (PK) studies (page 65)

- a. Submit literature information available on basic PK (ADME) for oxymorphone and its metabolite(s).
- b. Based on literature data, in addition to Study # 04, determine/conduct drug-drug interaction studies if necessary.
- c. Need single-dose PK comparison of IR with CR tablets as well:

From Study # 09 (multiple dose, BID dosing), collect 0 to 24 hr blood samples post "first dose" (skipping the 2nd dose on Day 1) and resume BID dosing on Day 2 for the proposed steady-state multiple-dose PK assessment.

The sponsor listed the proposed PK studies on the overhead projector.

Dr. Chen commented that the single-dose PK study, Study 003, is adequate since this formulation is the same as the final formulation.

- d. Pediatric issue needs to be addressed (Study # 06 for Age/Gender?)
4. Regarding the proposed clinical Phase III studies (page 66), select a subset of patients from the pivotal clinical trial and collect sparse blood samples for PK/PD analysis (optimal sampling strategy and population analysis may be employed). It is recommended that the sponsor submit the protocol to the Agency for review.

Dr. Theodorakis expanded on the issue raised by Dr. Chen and addressed the following chemistry, manufacturing and controls (CMC) questions raised by the sponsor in the meeting package.

4. *Chemistry, Manufacturing and Controls*

- a. *Manufacturing - At least one batch of each strength (10 mg, 20 mg, 40 mg) of the finished product has been manufactured at _____ and there will be a new manufacturer for the remaining NDA exhibit batches. We will demonstrate equivalency of the finished product for both manufacturers. These additional batches will also be placed on accelerated stability (40°C/75%RH) and long term stability (25°C/60%RH) conditions as per ICH requirement.*

Dr. Theodorakis reiterated that 3 batches per strength are required to support the NDA. The data from _____ may be submitted as supportive data.

b. Tablet Imprint - The commercial tablets will be coated and printed. The current exhibit batches are all coated but no tablets have been printed. Once we finalize the ink for printing, we will validate the analytical method to ensure no interference of the ink. We propose to have the remaining exhibit batches of each strength coated and printed and demonstrate equivalency between the imprinted tablets and non-imprinted tablets. These batches will also be placed on stability testing at conditions of 40°C/75%RH and 25°C/60%RH per ICH requirement. We will ensure the addition of the ink on the tablet will not impact the stability and release of this product.

Dr. Theodorakis stated that this is acceptable.

The sponsor inquired whether the osteoarthritis, chronic back pain and cancer studies will be considered as pivotal trials. Dr. McCormick replied that Studies 015 and 016 are considered pivotal. Dr. Chen added that PK data should be collected for the back pain study as well.

Dr. Rappaport adjourned the meeting.

Action Items:

- The Agency will provide the sponsor with a copy of the official meeting minutes.

Minutes prepared by: Laura Governale, Pharm.D.

Minutes concurred by Chair: Bob Rappaport, M.D., Deputy Director

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CC:

HFD-170/Division Files

HFD-170/L. Governale

HFD-170/K.Haberny, L.Jean, R.Uppoor, A.Chen, A.D'Sa, M.Theodorakis, H.Blatt,
T.Permutt, S.Koepke

HFD-170/C.Schumaker, B.Rappaport, C.McCormick

Drafted by: L. Governale/5-25-00

Initialed by: C. Schumaker/5-31-00, Blatt/5-31-00, Haberny/5-31-00, Chen/6-1-00,
Theodorakis/6-1-00, Jean/6-1-00, D'Sa/6-2-00, Uppoor/, Rappaport/6/8/00,
Permutt/6-9-00, McCormick/6-19-00

Final: B.Rappaport/6-20-00, L.Governale/6-20-00

FILE NAME: 56919(Endo)EOP2.MM.051100.doc

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/s/

Lisa Basham-Cruz
3/21/03 10:08:04 AM
CSO

R. Daniel Mellon
3/21/03 10:12:17 AM
PHARMACOLOGIST

Timothy McGovern
3/24/03 09:00:40 AM
PHARMACOLOGIST
I concur.



NO FILING REVIEW ISSUES IDENTIFIED

NDA 21-611

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

Attention: Mary Alice Raudenbush
Vice President, Regulatory Affairs

Dear Ms. Raudenbush:

Please refer to your December 20, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Hydrochloride Immediate-Release Tablets (5 and 10 mg).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 18, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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NO FILING REVIEW ISSUES IDENTIFIED

NDA 21-610

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

Attention: Mary Alice Raudenbush
Vice President, Regulatory Affairs

Dear Ms. Raudenbush:

Please refer to your December 19, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxymorphone Hydrochloride Extended-Release Tablets (5, 10, 20, and 40 mg).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 17, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
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mg/day), or to less than _____ if the TDD is high (e.g., 1 gram/day). The latter is the situation with these NDAs. These numbers represent targets and might be adjustable, as appropriate.

Endo Pharmaceuticals informed the Division that they are planning to initiate testing of the impurity in both the Ames test and an in vitro cytogenicity test in March, 2003. Dr. McGovern requested that the Sponsor submit the study results as soon as they are available for review. If results of these two tests are positive, the concentration of this impurity must be brought down to _____ for the drug substance. Alternatively, Dr. McGovern suggested further testing in a SHE-cell assay or a transgenic mouse assay. Negative results in these assays may preclude the need to lower the specification to _____. The potential for occurrence in the drug product also should be investigated.

