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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 21-044

Trade Name: Palladone ER Capsules, 12-, 16-, 24-, and 32 mg mg

Generic Name(s): (hydromorphone HCl)

Sponsor: Purdue Pharma, L.P.

Agent:

Approval Date: September 24, 2004

Indication: Provides for the management of persistent, moderate-to-severe pain in opiate-tolerant patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time, generally weeks to months or longer

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-044

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-044

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your new drug application (NDA) dated December 28, 1998, received December 29, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Palladone ™ (hydromorphone hydrochloride extended-release) Capsules, 12-, 16-, 24-, and 32-mg.

We acknowledge receipt of your submissions dated February 12, March 5 and 8, April 16 and 29, July 15, 20, and 23, August 3, 12, and 26, September 15 and 30, October 11, and November 11, 17, and 18, 1999, March 29, May 3, August 7, 23, and 25, and October 5, and 17, 2000, March 30, April 6, and 20, June 19, July 7 and 20, August 8, 13, and 17, October 9 and 18, 2001, January 29, March 12, April 15 and 29, May 23, July 2 (2) and 24, August 1 (2) and 6, September 5, 6 (2), 9, 10, 11, 12, 13, and 18, October 4, 8, and 10, November 26, and December 10, 13, 19, and 23, 2002, January 21, March 12, May 12, July 30, August 26, September 2 and 15, October 14, November 4, and December 10, 2003, January 16 and 20, February 12, April 15, May 17 and 20, June 7, July 1, 6 (2), 7, 13, 19, 23, and 28, August 23, and September 9, 10, 13, 14 (2), 17, 20, (2), and 21(3), 2004.

The July 23, 2004, submission constituted a complete response to our July 16, 2004, action letter.

This new drug application provides for the use of Palladone (hydromorphone hydrochloride extended-release) Capsules 12-, 16-, 24-, and 32-mg for the management of persistent, moderate to severe pain in opiate-tolerant patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time, generally weeks to months or longer.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of all FDA regulations and the commitments you have made regarding specific risk management and use described below.

Risk Management Program

We remind you that your Palladone Risk Management Program is an important part of the postmarketing risk management for Palladone. Your Risk Management Program must include the following components:

1. Labeling
    a. Package Insert

    b. MedGuide

2. Education
    a. Professional Labeling

    b. Healthcare Professional Education

    c. Patient and Caregiver Education

3. Surveillance
    a. Monitoring for significant safety issues, with initiation of specific interventions when monitoring reveals a safety issue and evaluation of the effectiveness of those interventions.

You have also committed to the following:

4. Launch Program
    a. Sales Force Training and Product Promotion

    b. Limited Rollout Proposal with Evaluation Metrics

5. Other components of your RMP
    a. Policies, procedures and interventions dealing with material handling and supply chain integrity.

    b. Participation in or support of broad-based coalitions seeking systems solutions leading to appropriate use and reduced abuse and diversion of scheduled analgesics.

The Palladone Risk Management Plan, as submitted on September 21, 2004, adequately addresses each of these requirements. Any change to the program must be discussed with FDA prior to its institution and is subject to FDA concurrence. We expect your continued cooperation to resolve any problems regarding the Palladone Risk Management Program that may be identified following approval of this application.

We remind you of your September 10, 2004 submission, our letter dated September 17, 2004, and the August 30, 2004 meeting with the Agency and your commitment to provide reports regarding serious adverse events in patients who have received Palladone. The reports and their contents are listed below:

Within 15 days of receipt

1. Expedited Safety Reporting as per 21CFR 314.80

2. In-transit cargo theft of Palladone reported through your supply chain management.

Monthly reports

All monthly reports will have a cut-off date of the last calendar day of the month and will be submitted to the FDA within two weeks of that date. Data analysis will not be required beyond what is usually done for these reports. The reports will be sorted and separated into appropriate categories and include the following:

1. MedWatch forms for all adverse events that have been finalized in your ARGUS safety database associated with the following conditions that do not qualify for expedited reports. The reports will include:

   a. Labeled overdoses and deaths associated with Palladone Capsules.

   b. Reports of abuse, addiction and/or misuse (i.e., the use of the medication in a manner inconsistent with the labeling, whether willful or unintentional) associated with Palladone.

   c. Adverse events associated with reports of exposure to Palladone involving children 18 years of age or younger.

   d. Adverse events occurring in "opioid naïve" persons who use Palladone.

   e. Medication errors associated with the administration of Palladone.

   f. Reports of documented safety concerns identified via surveillance do not need to be submitted on MedWatch forms but should be submitted and clearly labeled in a format to allow review and analysis by FDA.

   g. Adverse events identified as items a, b, c, d, and e that will be submitted in the monthly report should also be submitted in the subsequent periodic report as normally required by the regulations 21CFR 314.80. This will ensure that the adverse events (AEs) are entered into the AERS database.

