Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 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Draft Guidance for Industry Describing Product-Specific Bioequivalence Recommendations for Naltrexone Extended Release Suspension/Intramuscular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 or the Company) respectfully submits these comments in response to the April 2, 2014 notice[1] by the Food and Drug Administration (FDA or the Agency) announcing a draft guidance for industry on product-specific bioequivalence (BE) recommendations for naltrexone extended release intramuscular (IM) injection (the 2014 Draft Guidance).[2] The 2014 Draft Guidance is a revised version of an earlier draft BE guidance for naltrexone extended release IM injection that FDA issued in August 2009 (the 2009 Draft Guidance).[3] Alkermes submitted comments on the 2009 Draft Guidance on July 11, 2011.

Alkermes developed, manufactures, and markets Vivitrol® (naltrexone for extended release injectable suspension), the reference listed drug that serves as the basis for the 2009 and 2014 Draft Guidances. Alkermes is a fully integrated pharmaceutical and biotechnology company that develops medicines designed to yield better outcomes and improve patients' lives. The Company's products, which integrate both novel and well-known molecules with innovative drug delivery technologies, target widespread diseases including addiction, central nervous system disorders, and diabetes.

Alcohol and opioid dependence are chronic, life-threatening diseases that affect a growing number of Americans. Vivitrol is the first and only non-narcotic, non-addictive product approved by FDA for the treatment of alcohol dependence in patients who are able to abstain

[1] 79 FR 18561 (Apr. 2, 2014). The Federal Register notice encouraged the submission of comments on the 2014 Draft Guidance by June 2, 2014.

[2] Food and Drug Administration, Draft Guidance on Naltrexone (Feb. 2014), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM179182.pdf.

[3] A copy of the 2009 Draft Guidance is attached at Tab 1.

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 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 then 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 the 2014 Draft Guidance. The Company recognizes that in this newly revised version of the guidance, the Agency has made the significant addition of recommending that generic sponsors conduct an *in vitro* drug release study. Alkermes supports the addition of this new study. However, further amendment of the 2014 Draft Guidance is needed to assure that any proposed generic products match Vivitrol's proven safety and efficacy profile.

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.

The multiphasic release of naltrexone from the Vivitrol microspheres ensures that circulating naltrexone levels are quickly raised to a therapeutic level and then sustained over the course of the month-long dosing interval. Vivitrol therefore strikes a careful balance between potent early release of the active drug substance and conservation of a sufficient amount of drug

profile of Vivitrol, Alkermes believes that the 2014 Draft Guidance should be further revised in two key respects.

First, consistent with Alkermes' 2011 comments, the *in vivo* study included in the 2014 Draft Guidance should be amended to include statistical analyses of additional pharmacokinetic (PK) parameters that are necessary to ensure equivalence to a multiphasic, modified release, depot product such as Vivitrol. In support of this request, Alkermes has completed a series of *in silico* (computer-based) simulations comparing Vivitrol against potential comparator formulations. These simulations found that the traditional *in vivo* bioequivalence metrics (*i.e.*, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) are inadequate and could lead to non-equivalent generic versions of Vivitrol passing the Agency's proposed BE standards.

Thus, to the extent the 2014 Draft Guidance relies solely on conventional BE measures, the Guidance is insufficient to ensure equivalence. Because matching Vivitrol's *in vivo* release profile is critical for generic products, at least one additional PK parameter is needed to ensure true bioequivalence. As proposed herein, the 2014 Draft Guidance should be revised to include the partial AUC metric AUC_{10-28}. This additional metric is able to detect significant differences in the segment of the concentration-time profile that is most susceptible to potential therapeutic equivalence deficiencies.

Second, also consistent with Alkermes' 2011 comments, FDA should revise the 2014 Draft Guidance to ensure that no significant difference in injection site reactions would exist between Vivitrol and generic products. In particular, the Company asks the Agency to include an *in vivo* comparative study designed to assess local injection site safety for any proposed generic. This injection site study could be conducted as its own stand-alone study, or incorporated as part of the required *in vivo* PK study.

We appreciate FDA's continued efforts to develop guidance and to request public comment on recommended studies for generic drugs. In light of Alkermes' experience with Vivitrol and with sustained release drug formulations, we submit the following comments on the 2014 Guidance for the Agency's consideration.