The Sponsor requested further discussion, should the genotoxicity results be positive.

Following the Chemistry/PharmTox discussion above, Dr. Comfort and Dr. Hertz addressed their question regarding the 120-day safety update. They inquired whether the data from the update would be fully integrated with the ISS data. Dr. Comfort was comfortable with the Sponsor's plans for integration of the two datasets.

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/s/

Lisa Basham-Cruz
2/20/03 05:20:31 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-610

Endo Pharmaceuticals
100 Painters Drive
Chadds Ford, PA 19317

Attention: Mary Alice Raudenbush
Vice President, Regulatory Affairs

Dear Ms. Raudenbush:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Oxymorphone HCl Extended-Release Tablets (5, 10, 20, 40 mg)

Review Priority Classification: Standard

Date of Application: December 19, 2002

Date of Receipt: December 19, 2002

Our Reference Number: NDA 21-610

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 19, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-610

Page 2

If you have any questions, call me at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-611

Endo Pharmaceuticals
100 Painters Drive
Chadds Ford, PA 19317

Attention: Mary Alice Raudenbush
Vice President, Regulatory Affairs

Dear Ms. Raudenbush:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Oxymorphone HCl Immediate-Release Tablets (5 and 10 mg)

Review Priority Classification: Standard

Date of Application: December 20, 2002

Date of Receipt: December 20, 2002

Our Reference Number: NDA 21-611

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 20, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
Attention: Fishers Document Room, Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-610
Page 2

If you have any questions, call me at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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Lisa Basham-Cruz
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Pre-NDA meeting
July 11, 2002



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,919
IND 58,602

Endo Pharmaceuticals
100 Painters Drive
Chadds Ford, PA 19317

Attention: Mary Alice Raudenbush
Director, Regulatory Affairs

Dear Ms. Raudenbush:

Please refer to the meeting between representatives of your firm and FDA on July 11, 2002. The purpose of the meeting was to discuss the content and format for the planned Numorphan® (oxymorphone HCl) Immediate-Release and Extended-Release Tablet New Drug Applications (NDAs).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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Dionne Price, PhD
Ann Nguyen
Lisa Basham-Cruz, MS

Statistics Reviewer
Pharmacy Student
Regulatory Project Manager

Representing: Division of Anesthetic, Critical Care, and Addiction Drug Products, FDA

Meeting Minutes:

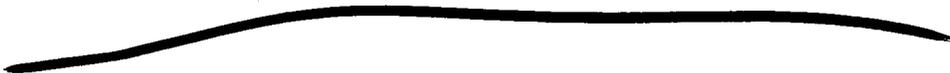
Following introductions, the discussion moved to the questions included in the June 11, 2002, meeting package. The questions were addressed by discipline and are shown below in italics. Information presented on slides is bolded. Discussion is in normal typeface.

Chemistry:

Dr. Harapanhalli addressed chemistry questions 1-4.

Chemistry Question 1. Does the Agency concur that...[the July 18, 2001] ...submission addresses the ...[May 18, 2000 request for in vitro dissolution info/data to support an optimal dissolution method for oxymorphone ER tablets]...?

d.



Dr. Harapanhalli added that, if the majority of the dissolution data for the ER tablets were generated in 0.1N HCl, then this data will need to be linked to data generated with the phosphate buffer, pH 4.5. Dr. Koble suggested the Sponsor begin generating data on clinical batches at each timepoint using the phosphate buffer, pH 4.5. He added that testing of retains from the clinical batches and stability batches with the new method may provide the required linkage between the two methods. The establishment of a linkage between the two methods is not an NDA filing issue, but may be an approvability issue. The Agency was willing to discuss this further in a future teleconference.

Chemistry Question 2. For all batches used only for clinical studies (i.e. they were not exhibit batches), it is our intent to submit the following in the NDA:

- Executed batch records which provide the details of the composition and the manufacturing process.
- The release test results and stability data for these clinical batches.
- A cross reference of the clinical batches with the clinical study numbers.

Does the Agency agree that this approach is acceptable?

- Yes.
- **However, the release test results and stability should include impurities/degradation products (ICH Q3A/B) and dissolution/drug release in addition to other test attributes.**

Chemistry Question 3. The Sponsor is proposing to submit the following:

- Statement indicating that the compendial inactive ingredients will be tested in accordance with the current USP/NF for all such materials.
- Test methods and specifications for all non compendial inactive ingredients and representative test results.

Does the Agency agree with this approach?

- No.
- **The quality of compendial excipients will be evaluated based on performance-related attributes. Therefore, additional tests may or may not be required.**

- **Test results for all compendial excipients should also be provided in the NDA.**

The Sponsor inquired whether it would be sufficient to provide one representative COA for each inactive ingredient. Dr. Harapanhalli agreed.

Chemistry Question 4. The Sponsor is proposing to submit test results for one lot of each packaging component, which is representative of all other lots of the same component.

Does the Agency agree with this approach?

- **Acceptable.**

Dr. Harapanhalli presented some additional chemistry comments on a slide.