2. Rx Patrol Reports that are reports of pharmacy level losses.

3. Media reports of any misuse/abuse/addiction/diversion cases involving Palladone Capsules.

Quarterly Reports

1. Periodic Safety Update Reports for Palladone Capsules as per 21 CFR 314.80

2. Research Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System information on Palladone which will include the following:

    a. Beginning 6 months after the product is available, information will be provided on a quarterly basis alternating every three months between Summary Information without verification or analysis/synthesis and Full Report with analysis and synthesis of information.

    b. The information will include data from the Key Informant Network, Drug Diversion Study, Poison Control Centers, American Association for the Treatment of Opioid Dependence (AATOD) Study, and when available, usually once a year Federal Data sources will include Drug Abuse Warning Network (DAWN), National Survey on Drug Abuse Use and Health (NSDUH), and Treatment Episode Data Set (TEDS).

    c. Information will also be included to address FDA's "Minimum Candidate Rollout Metrics-2." The RADARS System will monitor for signals of abuse and diversion of Palladone and will include the outpatient drug use patterns in the following manner:

        (1) Use of sale and prescription data to monitor for disproportionate increases by geographic area

        (2) Look for inappropriate prescribing by using patient-level, prescription drug use longitudinal data to look for evidence of patients switching between insurance and cash payments and/or doctor/pharmacy shopping by geographic area.

3. The quarterly reports should also include:

    a. Interventions undertaken and known consequences/impacts

    b. External Advisory Board (EAB) meeting minutes

    c. Field force SOP findings

Six Month Reports

FDA's "Minimum Candidate Rollout Metrics-1," will be a semiannual report focused on serious adverse events, particularly overdose and deaths. These reports will also include your investigations to determine, where possible, whether the use was medical or nonmedical.

Report of Limited Rollout Evaluation Metrics

You will provide a report after distribution of Palladone Capsules begins that will include, but not be limited to, the Prior Therapy Report, Prescription by Specialty Report and the Primary Research Report of Key Messages.

1. The Prior Therapy Report will be clearly labeled and submitted not 15 months after dispensing of Palladone begins, but as part of the Six-Month Reports.

2. The Prescription by Specialty Report will be clearly labeled and submitted as part of the Quarterly Reports.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0-16 years until September 2009.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the use of Palladone (hydromorphone hydrochloride extended-release) Capsules 12-, 16-, 24-, and 32-mg for the management of persistent, moderate to severe pain in opiate-tolerant pediatric patients (0-16 years) requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time, generally weeks to months or longer.

   Final Report Submission: September 24, 2009

   Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**."

We remind you of your agreement, submitted September 21, 2004, to decrease the level of the morphinone impurity [ ] for the drug substance and submit a supplement for this change to the NDA by September 2006.

We have determined that Palladone poses a serious and significant public health concern requiring distribution of a Medication Guide under 21 CFR 208. This Medication Guide is necessary for patients' safe and effective use of Palladone.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide,) and labeling for immediate container and carton labels submitted September 20, 2004. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and unapproved new drug.

Please submit an electronic version of the FPL according to the guidances for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* and *Providing Regulatory Submissions in Electronic Format-Content of Labeling*. Alternatively, except for the content of labeling, which must

be submitted electronically in PDF format, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-044.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of your September 10, 2004 submission, our letter dated September 16, 2004, and the following commitments to the Division of Drug Marketing, Advertising, and Communications (DDMAC):

1. Core launch material will be submitted to DDMAC at least 15 business days prior to actual use.

2. For the first 6 months following approval, any new core promotional material will be submitted at least 15 days prior to actual use for review and prior approval by DDMAC.

