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VIA HAND DELIVERY

July 11, 2011

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. FDA–2007–D–0369
Draft Guidance for Industry Describing Product-Specific Bioequivalence Recommendations for Naltrexone Extended Release Suspension/Intramuscular

Dear Sir or Madam:

Alkermes, Inc. ("Alkermes") respectfully submits the following comments on the Food and Drug Administration's ("FDA") draft product-specific bioequivalence recommendations for naltrexone extended release intramuscular ("IM") injection.[1] Alkermes developed, manufactures, and markets Vivitrol® (naltrexone for extended release injectable suspension), the reference listed drug that serves as the basis for the draft guidance document.

Alkermes is a fully integrated pharmaceutical and biotechnology company that develops medicines designed to yield better outcomes and improve patients' lives. Our products, which integrate both novel and well-known molecules and innovative drug delivery technologies, target widespread diseases including addiction, central nervous system disorders, and diabetes. We partner with the world's leading pharmaceutical companies to manufacture and market the products we develop, and also work independently to commercialize our own products.

Alcohol and opioid dependence are chronic, life-threatening diseases that affect a growing number of Americans – approximately nine million Americans are dependent on alcohol, and

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[1] The agency's draft recommendations are available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM179182.pdf.

approximately 1.6 million are dependent on opioids.[2] Vivitrol is the first and only non-narcotic, non-addictive product approved by FDA for the treatment of alcohol dependence and for the prevention of relapse to opioid dependence, following opioid detoxification. It is designed to deliver therapeutic levels of naltrexone both quickly and on a sustained basis, to help patients avoid relapse during the early stages of their therapy and then to provide maintenance levels of naltrexone over a full, 30-day dosing cycle.

To achieve the release profile on which FDA's approval is based, Vivitrol relies on a precise formulation of polylactide-co-glycolide ("PLG") microspheres, as well as a delivery system that essentially deposits the microspheres locally at the IM gluteal injection site. From the local depot site, the release of the drug is characterized by an initial peak approximately two hours after injection, followed by a second peak approximately two to three days after injection. Plasma concentration levels begin a slow decline at or about day 14. The release of the drug is dependent on, among other factors, the specific composition and formulation of the microspheres and the accompanying diluent, manufacturing and product quality, and the dynamic interaction between the microspheres and the conditions at the IM injection and depot site.

Alkermes appreciates this opportunity to comment on FDA's effort to develop *in vitro* dissolution and *in vivo* bioequivalence methodologies for products that reference Vivitrol. As described below, Vivitrol relies on, and was approved based on, a specific release and absorption profile. Without dissolution and bioequivalence methodologies tailored to these unique properties, FDA risks approving a generic product that fails to match Vivitrol's proven safety and efficacy.

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[2] *See* Substance Abuse and Mental Health Services Administration, Office of Applied Studies, *National Survey on Drug Use and Health* (2009) at: www.oas.samhsa.gov/NSDUH/2k9NSDUH/tabs/Sect5peTabs1to56.htm#Tab5.14A.

I. EXECUTIVE SUMMARY

Vivitrol is a long-acting, modified release injectable drug product that delivers its active ingredient in three, clinically significant phases:

- An "initial phase," during which naltrexone is immediately absorbed from the surface of the formulation's microspheres into the systemic circulation;
- A "hydration phase," during which physical erosion of the microspheres begins, triggering the release of subsurface naltrexone; and
- A "sustained release phase," during which the microspheres steadily erode and allow a constant amount of drug to be absorbed.

Unlike traditional injectable drug products, where pharmacokinetics are driven by the metabolism and elimination of the drugs, the pharmacokinetics of Vivitrol are "flip-flop," driven by the multiphasic release of naltrexone from the Vivitrol microspheres. This multiphasic release profile ensures that circulating naltrexone levels are quickly raised to a therapeutic level and then are sustained over the course of the month-long dosing interval.