- **Oxymorphone drug substance specifications for reporting, identifying, and qualifying individual impurities/degradation products should follow ICH Q3A/(Q3AR) and that for the drug product should follow ICH Q3B guidelines.**
POST MEETING NOTE: The potential presence of [redacted] impurities, which are structural alerts for mutagenicity, in the drug substance should be evaluated. If present, these impurities will need to be evaluated for genotoxicity and limited to appropriate safe, acceptable levels.
- **Oxymorphone drug substance assay should be revised to — - 102.0%.**
- **Oxymorphone IR tablets: Dissolution medium should be either 0.1 N HCl or simulated gastric fluid instead of water.**
- **The dissolution time profiles should be collected to select the [optimum] time point and the Q value.**
- **Safety information should be provided on the two proprietary inactive ingredients TIMERx-N® and [redacted].**

The Sponsor stated that the drug substance assay specification of 97.0% - 102.0% was based on USP. Dr. Koble responded that the USP is sometimes inconsistent and that the Agency wants a tighter specification of — - 102.0%.

The Sponsor inquired about the last bullet regarding safety information for TIMERx-N® and [redacted]. Dr. Koble responded that these compounds must be appropriately qualified for use in humans. The Sponsor responded that both compounds are used in approved ANDA/NDA products. Dr. Koble said that the Sponsor may cross-reference the appropriate DMFs for these compounds to support the oxymorphone ER NDA.

Preclinical:

Dr. Mellon addressed the pre-clinical questions.

Preclinical Question 1. Does the Agency concur with the Sponsor's plans to submit the results of the rodent carcinogenicity studies following the review and approval of the Oxymorphone ER NDA application (as a Phase IV Commitment)?

- No.
- **Carcinogenicity assessment must be included with the NDA submission.**
- **As indicated during the EOP2 meeting in May 2000, "if the results of the [genotoxicity] battery of tests are positive, the carcinogenicity studies should be conducted before approval of the NDA."**

The Sponsor noted that, although oxymorphone was positive in the *in vivo* micronucleus assay in rats and mice, it was not mutagenic at high concentrations *in vitro*. They added that there is evidence that oxymorphone is not a direct acting mutagen and that this suggests a threshold exists for opiate-mediated clastogenesis. Dr. Mellon expressed concern over the 3-fold safety margin observed in the rat micronucleus assay since it is unclear how this result relates to carcinogenicity. The Sponsor noted that their 2-year rat and mouse carcinogenicity protocols have been approved by the Carcinogenicity Assessment Committee and will be initiated within the next two weeks.

The Sponsor considered filing the NDAs as 505(b)(2) applications using oxycodone as the reference listed drug since oxymorphone is a metabolite of oxycodone. Dr. Rappaport stated that the Sponsor would have to ensure that exposure levels of oxymorphone are appropriate to make this link to an approved oxycodone formulation.

The Sponsor noted the positive genotox findings with morphine and suggested this is a class effect. Dr. Rappaport responded that there is not enough evidence available to fully understand the carcinogenic potential of morphine and that the Agency is requesting carcinogenicity studies for all old opiates that have not been evaluated by the FDA. The Sponsor must provide a rationale and argument to convince the Agency why the positive *in vivo* findings are not a safety concern. The Sponsor proposed a p53^{+/-} transgenic mouse study be conducted prior to NDA filing. Dr. Rappaport responded that results from a p53^{+/-} transgenic mouse study could be submitted as part of a comprehensive justification to submit the 2-year rat bioassay as a Phase 4 commitment. However, the materials would have to be reviewed prior to the Division's determination of whether the full carcinogenicity assessment can be deferred.

The Sponsor inquired whether the carcinogenicity studies would be required at submission for the immediate-release formulation. Dr. Rappaport said that the acute indication may not require carcinogenicity assessment, however, the administration of the immediate-release product for acute pain over a period of time (breakthrough pain) causes similar safety concerns as the controlled-release product. Dr. Rappaport said that the Agency will consider a compelling scientific argument for why the positive findings in the micronucleus assays should not be a safety concern. The Sponsor will prepare a submission on the genotoxicity issue for submission to the Agency. A subsequent teleconference may be scheduled to further discuss the carcinogenicity requirements for the NDAs.

Preclinical Question 2. At the End of Phase II meeting, the Toxicology studies needed to adequately evaluate the preclinical safety of oxymorphone were outlined. These toxicology studies have been completed and are summarized in this pre-NDA package.

Does the Agency concur that these studies will be adequate to allow filing of the NDA?

- No
- **Carcinogenicity assessment will be required as part of the NDA submission.**
- **Adequate qualification of all impurities which exceed ICH guidelines will be required for the NDA.**
- **Adequate qualification of all excipients will be required for the NDA.**
- **The overview of the toxicology should include data on the safety pharmacology as outlined in ICH S7A.**

Human Pharmacokinetics (PK) and bioavailability (BA):

Dr. Lee addressed the Human PK and BA questions 1 and 2.

Human PK and BA Question 1. The Sponsor will submit the following Phase I studies in support of the oxymorphone ER application.... In addition, in vitro drug-drug interaction studies will be included in the preclinical section of the NDA.

Does the Agency agree that these studies address the questions raised at the End-of-Phase II meeting and support the biopharmaceutical requirements of the oxymorphone ER application?

- **The types of the proposed studies appear to be adequate.**

Human PK and BA Question 2. The Sponsor will submit the following Phase I studies in support of the oxymorphone IR application..... In addition, in vitro drug-drug interaction studies will be included in the preclinical section of the NDA.

