DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021897/S-015

SUPPLEMENT APPROVAL

Alkermes, Inc.
852 Winter Street
Waltham, MA 02451-1420

Attention: Dennis Bucceri
Vice President, Regulatory Affairs

Dear Mr. Bucceri:

Please refer to your supplemental new drug application (sNDA) dated April 12, 2010, received April 12, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Vivitrol (naltrexone for extended-release injectable suspension).

We acknowledge receipt of your amendments dated April 28, May 7, July 6, 9, and 29, August 10, 13, 19 (2), and 26, September 7, 24, 28, and 30 (2), and October 4, 5 and 8, 2010. We also acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated October 5, 2010.

This supplemental new drug application proposes a new indication for Vivitrol for the prevention of relapse to opioid dependence, following opioid detoxification, and a proposed modification to the approved REMS.

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

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, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert, Medication Guide and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on September 30, and October 5, 2010, 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 titled "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 "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 21897/S-015**." Approval of this submission by FDA is not required before the labeling is used.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 11 years because the necessary studies are impossible or highly impracticable. This is because of the low prevalence of opioid addiction in this pediatric population that is appropriately treated with antagonist therapy.

We are deferring submission of your pediatric study for ages 12 to 16 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1694-1 To conduct a study to determine the multiple-dose pharmacokinetics (PK) of Vivitrol in pediatric patients in order to determine the appropriate doses for pediatric patients ages 12 through 16. The PK study will be conducted following a postmarketing assessment of the use of Vivitrol in pediatrics ages 12 through 16.

Final Protocol Submission:	January 31, 2012
Study/Trial Completion:	January 31, 2013
Final Report Submission:	March 31, 2013

1694-2 To conduct an efficacy study to determine the effectiveness of Vivitrol in pediatric patients ages 12 through 16.

Final Protocol Submission:	May 31, 2013
Study/Trial Completion:	June 30, 2014
Final Report Submission:	September 30, 2014

Submit all clinical protocols to your IND 061138. Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)**".

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.

While the US population meeting criteria for alcohol dependence is approximately two-thirds male, the population meeting criteria for opioid dependence is more evenly distributed across genders. Therefore, after approval of this supplement, more female patients are expected to receive treatment with Vivitrol. Because serious injection site reactions appear to occur disproportionately in female patients, the number of such reactions may be expected to increase after marketing for the new indication. Specialized follow up and periodic analysis of the adverse event reports will provide information necessary to understand the factors contributing to these reactions to better characterize the population at risk.

In summary, since Vivitrol was approved on April 13, 2006, and with the approval of this supplemental application, we have become aware of the potential for an increased number of serious injection site reactions in female patients treated with Vivitrol, based on the broadening of the treatment population. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 a known serious risk of injection site reactions and to determine the characteristics of patients who are at risk for development of these reactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

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

1694-3 An assessment and analysis of spontaneous reports of injection site reactions associated with Vivitrol. Following approval, and according to the following timetable, submit the reports (containing both interval-based and comprehensive data) analyzing spontaneous adverse event reports received that describe serious skin reactions. Specialized follow-up should be obtained on these cases to collect additional information on the event. The summaries of reported cases of injection site reactions should include an analysis of patient factors, provider factors and administration technique factors, or any other information that may lead to improved directions for patient selection, needle selection, or administration technique to reduce the risk of serious injection site reactions. When available, provide summaries of pathology and surgical reports.

Semi-annual Report Submissions:	04/2011
	10/2011
	04/2012
	10/2012
Annual Reports Submissions:	10/2013
	10/2014
Final Report Submission:	10/2015

Patient, provider, and administration technique factors should include, but not be limited to, the following:

Patient:
- Weight
- Waist and hip circumference
- BMI
- Gender
- Indication

Provider:
- Medical qualifications
- Dedicated training on administration procedures

Administration technique:
- Needle length selection
- Precise location of injection

Submit all report(s) 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 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 investigation 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

The REMS for Vivitrol (naltrexone for extended-release injectable suspension) was originally approved on March 22, 2010. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of a revised Medication Guide with additional information about the risks associated with the use of Vivitrol for the treatment of opioid dependence.

The proposed modified REMS, submitted on October 5, 2010 and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on March 22, 2010.

There are no changes to the REMS assessment plan described in our March 22, 2010 letter.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in

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