The agency's draft recommendations for Vivitrol lack the specificity needed to ensure that proposed generics will indeed be therapeutically equivalent to the reference drug. This can be addressed by improving the guidance in three areas:

First, the draft directs sponsors to an *in vitro* dissolution methodology that is essentially void of any direction or limitations. In contrast, and with the agency's support, Alkermes developed a specific, multipoint *in vitro* methodology that tracks the multiphasic release profile of the product. This unique *in vitro* methodology, which includes sampling at days 1, 7, 14, and 28, should be considered the starting point for any generic sponsor that purports to make a comparable version of Vivitrol.

Second, the draft should be amended to include statistical analysis of additional pharmacokinetic parameters that are necessary to ensure equivalence to a multiphasic, modified release product such as Vivitrol. Vivitrol strikes a careful balance between potent early release of the active drug substance and conserving a sufficient amount of drug to ensure therapeutic maintenance over the full, 30-day dosing cycle. The guidance should be revised so that a generic that releases the same amount of total drug, but does so in different phases or with a different pattern from that of Vivitrol, is not declared bioequivalent.

Third, the guidance should be revised to address the need to show no significant difference in injection site reactions. Vivitrol deposits a substantial amount of drug product at or about the local injection site, for a substantial amount of time. The injection site tolerance and safety of the drug is dependent on local interactions that cannot be characterized solely by analysis of formulation and *in vivo* systemic pharmacokinetics. As the agency has done with other local products, including transdermal systems, FDA should include an *in vivo* comparative study designed to assess local injection site safety for any proposed generic drug product.

II. BACKGROUND

The agency first approved Vivitrol on April 13, 2006, under new drug application ("NDA") 21-897. Vivitrol is currently approved (a) for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to the initiation of treatment, and (b) for the prevention of relapse to avoid opioid dependence, following opioid detoxification. In both cases, treatment with Vivitrol should be part of a comprehensive management program that includes psychosocial support.

The active ingredient in Vivitrol, naltrexone, is microencapsulated in a high molecular weight 75/25 PLG polymer at a concentration of 337 mg of naltrexone per gram of microspheres. The diluent is a clear, colorless, odorless solution of carboxymethylcellulose sodium salt, polysorbate 20,

sodium chloride, and water for injection. Each Vivitrol unit is packaged with one, 380 mg vial of Vivitrol microspheres, one vial containing 4 mL (to deliver 3.4 mL) of diluent, one 5 mL prepackaged syringe, one 1 inch 20-gauge preparation needle, two 1.5 inch 20-gauge administration needles, and two 2 inch 20-gauge administration needles. Physicians are instructed to reconstitute the microsphere suspension using the diluent and the 1 inch preparation needle, and then to administer the product as an IM gluteal injection, using only the needles provided, alternating sides for subsequent injections.[3] The recommended dose is one injection every four weeks or once a month.

Naltrexone is an opioid antagonist with affinity for the mu opioid receptor. The competitive occupation of opioid receptors by naltrexone markedly attenuates or completely blocks the subjective effects of exogenous opioids. Vivitrol is not associated with the development of tolerance or dependence. However, in subjects physically dependent on opioids, Vivitrol will precipitate withdrawal symptoms. The reversible blockade produced by Vivitrol is potentially surmountable, but overcoming a full blockade by administration of exogenous opioids may result in non-opioid receptor-mediated symptoms such as histamine release. The mechanisms responsible for the reduction in alcohol consumption observed in alcohol-dependent patients are not entirely understood. However, preclinical data suggest the involvement of the endogenous opioid system.

After a single IM injection of Vivitrol, there is an initial drug release phase, which takes place over the first 24 hours after dosing. During this time, water uptake begins at the injection site and the Vivitrol microspheres begin to swell. Naltrexone-catalyzed polymer hydrolysis causes a significant drop in the molecular weight of the microspheres. Naltrexone at or near the surface of the

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[3] The different length administration needles are provided to accommodate varying body physiques, given the importance of administering the drug as an IM gluteal injection. As discussed below, inadvertent subcutaneous injection of Vivitrol increases the likelihood of severe injection site reactions. According to Vivitrol's labeling, alternate treatment should be considered for patients whose physiques preclude IM injection with one of the provided needles.

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