Does the Agency agree that these studies address the questions raised at the End-of-Phase II meeting and support the biopharmaceutical requirements of the oxymorphone IR application?

- **Again, the types of the proposed studies appear to be adequate.**

Dr. Lee presented some additional clinical pharmacology comments on a slide.

- **Please discuss in vivo drug-drug interaction program for oxymorphone, as discussed previously at the End-of-Phase 2 meeting.**

- **Please submit in vitro drug-drug interaction/ metabolism information in Clinical Pharmacology Section as well as in Preclinical section.**
- **Please submit in vitro release characterization (dissolution) for IR formulation**

The Sponsor agreed to address the above points and added that drug-drug interaction/metabolism studies are underway.

Clinical:

Dr. Comfort addressed the Clinical Questions with input from Dr. Price (statistics) where appropriate.

Clinical Question 1. Does the Agency agree with the Sponsor that we have adequately addressed the issue of total exposure and long-term exposure for the oxymorphone ER and IR NDAs?

- **Yes, the Agency agrees that these requirements have been met.**

Clinical Question 2. We plan to submit one combined ISS containing summary data for both the oxymorphone ER and oxymorphone IR formulations. Within the ISS, data will be presented separately for each formulation and combined for both formulations. Therefore, the same ISS (including datasets) will be submitted twice, once in each of the oxymorphone ER and oxymorphone IR NDAs.

Does the Agency accept this approach?

- **This approach appears acceptable.**

Clinical Question 3. Does the Agency agree with this proposed revised Oxymorphone Pediatric Plan?

Dr. Rappaport noted that the Agency will defer pediatric studies, but will not waive them.

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Dr. Rappaport recommended the Sponsor consider whether they would seek pediatric exclusivity. If so, a Pediatric Written Request (PWR) must be obtained from the Agency through submission of a Proposed Pediatric Study Request (PPSR). The requirements for a PWR are more stringent and will require study of the ER tablet in children below 12 years of age.

Clinical Question 4. Does the Agency agree with the Risk Management proposal?

- **The Agency agrees, in principle, with the current RMP proposed outline.**

Additional Agency Comments:

- **Detailed RMP proposal should be submitted with the NDA**
- **An Abuse Liability Package must be included with the NDA**
 - ✓ **An Abuse Liability Package needs to be submitted as part of the NDA.**
 - ✓ **Schedule II Status**
 - ✓ **Additional Clinical Trial Responsibilities:**
 - ❖ **Sponsor's responsibility to maintain careful drug accountability during trials. Appropriate tracking system should be designed to detect diversion.**
 - ❖ **Request that patients keep a diary of all AEs and subjective events.**
 - ❖ **Sponsor's responsibility to report overdose and misuse events.**

Clinical Question 5A. Does the Agency agree that the issues raised in the letter dated November 26, 2001 [regarding clinical study EN3202-025] is no longer an issue based on the Sponsor's response of January 8, 2002?

- **The Agency agrees that this issue has been addressed.**

Dr. Price addressed clinical question 5B.

Clinical Question 5B. Does the Agency agree with the revised statistical analysis plan for study EN3202-025?

- **Addressed in letter dated 6/4/02.**
- **Although the change to an intent-to-treat population is desirable, it raises concern regarding the appropriateness of the planned last observation carried forward analysis.**
- **When considering missing data, the pattern of withdrawal should be thoroughly investigated. For example, the possibility exists that patients discontinue due to intolerable side effects. The last record of such a discontinued patient may consist of a high score apparently suggesting treatment effectiveness at the time of withdrawal; however, the dose required for effectiveness may also have caused intolerable side effects.**
- **Since the pattern of withdrawal is treatment related, conclusions formulated based on a last observation carried forward analysis could be misleading. To offset potentially misleading conclusions, the sensitivity of the results of the analysis to the procedure utilized for handling missing data should be investigated. Moreover, alternate strategies such as various ranking procedures that incorporate information about the withdrawals may prove to be useful.**

The Sponsor understood the Agency's concerns and intend to explore alternate strategies.

Clinical Question 5C: Overall does the Agency agree that the above listed adequate and well-controlled studies are sufficient to support the indication and dosing recommendations for oxymorphone ER if primary outcome measures are met?

- **The pivotal trials (015 & 016) appear, on the surface, to support the proposed indication.**
- **Support for "dosing recommendations" is not as clear. An in-depth analysis to determine the appropriate dosing interval would be useful. This analysis should be included in the NDA as support for your proposed dosing recommendations.**

The Sponsor proposed dosing of twice-per-day for the ER tablets, and four times-per-day for the IR tablets. They will provide data supporting this dosing regimen in the NDA.

Clinical Question 6. Does the Agency agree with the proposal [of combining data from EN3202-015 and EN3202-025] to investigate dose-response and to perform subgroup analysis by providing descriptive statistics of the efficacy parameters by baseline characteristics (demographics, prior opioid experience, etc...)]?

- **Yes, the Agency agrees with this proposal.**

Clinical Question 7. Studies EN3202-016, EN3202-017, EN3202-018, and EN3202-019 will be used to support a table for the oxymorphone ER label which will instruct the prescriber how to convert from a pre-existing opioid to oxymorphone.

Does the Agency agree with this proposal?