3. Items not considered core promotional material will be submitted at the time of first use.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sara Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Division Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Meyer
9/24/04 04:53:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-044

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Senior Director

Dear Dr. Fanelli:

Please refer to your new drug application (NDA) dated December 28, 1998, received December 29, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride extended-release) Capsules.

We acknowledge receipt of your submissions dated May 17 and 20, June 7, and July 1, 6, 7, and 13, 2004.

The May 17, 2004 submission constituted a complete response to our September 13, 2002 action letter.

We also acknowledge receipt of your submission dated July 13, 2004. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and it is approvable. The following deficiencies must be resolved:

The product labeling must be revised and finalized.

1. We have reviewed and revised your proposed labeling. The revised labeling is enclosed. Prior to approval, you must submit revised draft labeling for the drug that is identical in content to the enclosed labeling. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

2. Pursuant to 21 CFR Part 208, FDA has determined that Palladone poses a serious and significant public health concern requiring distribution of a Medication Guide. Palladone is a drug product for which patient labeling could help prevent serious adverse effects. Palladone has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or to continue to use, the product. Palladone is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness. The Medication Guide for

Palladone should address concerns about overdose, addiction, and proper use. In accordance with 21 CFR 208.24, you will be responsible for ensuring the following:

a. That a Medication Guide for Palladone is available for every patient who is dispensed a prescription for Palladone.

b. That the label of each container of Palladone includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom Palladone is dispensed.

c. That the label of each container includes a statement about how the Medication Guide is provided.

In addition, the following issues have yet to be resolved. You have agreed to implement a risk management plan (RMP) to ensure the safe use of the product post-approval. We would like to have further discussions with you regarding the following issues with your RMP, which remain unresolved:

1. Establishing a baseline for current hydromorphone exposure, using information collected as part of Purdue's current active surveillance systems. This baseline information and any subsequent changes will allow for the assessment of the utility and value of your proposed surveillance tools as part of the Palladone RMP.

2. Timely analysis of safety issues, including overdose and deaths, related to Palladone and how FDA may be notified of these issues. For instance, it would be useful to include the following postmarketing adverse event reports as 15-day "Alert Reports," in addition to those required to be reported under 21 CFR 314.80(c)(1)(i):

   a. All overdoses and deaths associated with Palladone

   b. All reports of abuse, addiction, and misuse associated with Palladone

   c. All adverse events and reports of exposure to Palladone involving children 18 years of age or younger*

   d. All adverse events occurring in "opioid-naïve" persons who use Palladone

   e. All medication errors associated with the administration of Palladone

   *we suggest using a modified case definition of "any pediatric exposure" and including all children who are exposed to Palladone via prescription, accidental exposure, inadvertent exposure, abuse, or any other avenue.

3. Timely submission of RADARS reports as well as reports from other surveillance mechanisms (e.g., DAWN, NSDUH, pertinent product inquiries, and media/medical literature surveillance) to FDA on a regular and frequent basis would facilitate evaluation of your RMP.

4. Modification of your RMP to provide for the submission, within 15 calendar days of identification, of all reports documenting safety concerns by geographical area that are identified via any surveillance methodologies.

5. Timely reporting to FDA of any interventions you initiate in response to the adverse event information you receive related to Palladone, and how you plan to (1) assess the results of these interventions and (2) apprise FDA of the results.

6. Notification to FDA of instances where you have officially communicated with other Federal, State, and/or local authorities of reports of possible inappropriate prescribing or dispensing of Palladone.

7. Detailed information about the elements of the RMP aimed at educating prescribers regarding the identification of patients who are at risk for developing addiction, and your efforts to minimize those risks.

8. Additional details about your proposed roll-out plan and how you will implement this plan over its various phases to assure that the plan meets your goals.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 8247-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Division Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

9/13/02

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard Fanelli, Ph.D.
Director, U.S. Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your new drug application (NDA) dated December 28, 1998, received December 29, 1998, pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride) extended-release capsules.

We acknowledge receipt of your submission dated March 12, 2002 which constituted a complete response to our October 4, 2001 action letter. We also acknowledge receipt of your submissions dated April 15 and 29, May 23, July 2 (2) and 24, August 1 (2) and 6, September 5, 6 (2), 9, 10 and 12, 2002.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

1. A withhold recommendation was received from the CDER Office of Compliance for the drug product manufacturing site (CFN [ ]). An approval recommendation from the Office of Compliance is needed prior to approval of your NDA application.

