



NDA 205777

**NDA APPROVAL**

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

Attention: Edward Liao, Pharm.D.  
Director, Regulatory Affairs

Dear Dr. Liao:

Please refer to your New Drug Application (NDA) dated September 22, 2013, received September 23, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TARGINIQ ER (oxycodone hydrochloride/naloxone hydrochloride extended-release tablets).

We acknowledge receipt of your amendments dated October 14, 21, 22, 25, 28, 30, and 31, December 9 (2), 24, and 30, 2013, and January 7, 14, 22, and 30, February 14 and 26, March 19 and 24, April 1, 10 (2), 16, 17, and 30, May 8 (2), 20, 22, and 27, June 5, 18, and 25, and July 21, 2014.

This new drug application provides for the use of TARGINIQ ER (oxycodone hydrochloride/naloxone hydrochloride extended-release tablets) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**WAIVER OF HIGHLIGHTS SECTION**

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels that were submitted on June 25, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 205777.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 7 years because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients with chronic pain in this age group is extremely small.

We are deferring submission of your pediatric studies for ages 7 to less than 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

- 2762-1. Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of oxycodone hydrochloride/naloxone hydrochloride extended-release tablets in patients from ages 7 to less than 17 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Final Protocol Submission:	12/2014
Study Completion:	12/2018
Final Report Submission:	06/2019

Submit the protocol to your IND 070851, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of misuse, abuse, addiction, hyperalgesia, overdose, and death associated with the long-term use of extended-release or long-acting (ER/LA) opioid analgesics, of which TARGINIQ ER (oxycodone hydrochloride/naloxone hydrochloride) is a member; to identify an expected serious risk of exposure to a potentially genotoxic compound, i.e., cancer; or to identify an unexpected serious risk of cardiovascular thromboembolic events. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

- 2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term

use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

- a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.
- b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission:	08/2014
Study Completion:	01/2018
Final Report Submission:	06/2018

- 2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	11/2015

- 2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	11/2015

- 2065-4 Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	11/2015

Please note the following considerations regarding the postmarketing requirements detailed above. Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate. Because many of the risk factors for misuse, abuse, addiction, overdose, and death cannot be captured using administrative databases alone, FDA is unlikely to find adequate protocols or strategies that evaluate administrative databases only as meeting the objectives outlined above.

We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on the above studies to provide the best information possible.

FDA has determined that you are also required to conduct the following individual post-marketing studies of Targiniq ER (Oxycodone hydrochloride and naloxone hydrochloride) extended release tablets.

- 2762-2. Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of TARGINIQ ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of TARGINIQ ER (oxycodone hydrochloride/naloxone hydrochloride). To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013), and proposed study populations and drug comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	07/2015
Study Completion:	07/2019
Final Report Submission:	01/2020

- 2762-3. Conduct a combination in vivo micronucleus and comet assay for [REDACTED]. [REDACTED] The comet assay portion of the study should include assessment of both stomach and liver tissue and include doses of the drug substance that would be obtained at the maximum recommended daily dose of the drug product and result in adequate toxicity to ensure assay validity.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	12/2014
Study Completion:	04/2015
Final Report Submission:	09/2015

- 2762-4. A postmarketing observational cohort study comparing TARGINIQ ER (oxycodone hydrochloride/naloxone hydrochloride) to other drugs approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The study's outcome is serious cardiovascular thromboembolic events; a concise case definition should be provided. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to TARGINIQ ER (oxycodone hydrochloride/naloxone hydrochloride) -exposed patients. Design the study around a testable hypothesis to assess, with sufficient

sample size and power, a clinically meaningful increase in serious cardiovascular thromboembolic risk above the comparator background rate, using a pre-specified statistical analysis method. For the TARGINIQ ER (oxycodone hydrochloride/naloxone hydrochloride) -exposed and comparator(s)-exposed patients, the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least six months of TARGINIQ ER(oxycodone hydrochloride/naloxone hydrochloride) exposure at the end of the study.

Final protocol submission:	04/2015
Study completion:	04/2019
Final study report:	11/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioids, of which TARGINIQ ER(oxycodone hydrochloride/naloxone hydrochloride) is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this trial:

Final Protocol Submission:	08/2014
Trial Completion:	08/2016
Final Report Submission:	02/2017

We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on this clinical trial to provide the best information possible.

Submit the protocols to your IND 070851, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for TARGINIQ ER to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that TARGINIQ ER poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of TARGINIQ ER. FDA has determined that TARGINIQ ER is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use TARGINIQ ER. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed TARGINIQ ER.

Pursuant to 505-1(f)(1), we have also determined that TARGINIQ ER can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse that are listed in the labeling. The elements to assure safe use will inform and train healthcare providers about the potential risks and the safe use of TARGINIQ ER.



We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on July 21, 2014, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

A single shared system for the elements to assure safe use will be used in the approved REMS. This single shared system, known as the extended-release/long-acting (ER/LA) opioid analgesics REMS, currently includes the products listed on the FDA REMS website available at <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf>. Other products may be added in the future if additional NDAs or ANDAs are approved.