- **It is unclear to the Agency how the listed studies will be used to guide opioid conversion for prescribers.**

The Sponsor stated that they have performed multiple studies in both single and multiple-dose settings to support labeling for analgesic equivalency. Dr. Rappaport expressed interest in this effort. The Division has not, of late, allowed use of conversion tables in labeling due to insufficient data to support the recommendations presented in those tables.

Clinical Question 8. The Sponsor intends to include four dosage strengths in the NDA: 5 mg, 10 mg, 20 mg, and 40 mg. The 5 mg dosage strength has been evaluated as part of a dose-proportionality study (EN3202-007). The Sponsor is proposing to include the strength in the NDA to permit the prescriber the increased dosing flexibility and to allow for a lower starting dose where appropriate.

Does the Agency agree with this proposal?

- **The 5 mg ER dosage has not been studied in subjects beyond this PK study population. Without specific efficacy data we would be unable to determine reliable dosing recommendations for the label.**

The Sponsor will further address this in the submission. They stated that the 5 mg dose has been shown to be dose proportional at steady state in PK study EN3202-007 and would be needed for titrating, special populations and pediatrics. Dr. Rappaport acknowledged the potential clinical benefit of such a dose, but explained that regulatory requirements will likely prohibit approval of the 5 mg dose without efficacy data. This is not, however, a filing issue.

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Clinical Question 9. Does the Agency agree that the above listed adequate and well-controlled studies are sufficient to support the indication and dosing recommendation for oxymorphone IR if primary outcome measures are met?

- **The pivotal trials do appear, on the surface, to support the proposed indication.**
- **However, support for “dosing recommendations” is not as clear. An in depth analysis to determine the appropriate dosing interval would be useful. This analysis should be included in the NDA as support for your proposed dosing recommendations.**

Overall Statistical Concerns:

- **In several studies, multiple comparisons are of interest. The method of controlling the Type I error should be specified.**
- **The appropriateness of a last observation carried forward strategy should be thoroughly considered.**

Clinical Question 10. To support the efficacy indication, the Sponsor is planning to present efficacy results side-by-side from studies EN3202-004 and En3203-005 in the ISE. Data from these two studies also will be combined to perform Kaplan-Meier survival analysis on time to perceptible pain relief, time to meaningful pain relief, and time to rescue medication. In addition, the Sponsor will perform subgroup analysis on the combined dataset by providing descriptive statistics of the efficacy parameters by demographic variables.

Does the Agency agree with this proposal?

- **Yes, the Agency agrees with this proposal.**

Clinical Question 11. The Sponsor received a fax dated December 19, 2001 regarding Study 3203-006. Specifically, the Division raised questions regarding the formulations' composition and the proposed dose range/regimen intended for NDA approval. The Sponsor provided a response on December 21, 2001 (Serial # 48), and is awaiting feedback from the Division.

Does the Agency agree that this is no longer an issue based on the Sponsor's response of December 21, 2001?

Yes, the Agency agrees that this issue has been resolved.

General Issues and e-NDA Specifications:

These questions were addressed by the team, with appropriate reviewers addressing their relevant interests.

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Question 1. Is the overall strategy for preparing the archive copy acceptable to the Agency?

- **The proposed overall strategy is acceptable.**

Question 2. Is the intended preparation of the review copy adequate to facilitate the review?

- **The intended preparation is acceptable, based upon the provided information.**

Question 3. Is the selection of e-submission media acceptable to the Agency?

- **Specific questions regarding file size, transport media, etc., are discussed in the guidance documents for electronic submissions, at the following web address: www.fda.gov/cder/regulatory/ersr**
- **If the necessary answers to these questions are not addressed in the regulatory documents, Dr. Randy Levin recommends that the Sponsor contact the electronic submissions officer at: esub@cder.fda.gov**

Question 4. Does the Agency agree with this proposal [to provide bookmarks for each item in the TOC]?

- **The bookmark proposal is acceptable.**

Question 5. Does the Agency agree with this proposal [to provide hyperlinks throughout the body of the document]?

- **The hyperlink proposal is acceptable.**

Question 6. Does the Agency agree with this proposal for handling large file sizes?

- **See response to question 3.**

Question 7. Does the Agency agree with this proposal for handling publications?

- **The publication proposal is acceptable. In addition, the Sponsor is requested to provide the following:**
 - ✓ **Hyperlink connections to all publications, referenced in the NDA.**
 - ✓ **Brief synopsis of hyper-linked study with as indication of how/where the publication is applicable to the NDA.**

Question 8. Item 1: Index (Table of Contents). Does the Agency agree with this proposal [to provide a TOC with 3 levels of detail]?

- **The proposal is acceptable.**

Question 9. Item 2: Labeling. Endo intends to propose the following:

- ✓ *Proposed Labeling test (in PDF and Word 97)*
- ✓ *Carton labeling*
- ✓ *Container labeling*

Does the Agency agree with this proposal?

- **The proposal is acceptable.**

Question 10. Item 3: Summary. Does the Agency agree with this proposal [to provide the summary section as a single PDF file with hyperlinks to the page containing the referenced material]?

- **The proposal is acceptable.**

Question 11. Item 4: CMC. Does the Agency agree with this proposal for the CMC section?

- **Stability data should be provided in SAS files. The stability data analysis should have regression plots with upper and lower bounds. Applicable Agency and ICH guidelines should be followed.**

The Sponsor inquired about the lack of current guidelines for CMC. Drs. Koble and Harapanhalli agreed to further discuss dataset structure with the Sponsor prior to filing. The Sponsor will request a teleconference.