2. The following comments refer to the drug substance [ ]' specification.

   a. A deficiency letter has been forwarded to the holder of DMF [ ]

   b. Provide a revision of the [ ] acceptance criteria to be consistent with the supplier's updated acceptance criteria.

   c. Provide a specification (test, test method, and acceptance criteria, with validation) for the impurity morphinone in the Hydromorphone HCL drug substance with an acceptance criteria of "less than [ ]

   d. Provide an updated drug substance specification (tests, test methods, and acceptance criteria).

3. Provide adequate qualification of the genotoxic potential of the drug substance impurity morphinone (one point mutation assay and one cytogenetic assay with the isolated impurity tested

up to the limit doses for each assay). Alternatively, provide a specification (test, test method, and acceptance criteria) and validation for this impurity with a limit of — ppm."

While not specifically a condition of approval, agreement on the elements of the Risk Management Program designed at minimizing the risk of abuse and diversion of this product should be resolved before this product is marketed.

In addition, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on the information submitted, we conclude the following:

[ ]

- ☐ We are deferring submission of pediatric studies for patients 0-16 years of age until December 31, 2005.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Sara Shepherd, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
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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/s/

Cynthia McCormick
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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-044

10/4/01

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard Fanelli, Ph.D.
Director, U.S. Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your new drug application (NDA) dated December 28, 1998, received December 29, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride) extended-release capsules.

We acknowledge receipt of your submissions dated March 30, April 20, August 13, and August 17, 2001. Your submission dated March 30, 2001, constituted a complete response to our December 29, 1999, action letter.

We also acknowledge receipt of your submissions dated July 7 and July 20, 2001, that contain a proposed Palladone Risk Management Program and a request for a pediatric waiver respectively. These submissions were not reviewed for this action.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. The results from Study HMP-3005 do not adequately support efficacy of this formulation of hydormorphone hydrochloride as an oral extended-release analgesic product for single-daily dosing. The results of the study are not definitive, the effect size is small and the protocol was not adhered to for analysis of efficacy.

   Although the pre-determined primary efficacy endpoint demonstrates a statistically significant difference between study treatments in favor of the active treatment, a *post hoc* analysis of dropouts rather than the prespecified method of analysis in the protocol was used to obtain this result.

   The small difference between the pain scores of treatments at weeks 2 and 4 is only 7.25% (0.29/4) and 8.0% (0.32/4), respectively, and has not been justified as a clinically meaningful difference.

The worsening of pain control between baseline and weeks 2 and 4 as manifested by the doubling of pain scores during treatment for both the placebo and treatment arms does not support the assertion that this study documents the sustained efficacy of hydromorphone hydrochloride extended-release tablets.

You must conduct a new adequate and well-controlled study with multiple dosing in the setting of chronic pain that demonstrates superiority over placebo or another control in order to establish the efficacy of your product. In addition, evidence must be provided to support the effectiveness of all proposed doses, throughout the entire dosing interval.

2. There was a sufficient number of methodological deficiencies and unresolved questions of data integrity identified during the inspection of this study that the Division cannot justify the use of these data as the sole basis for an approval decision. There were unverifiable primary data, and a failure to adequately maintain an electronic trial of the data elements. We refer you to Form FDA 483 presented to you on September 21, 2001, for a detailed description of the List of Inspection Observations. The principle elements are also listed below.

   a. Primary efficacy data (test subject pain evaluations) submitted in support of this study were collected using a computerized "Interactive Voice Response System" (IVR). The IVR software program was not validated at the time of use (July 19, 2000-November 6, 2000). The computer system used to store the HMP-3005 study data collected by the IVR software at [ ] (CRO) failed to provide computer generated, time/date stamped audit trails of operator actions that created, modified, and/or deleted data to assure their accurate retrieval of study data. The data were stored on the CRO computer system from July 19, 2001, until they were electronically transmitted to Purdue Pharma on December 22, 2000, in a SAS file. You did not monitor these data while they were collected at the CRO to assure accuracy and completeness.