(a) the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment, and (b) the prevention of relapse to 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. Physicians are instructed to administer the product as an IM gluteal injection, using only the needles provided, alternating sides for subsequent injections.[4] The recommended dose is one injection every four weeks or once a month.

Vivitrol is a long-acting, modified release injectable drug product that delivers its active ingredient in the following 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. The extent of naltrexone released at each of these three clinically important phases is a carefully controlled manufacturing and formulation-dependent variable.

B. *In Vivo* Bioequivalence For IM Depot Products

With regard to the *in vivo* bioequivalence of systemically absorbed drugs, FDA generally recommends that applicants conduct single dose crossover or parallel group PK studies, measuring the concentrations of the generic and reference drugs in the blood or plasma. Applicants then calculate a variety of measurements of the resulting drug concentration versus time curve, including (1) the maximum concentration, C_{max}; (2) the time to maximum concentration, T_{max}; and (3) the area under the curve (AUC), both from dosing until the last measured time point, AUC_{0-t}, and extrapolated to infinity, $AUC_{0-\infty}$. C_{max} and T_{max} are believed to reflect the rate of the drug's absorption into the systemic circulation, and the AUC measures are believed to reflect the extent of the drug's absorption.

[4] Different length administration needles are provided to accommodate varying body physiques, given the importance of administering the drug as an IM gluteal injection.

CR.[7] In citizen petition responses regarding these products, FDA has stated it will require as a condition of ANDA approval that the generic product be BE to the RLD at the 90% confidence interval using appropriately tailored partial AUC metrics in addition to the conventional metrics C_{max}, AUC_{0-t} and AUC_{0-inf}.[8]

Products such as Vivitrol – long acting depot formulations that are injected, and that reside subcutaneously over the course of the dosing interval, releasing drug in a multiphasic and sustained fashion – are a particularly complex extended-release dosage form, and present a new and challenging BE problem. In the past 12 months, FDA has released revised BE guidance documents for several of these products. These revised guidances reflect FDA's ongoing process of addressing the BE challenges such products pose. Collectively, these BE guidances underscore the general principle that additional measures should be required for such products, but that there is no "one-size-fits-all" approach.

For example, in February 2014, in addition to the revised guidance for Vivitrol, FDA issued revised draft BE guidances for Trelstar (triptorelin pamoate for injectable suspension), Lupron Depot (leuprolide acetate for depot suspension), and Sandostatin LAR Depot (octreotide

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[5] *See, e.g.*, FDA Citizen Petition Response, Daytrana, Docket No. FDA-2012-P-0932 (Jan. 23, 2013) at 3 ("FDA recognizes that, under certain circumstances, it may be appropriate to use a partial AUC parameter to ensure comparable therapeutic effects.").

[6] *See generally* Briefing Package for the April 13, 2010 Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, *available at*: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm.

[7] *See* Draft Guidance on Methylphenidate Hydrochloride (Metadate CD) (Sept. 2012); Draft Guidance on Methylphenidate Hydrochloride (Concerta) (Sept. 2012); Draft Guidance on Methylphenidate Hydrochloride (Ritalin LA) (Nov. 2011); Draft Guidance on Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate (Adderall) (Sept. 2012); Draft Guidance on Dexmethylphenidate Hydrochloride (Focalin XR) (Mar. 2012); Guidance on Zolpidem (Ambien CR) (Final) (Oct. 2011). *Available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[8] *See* FDA Citizen Petition Response, Metadate CD and Concerta, Docket Nos. FDA-2004-P-0151 and FDA-2004-P-0290 (July 19, 2012); FDA Citizen Petition Response, Adderall XR, Docket No. FDA-2005-P-0120 (June 22, 2012); FDA Citizen Petition Response, Ambien CR, Docket No. FDA-2007-P-0182 (Oct. 13, 2010). FDA has also required the use of partial AUC metrics in cases where the RLD displays time-dependent localization of absorption within the gastrointestinal tract. *See* FDA Citizen Petition Response, Asacol, Asacol HD and Pentasa, Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507 (Aug. 20, 2010).

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