Question 12. Item 5: Pharmtox. Individual animal line listings will be provided as pdf files. The major sections within these files will be bookmarked.

Does the Agency agree with this proposal for the Pharmtox section?

- **PDF files will be acceptable for all data except carcinogenicity data.**
 - ✓ **Tumor data sets should be submitted as a SAS transport file for statistical analysis as described in Guidance to Industry IT2 (Providing Regulatory Submissions in Electronic Format – General Considerations).**

- ✓ **The Sponsor is also referred to Guidance to Industry IT3 (Providing Regulatory Submissions in Electronic Format – NDAs, appendix 1) for recommended datasets and data elements.**

Question 13. Item 6: Human PK/Bio. Is this proposal acceptable to the Agency? Specifically, is our plan to provide one summary document for human pharmacology and bioavailability/bioequivalence acceptable?

- **The Sponsor's proposal is acceptable.**

Question 14. Item 8/10: Clinical/Statistical. Is the organization of item 8/10 described above acceptable to the Agency?

- **The 8/10 organization is acceptable.**

Question 15. Item 11: CRTs. Is the organization of the (CRT) data described above acceptable to the Agency?

- **The proposed formats and content are acceptable. In addition to the items outlined, please add the following for CRT Datasets:**
 - ✓ **Include all date and time variables in consistent date/time formats.**
 - ✓ **Where applicable, dates should be accompanied by "study day" and "duration".**
 - ✓ **All provided data should be in SAS transport files that are compatible with JUMP 4.0 (used to convert SAS files and review data).**

Dr. Comfort provided a document to the Sponsor outlining his preferences for data presentation. He instructed the Sponsor to contact the Division with any additional questions.

Question 16. Is our plan to include patient profiles only for adequate and well-controlled studies acceptable to the Agency?

- **This is acceptable provided that narratives are also provided for all SAEs and Discontinuations due to AEs, for all studies.**

Question 17. Item 12: CRFs. Is this proposal [regarding CRFs] acceptable to the Agency?

- **This appears acceptable. Additional guidance can be obtained from the regulatory guidelines listed at: www.fda.gov/cder/regulatory/ersr.**

Question 18. Electronic CRFs. Is this proposal to make the audit trail available on request acceptable to the Agency?

- **This appears acceptable depending on how the CRFs are created. Are the CRFs “images” of paper CRF pages or are they electronically generated? This could affect how the Audit trail is generated.**

The Sponsor explained that the e-CRFs are text based PDF files derived from the electronic data capture system. An audit trail is available, but is not directly attached to the case report because it is not “reviewer friendly.” The Division expressed discomfort with this proposal, specifically due to the inability of the reviewer to identify questionable entries. The Sponsor proposed the inclusion of an audit trail as a review tool to inform the reviewer of the number of changes made to the CRFs. Dr. Permutt suggested the inclusion of a summary of the scope of changes. Dr. Rappaport advised the Sponsor to work through their own data to ensure that the numbers and codes are defined and navigable. If not, the NDA will be rejected, either not filed or not approved.

Action Items:

CMC: Primary issues are non-compendial excipients, setting specifications for drug substance and drug product, and the dissolution method. The Sponsor will request a teleconference in the near future to discuss linkage of the old dissolution method with the new.

Pharm/Tox: The Sponsor will prepare and submit a scientifically compelling argument for why they believe the genotoxicity results do not necessitate carcinogenicity testing prior to NDA submission. The focus should be on the nonclinical data, mechanism of action, etc. explaining why the two *in vivo* studies in rodents are not relevant to humans. The oxymorphone ER and IR NDAs may be considered separately by the Agency with regard to this issue. The Sponsor will request a teleconference to discuss their submitted materials and to resolve the issue.

Clinical: The pediatric plan will be revised to consider today’s discussion points and submitted with both NDAs. Pediatric studies will be deferred until review of the adult data is completed.

e-NDA: The Sponsor will request a teleconference to discuss the proper format for the CMC stability SAS datasets. The Sponsor will provide an audit trail review tool for the CRFs.

- Lisa E. Basham-Cruz/minutes recorder
- Bob Rappaport, M.D./concurrence

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lisa Basham-Cruz
9/4/02 10:35:29 AM

Bob Rappaport
9/5/02 10:09:31 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21,610	Efficacy Supplement Type SE-	Supplement Number
Drug: OPANA ER (Oxymorphone Hydrochloride Extended-Release) Tablets, 5 mg, 10 mg, 20 mg, 40 mg.		Applicant: Endo Pharmaceuticals, Inc.
RPM: Lisa Basham-Cruz	HFD-170	Phone # 301-796-1175
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		Type 3
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		June 22, 2006
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number 4485
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Summary Completed, 505(b)(1)
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	PM Filing Review: 3/24/03 Action Pkg Checklist:

General Information	
Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE, 10/15/03
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	FINAL ONLY: In Approval Letter
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS, 8/25/03; DDRE, 9/16/03 DSRCS, 9/30/03; DMETS, 12/23/04; DDMAC, 6/13/06; DSRCS, 6/14/06; DMETS, 6/12/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	OxyContin NDA 20-553/S-035 Avinza NDA 21-260/S-006
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	FINAL ONLY: In Approval Letter
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	PREA requirement 0-16 deferred
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	May 11, 2000
• Pre-NDA meeting (indicate date)	July 11, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other: Post AE Action meeting	April 15, 2005
❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	1 st Cycle Team Leader: 10/15/03 1 st Cycle Director: 10/15/03 2 nd Cycle Director: 6/22/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	1 st Cycle: Safety 10/15/03 1 st Cycle Efficacy: 10/15/03 2 nd Cycle: 6/22/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	1 st Cycle: CSS 10/14/03 DDRE, DSRCS, 10/14/03 DMETS, 10/3/03 DDRE, DSRCS, 6/20/03 Clinical, 10/15/03 2 nd Cycle: CSS, 6/9/06 ODS, 6/19/06
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	6/22/06/
❖ Demographic Worksheet (NME approvals only)	NA
❖ Statistical review(s) (indicate date for each review)	1 st cycle: 10/2/03 2 nd Cycle: 6/5/06
❖ Biopharmaceutical review(s) (indicate date for each review)	1 st Cycle: 9/23/03 2 nd Cycle: 6/16/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	6/9/06
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	6/19/06
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) (indicate date for each review)	
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	1 st Cycle: CMC review- page 112/121
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	1 st Cycle: 10/15/03 2 nd Cycle: 6/19/06
Nonclinical inspection review summary	NA

❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	6/2/06
CAC/ECAC report	6/5/06

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21,611	Efficacy Supplement Type SE-	Supplement Number
Drug: OPANA (Oxymorphone Hydrochloride) Tablets, 5 mg, 10 mg.		Applicant: Endo Pharmaceuticals, Inc.
RPM: Lisa Basham-Cruz		HFD-170 Phone # 301-796-1175
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Type 3
❖ User Fee Goal Dates		June 22, 2006
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver 		<input checked="" type="checkbox"/> Paid UF ID number 4486 <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

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If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

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❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Summary Completed, 505(b)(1)
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	PM Filing Review: 3/24/03 Action Pkg Checklist:

Confidential Information	
Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	AE, 10/15/03
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	FINAL ONLY: In Approval Letter
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS, 8/25/03; DDRE, 9/16/03 DSRCS, 9/30/03; DMETS, 12/23/04; DMETS, 6/12/06, DDMAC, 6/13/06; DSRCS, 6/14/06;
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	OxyContin NDA 20-553/S-035 Avinza NDA 21-260/S-006
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	FINAL ONLY: In Approval Letter
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	PREA requirement 0-16 deferred
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	May 11, 2000
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• Other: Post AE Action meeting	April 15, 2005
❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	1 st Cycle Team Leader: 10/15/03 1 st Cycle Director: 10/15/03 2 nd Cycle Director: 6/22/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	1 st Cycle: Safety 10/15/03 1 st Cycle Efficacy: 10/15/03 2 nd Cycle: 6/22/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	1 st Cycle: CSS 10/14/03 DDRE, DSRCS, 10/14/03 DMETS, 10/3/03 DDRE, DSRCS, 6/20/03 Clinical, 10/15/03 2 nd Cycle: CSS, 6/9/06 ODS, 6/19/06
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	6/22/06/
❖ Demographic Worksheet (NME approvals only)	NA
❖ Statistical review(s) (indicate date for each review)	1 st cycle: 10/2/03 2 nd Cycle: 6/5/06
❖ Biopharmaceutical review(s) (indicate date for each review)	1 st Cycle: 9/23/03 2 nd Cycle: 6/16/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	6/9/06
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	6/19/06
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) (indicate date for each review)	
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	1 st Cycle: CMC review- page 112/121
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	1 st Cycle: 10/15/03 2 nd Cycle: 6/19/06
Nonclinical inspection review summary	NA

❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	6/2/06
CAC/ECAC report	6/5/06

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NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

NDA 21-610: Oxymorphone HCl Extended-Release Tablets (5, 10, 20, 40 mg)

Applicant: Endo Pharmaceuticals Inc.

Date of Application: December 19, 2002

Date of Receipt: December 19, 2002

Date of Filing Meeting: February 11, 2003

Filing Date: February 17, 2003

Indication(s) requested: Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time.

Type of Application: Full NDA Supplement _____
(b)(1) (b)(2) _____

[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S P _____
Resubmission after a withdrawal or refuse to file no _____
Chemical Classification: (1,2,3 etc.) 3 _____
Other (orphan, OTC, etc.) N/A _____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES NO _____
User Fee ID# 4485
Clinical data? YES NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: October 19, 2003

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? YES NO
 - Form 356h included with authorized signature? YES NO
- If foreign applicant, the U.S. Agent must countersign.**

- Submission complete as required under 21 CFR 314.50? YES NO
 If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO NA
If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? YES NO NA
- Patent information included with authorized signature? YES NO
- Exclusivity requested? YES; If yes, 3 years NO
 Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, the U.S. Agent must countersign.
 Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, "To the best of my knowledge,"
- Financial Disclosure included with authorized signature? YES NO
 (Forms 3454 and/or 3455)
If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
 If no, for what ages and/or indications was a waiver and/or deferral requested:

 Waiver requested for 0-11 years. Deferral requested for 12-16 years. Plan submitted.
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: 56,919

End-of-Phase 2 Meeting? Date May 11, 2000 NO
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date July 11, 2002 NO
 If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC?	<u>YES</u>	NO	
Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?	<u>YES</u>	NO	
MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?	YES	NO	<u>NA</u>
OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support?	YES	NO	<u>NA</u>
Advisory Committee Meeting needed?	YES, date if known _____		<u>NO</u>

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

YES

NO

Chemistry

- Did sponsor request categorical exclusion for environmental assessment?