   b. Primary efficacy data collected in study HMP-3005 were transmitted directly to you without being retained at the clinical investigator site. There was no documentation that the clinical investigator and the test-subject-verified-changes made to the study efficacy data.

   c. SOP for Verification of Electronic Data Transmissions, CDM-01-03.00 effective October 27, 1997, Section 2.1, requires that electronic data be re-transmitted to the source in the original format for verification and certification by the source. There is no documentation that the electronic data, which were used as the efficacy data (files avepain2.dat and avepain3.dat) in support of Clinical Study HMP-3005 were verified.

   d. The — data base which maintains data used in support of Clinical Study HMP-3005 has no electronic audit trail to indicate if the database was changed from "locked" to "unlocked," only the final "lock" date is retained.

e. Changes made to the computerized — ' database software used to maintain electronic data at Purdue Pharma were subject only to "partial" validation after changes as identified CCR #47 and CCR #15. Change Control documentation lacks sufficient detail to justify the "partial" re-validation in lieu of full system re-validation.

As noted in 1. above, you must conduct a new adequate and well-controlled study in the setting of chronic pain, with multiple dosing, that demonstrates superiority over placebo or another control in order to establish the efficacy of your product. The deficiencies that are listed in the FDA form 483 must be corrected in this new study.

3. The following comments pertain to the stability and expiration dating period for the drug product.

a. The statistical analysis (general linear models) of the [ ] mean 8-hour dissolution data provided, failed to support your proposed expiration dating period.

1) For the batches on stability at [ ], each data set showed a statistically significant slope. In order to assess whether this stability problem is due to the excursion in temperature and humidity that occurred at [ ] provide the following:

(a) An analysis of the first [ ] mean 8-hour dissolution data via general linear models. The various factors [strength, package types (four different bottle sizes and blister packs), the nested lot factor, and the matrixed nature of time] need to be considered in the models. Subsetting the data by package type may be appropriate. The model considering all relevant factors and interactions may be reduced if terms can be pooled (in the proper sequence) at alpha=0.25. One-sided 95% confidence limits for the individual observation should be fitted around the final regression line(s).

(b) An analysis of all [ ] 8-hour dissolution data for the drug product stored at — at 30°C/ — RH with the same approach as noted in (a) above.

2) For batches on stability at Totowa, some data analysis indicated that some future batches will fall outside the acceptance criteria (lower as well as higher) for mean dissolution at 8 hours at any time point. Provide a correction for this problem (e.g., tightening of release acceptance criteria for dissolution).

b. There was a decrease in dissolution of the drug product stored at [ ] as early as [ ] and in the batches stored at [ ] (after environmental excursion up to [ ] at [ ]

1) Provide additional stability data, e.g., short term [ ] at temperatures between [ ] under low and high relative humidity. The data will be used to support the stability of dissolution of the drug product when exposed to the environmental

excursions of temperature and humidity, which may occur in distribution. As appropriate, provide steps (e.g., labeling, shipping controls, expiration dating period adjustments) to ensure that the drug product remains within the dissolution specification during distribution and patient use.

2) Provide an investigation into the cause [ ] of the instability of drug product dissolution, and indicate the controls [ ] which will ensure the reproducible stability of the drug product under excursions of temperature and humidity.

4. Provide an updated drug product specification sheet.

5. Provide a post-marketing study commitment to evaluate the carcinogenic potential of hydromorphone hydrochloride. You are encouraged to initiate these studies as soon as possible. Your commitment should include the following information:

[

]

6. Provide a post-marketing study commitment to evaluate the potential effects of hydromorphone hydrochloride on fertility (Segment I). The timeline information should follow the scheme delineated in item 5.

7. Provide a post-marketing study commitment to evaluate the potential effects of hydromorphone hydrochloride on the pre-and post-natal development (Segment III). The timeline information should follow the scheme delineated in item 5.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-7440.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II

Center for Drug Evaluation and Research

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

/s/

Cynthia McCormick
10/4/01 07:23:12 PM

Fong

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-044

DEC 2 9 1999

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

Attention: James H. Conover, Ph.D.
Executive Director, U.S. Regulatory Affairs

Dear Dr. Conover:

Please refer to your new drug application (NDA) dated December 28, 1998, received December 29, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Palladone ™ (hydromorphone hydrochloride extended-release) capsules, 12, 16, 24, and 32 mg.