Your REMS must be fully operational before you introduce TARGINIQ ER into interstate commerce.

Because TARGINIQ ER will be a member of the ER/LA opioid analgesics REMS, the assessment plan will be the same assessment plan required for the other products covered by this single shared system. Because the 6-month, 12-month, and 24-month assessments have been submitted, the assessment plan for TARGINIQ ER will align with the fourth and subsequent assessments of the ER/LA opioid analgesic REMS. Therefore, your REMS assessment plan should include, but is not limited to the following:

### **Scheduled REMS Assessments**

1. The fourth and subsequent REMS assessments, due July 9, 2015, and annually thereafter, should include the following information:
  - a. Prescriber Letter 3: 1) number of prescriber letters electronically sent, received, undeliverable, and opened, and 2) number of prescriber letters mailed and undeliverable.
  - b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals, based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:
    - i. Within two years from the time the first REMS-compliant training became available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained;
    - ii. Within three years from the time the first REMS-compliant training became available, 160,000 prescribers (based on 50% of active prescribers) are to have been trained;

- iii. Within four years from the time the first REMS- compliant training became available, 192,000 prescribers (based on 60% of active prescribers) are to have been trained.
- c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by the CE providers to provide the REMS-compliant training .Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) REMS-compliant training not funded under the ER/LA Opioid REMS that will be counted as REMS-compliant training for purposes of meeting the milestones in 1b, and must evaluate:
- i. whether the content of the training covers all elements of the FDA “blueprint” approved as part of the REMS;
  - ii. whether the post-course knowledge assessment measures knowledge of all sections of the FDA “blueprint”; and
  - iii. whether the training was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies
- d. Evaluation of Prescriber Understanding:
- i. The results of an evaluation of ER/LA opioid prescribers’ awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.
  - ii. The results of any long-term evaluation of prescribers of ER/LA opioids who have taken ER/LA Opioid REMS-funded training to determine these prescribers’ knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training.
- e. Evaluation of Patient Understanding: The results of an evaluation of patients’ understanding of the serious risks of these products and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients.
- f. Surveillance Results: Results of surveillance and monitoring for misuse, abuse, overdose, addiction, and death. Surveillance needs to include information on changes in abuse, misuse, overdose, addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency departments, addiction treatment centers, poison control call centers). The information should be drug-specific whenever possible.

- g. Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioids, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills;
- h. Patient Access: An evaluation of changes in patient access to ER/LA opioids.
- i. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.
- j. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Definitions: For purposes of these REMS assessments, the following definitions apply:

1. *REMS-compliant training*: Training will be considered “REMS-compliant training” if 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA “blueprint”, 3) it includes a post-course knowledge assessment of all of the sections of the “FDA blueprint”, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.
2. *FDA Blueprint*: A document entitled, “Blueprint for Prescriber Continuing Education Programs Extended-Release and Long-Acting Opioids,” approved as part of this REMS, that contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioids.

### **Other REMS Assessment Requirements**

Under section 505-1(g)(2)(C), FDA may require the submission of a REMS assessment if FDA determines that that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug or minimize the burden on the health care delivery system of complying with the strategy.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the

submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 205777 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 205777 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 205777  
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 205777  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **EXPIRY DATING PERIOD**

A 24-month expiry dating period is granted for TARGINIQ ER, all dosage strengths in 100-count high density polyethylene (HDPE) bottles, when stored at 20° to 25°C (68° to 77°F) with excursions permitted from 15° to 30°C (59° to 86°F).

While the quality of the drug product meets criteria for approval, we remind you to submit further data as outlined below and agreed to in your amendment dated April 30, 2014, to demonstrate continued quality control for the drug substance and the drug product. Submit full reports, addressing each item and provide supporting data, in your first annual report, by September 1, 2015.

1. You will work with drug substance supplier(s) to tighten the proposed acceptance criteria for individual impurities (e.g., (b) (4) to reflect the data and to meet the ICH Q3A–recommended levels. Submit revised acceptance specifications for drug substances and include references to the nonclinical qualification studies as needed.
2. You will reevaluate the currently proposed drug product acceptance criteria for individual and total impurities to reflect the data representative of to-be-marketed product and to comply with ICH Q3B–recommended thresholds. We request that you submit one specification sheet for each strength of the drug product, specifying differences between the release and stability testing attributes, methods and acceptance criteria, as needed.
3. You will submit a statistical evaluation of the stability data for drug product supporting the proposed acceptance criteria and the requested expiry period. Discuss observed instability trends and provide graphic comparison of impurity profiles for drug product batches manufactured with naloxone HCl obtained from (b) (4) (old process), (b) (4) (new process) and from (b) (4). Clearly identify which batches are the most representative of the marketed product (the same formulation, manufacturing, container closure and tablet count) and focus your analysis and the proposed acceptance criteria on these batches.

### **REPORTING REQUIREMENTS**

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 Lisa Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling  
Carton and Container Labeling  
REMS

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

/s/  
-----

BOB A RAPPAPORT  
07/23/2014