YES

NO

 - If no, did sponsor submit a complete environmental assessment?

YES

NO
 - If EA submitted, consulted to Nancy Sager (HFD-357)?

YES

NO
- Establishment Evaluation Request (EER) package submitted?

YES

NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)?

YES

NO

NA

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
(Normally, FDA will refuse-to-file such applications.)

YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

**Appears This Way
On Original**

REGULATORY CONCLUSIONS/DEFICIENCIES:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

 The application is unsuitable for filing. Explain why:

Lisa Basham-Cruz, MS
Regulatory Project Manager, HFD-170

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lisa Basham-Cruz
3/24/03 04:47:37 PM
CSO

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

NDA 21-611: Oxymorphone HCl Immediate-Release Tablets (5, 10 mg)

Applicant: Endo Pharmaceuticals Inc.

Date of Application: December 20, 2002

Date of Receipt: December 20, 2002

Date of Filing Meeting: February 11, 2002

Filing Date: February 18, 2002

Indication(s) requested: Management of moderate to severe pain where the use of an opioid is appropriate

Type of Application: Full NDA Supplement _____

(b)(1) (b)(2) _____

[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S P _____

Resubmission after a withdrawal or refuse to file no

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.) N/A

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid Waived (e.g., small business, public health) _____

Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO _____

User Fee ID# 4486

Clinical data? YES NO _____ Referenced to NDA# _____

Date clock started after UN _____

User Fee Goal date: October 20, 2003

Action Goal Date (optional) _____

• Does the submission contain an accurate comprehensive index? YES NO

• Form 356h included with authorized signature? YES NO

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
 If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO NA
If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? YES NO NA
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- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
 If no, for what ages and/or indications was a waiver and/or deferral requested:

 Deferral requested for 0-16 years. Plan submitted.
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

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PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: 58,602

End-of-Phase 2 Meeting? Date _____ NO
 If yes, distribute minutes before filing meeting. Controlled-release 5/11/00)

Pre-NDA Meeting(s)? Date July 11, 2002 NO
 If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? YES NO NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO NA

Advisory Committee Meeting needed? YES, date if known _____ NO

Clinical

• If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

• Did sponsor request categorical exclusion for environmental assessment? YES NO
 If no, did sponsor submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

• Establishment Evaluation Request (EER) package submitted? YES NO

• Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO NA

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
 (Normally, FDA will refuse-to-file such applications.)

YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

**Appears This Way
On Original**

REGULATORY CONCLUSIONS/DEFICIENCIES:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

 The application is unsuitable for filing. Explain why:

Lisa Basham-Cruz, MS
Regulatory Project Manager, HFD-

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lisa Basham-Cruz
3/24/03 04:59:15 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-610

APPLICANT INFORMATION

NAME OF APPLICANT Endo Pharmaceuticals Inc.	DATE OF SUBMISSION December 19, 2002
TELEPHONE NO. (Include Area Code) (610) 558-9800	FACSIMILE (FAX) Number (Include Area Code) (484) 840-4290
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 100 Painters Drive Chadds Ford, PA 19317	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Oxymorphone Hydrochloride		PROPRIETARY NAME (trade name) IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)		CODE NAME (If any) EN3202
DOSAGE FORM: Extended Release Tablet	STRENGTHS: 5, 10, 20, 40 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time		

APPLICATION INFORMATION

APPLICATION TYPE (check one)			
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)		<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)	
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug _____		Holder of Approved Application _____	
TYPE OF SUBMISSION (check one)			
<input checked="" type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER	
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED <u>1</u>		THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC	
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.			
See attached			

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 56,919 ; IND 58,602; NDA 21-611; NDA 11-707; NDA 11-738; DMF 14502; DMF 11868

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>Endo Pharmaceuticals Inc. 100 Painters Drive Chadds Ford, PA 19317</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>21-610</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(610) 558-9800</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p> <p>_____</p> <p>(APPLICATION NO. CONTAINING THE DATA).</p>
<p>3. PRODUCT NAME</p> <p>Oxymorphone Hydrochloride Extended Release Tablets</p>	<p>6. USER FEE I.D. NUMBER</p> <p>4485</p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

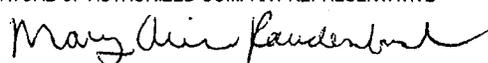
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Vice President, Regulatory Affairs	DATE December 17, 2002
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>Endo Pharmaceuticals Inc. 100 Painters Drive Chadds Ford, PA 19317</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-611</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(610) 558-9800</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>3. PRODUCT NAME</p> <p>Oxymorphone Hydrochloride Immediate Release Tablets</p>	<p>6. USER FEE I.D. NUMBER 4486</p>

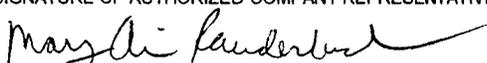
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Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Vice President, Regulatory Affairs	DATE December 17, 2002
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