We acknowledge receipt of your submissions dated February 12; March 5 and 8; April 16 and 29; July 15, 20, and 23; August 3, 12, and 26; September 15 and 30; November 11, 17, and 18, 1999.

We have completed the review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

1. The data submitted in this application do not demonstrate the effectiveness of hydromorphone hydrochloride 12, 16, 24, and 32 mg extended-release capsules. Study HD96-0505, using both an active and placebo control, was the only adequate and well-controlled study submitted in support of efficacy in this application. While on the surface and by your report, this study appeared to provide the necessary statistical evidence of superiority of hydromorphone over placebo based on the chosen methods, you have not adequately identified the final methods and explained how these methods were chosen and applied to the analysis of the primary endpoint, fentanyl consumption. Based on our review, the generalized least-squares test applied as part of a mixed-effects, repeated-measures analysis of variance has been incorrectly applied. The standard errors of the estimated treatment effects have been underestimated and the significance levels have therefore been overstated. We do not concur with your conclusions and do not agree that Study HD96-0505 provides evidence of the effectiveness of this new formulation of hydromorphone.

   The two active-control studies using immediate release hydromorphone did not demonstrate a statistically significant difference between Palladone and the immediate-release hydromorphone formulation on the primary outcome measures. Since the test drug did not demonstrate any difference from the comparator, any conclusions about its efficacy under these test conditions are speculative.

You must perform at least one adequate and well-controlled study in the setting of chronic pain, with multiple dosing, that demonstrates superiority over placebo or another control in order to establish the efficacy of your product. In addition, evidence must be provided to support the effectiveness of all proposed doses, particularly the lowest dose, 12 mg, throughout the entire dosing interval.

2. The proposed dissolution method is acceptable. However, the proposed dissolution specifications dated November 11, 1999 (Table 1), are considered too wide and are not acceptable. The dissolution specifications need to be tightened as follows.

Table 1: Dissolution Specifications—All four proposed strengths of Palladone™ Capsules

Time (hours)	Lower limit (%)	Upper limit (%)

However, if you would like to use the November 11, 1999, proposal as the final dissolution specifications, provide adequate justification for your proposed specifications, based on existing in vivo data or additional bioequivalence testing performed on lots with such dissolution data.

3. Provide certification that the packaging used in the stability studies and the to-be-marketed product is in compliance with 16 CFR 1700.14(a)(4) for controlled drugs.

4. The established name, hydromorphone hydrochloride controlled-release capsules, must be revised to hydromorphone hydrochloride extended-release capsules, to comply with the USP/NF compendial standards.

5. The name [redacted] is unacceptable. You may wish to retain the name Palladone without the — suffix.

Labeling comments will be provided following review of your response to this letter.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you have regarding your new drug at the time of resubmission. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission

Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Debbie Fong, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cynthia G. McCormick MD

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-044
HFD-170/Div. Files/DFS
HFD-170/D. Fong/C. Schumaker
HFD-170/C. McCormick
B. Rappaport
M. Scheinbaum
A. D'Sa
P. Maturu
L. Jean
K. Haberny
T. Permutt
M. Klein
HFD-870/R. Uppoor
S. Kim
HFD-002/J. Jenkins
HFD-95/DDMS
HFD-102/ADRA
HFD-40/DDMAC
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: I. Kumar for D. Fong 12-27-99 12:15pm
Revised: 12/20/99, 12/21/99, 12/22/99 D. Fong; 12/23/99 per C. Schumaker, D. Fong, B. Rappaport; 12/27/99 C. McCormick; 12/28/99 per I. Kumar, R. Uppoor, C. McCormick; 12/29/99 per D. Fong, C. McCormick, I. Kumar
Initialed by: A. D'Sa, R. Uppoor 12/28/99; M. Scheinbaum 12/29/99
Final: C. Schumaker
Filename: 21-044 (PPLP) AE LTR 12-29-99.doc

I. Kumar for CS 12/29/99
3:30p

APPROVABLE (AE)

Phase 4 (later)
1. Perform studies in populations of patients younger than 18 to define appropriate pediatric usage.
2. [ ]
3 Additional Mutagenicity studies

35 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

X § 552(b)(5) Draft Labeling