DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

SEP 18 2014

John C. Kulli, M.D.

exempt 6

RE: Docket No. FDA-2006-P-0453[1]

Dear Dr. Kulli:

This letter responds to your citizen petition, received on August 31, 2006 (Petition), regarding the abuse of central nervous system (CNS) stimulant drugs such as Adderall (amphetamine-dextroamphetamine), Concerta (methylphenidate), Ritalin (methylphenidate), Dexedrine (dextroamphetamine sulfate) and Focalin (dexmethylphenidate hydrochloride). Specifically, you request that the Food and Drug Administration (FDA or Agency) issue a regulation requiring drug manufacturers to reformulate CNS stimulant drugs, including generic[2] versions, to deter illegal use of these drugs.

For the reasons set forth below, FDA denies your petition. The Agency agrees that the abuse and misuse (collectively referred to in this response as "abuse") of controlled substances, including CNS stimulant drugs, present a serious public health concern, and we support efforts by drug manufacturers to modify formulations to reduce the risk of abuse. The Agency, however, declines to issue a general requirement to reformulate all products in this class of drugs at this time, and accordingly, we are denying your petition. We intend to continue to monitor abuse associated with CNS stimulant drug products, and will take regulatory action if appropriate.

I. BACKGROUND

A. CNS Stimulant Drugs

CNS stimulant drugs have been a component of the treatment of behavior and attention disorders in children in the United States since the first such drug was approved in 1955.[3] Since that time, FDA has approved several CNS stimulants for the treatment of what is now generally referred to as Attention Deficit/Hyperactivity Disorder (ADHD). According to the National Institutes of Health, ADHD is one of the most common disorders among children,

[1] This citizen petition originally was assigned docket number 2006P-0364. The number changed to FDA-2006-P-0453 as a result of FDA's transition to its new docketing system in January, 2008.

[2] The term "generic" is used in this petition response to refer to drug products for which approval is sought in an abbreviated new drug application submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(j)).

[3] Ritalin, the subject of NDA 10187, was first approved on December 5, 1955. In the Federal Register of October 7, 1970 (35 FR 15771), FDA announced that, under the Drug Efficacy Study Implementation (DESI) program, the Agency had determined that Ritalin was effective in the treatment of narcolepsy and hyperkinetic behavior disorders in children (DESI 10187).

and it can continue through adolescence and adulthood.[4] The specific CNS stimulants named in the Petition are controlled under Schedule II of the Controlled Substances Act (CSA), which is reserved for drugs with a high potential for abuse.

B. FDA's Support of the Development of Abuse-Deterrent Formulations of Controlled Prescription Drugs

FDA encourages the development of abuse-deterrent formulations of drugs with potential for abuse and works closely with the sponsors of potentially abuse-deterrent drugs on a product-by-product basis.

Since your petition was submitted, FDA has issued two draft guidances relevant to the development of abuse-deterrent formulations of controlled prescription drugs. The first, *Assessment of Abuse Potential of Drugs,* is about submitting an abuse potential assessment and proposal for scheduling under the CSA, and also discusses the design and implementation of studies that may be used to help assess whether a proposed abuse-deterrent formulation can be expected to reduce a product's abuse potential relative to an appropriate comparator product.[5] The second draft guidance is specific to opioids. *Abuse-Deterrent Opioids – Evaluation and Labeling* describes FDA's recommendations regarding the data that should be provided to demonstrate that a formulation of an opioid drug product has abuse-deterrent properties, how those data will be evaluated by the agency, and what labeling claims may be approved based on the data.[6]

FDA has devoted significant effort to developing the regulatory science of evaluating potentially abuse-deterrent drugs, and continues to explore ways in which it could further encourage sponsors to develop drug products with the potential to deter abuse. FDA takes appropriate regulatory actions regarding potentially abuse-deterrent products on a case-by-case basis.

II. DISCUSSION

You state that as currently formulated, CNS stimulant drugs lend themselves to abuse because they can be converted into a powder that can then be insufflated ("snorted") or

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[4] See NIH's ADHD Web page, available at http://www.nimh.nih.gov/health/publications/attention-deficit-hyperactivity-disorder/complete-index.shtml.

[5] See the draft guidance for industry on *Assessment of Abuse Potential of Drugs* (Abuse Potential Guidance) (Jan. 2010) at pages 8-9, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

[6] See the draft guidance for industry on *Abuse-Deterrent Opioids - Evaluation and Labeling* (Jan. 2013) (Abuse-Deterrent Opioids draft guidance), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. This draft guidance was produced following mandates in the White House prescription drug abuse plan, *Epidemic: Responding to America's Prescription Drug Abuse Crisis* (2011), available at http://www.whitehouse.gov /sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf, and the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. Law 112-144 (section 1122(c)).

dissolved in water and injected. You request that FDA require drug manufacturers to reformulate CNS stimulant drugs to make it difficult for these drugs to be converted into a powder. You maintain that requiring these drugs to be reformulated as you propose would reduce the likelihood that they would be used for illicit purposes.[7] You suggest several possible methods of reformulation of these drugs that you believe might render them abuse-deterrent, including use of gels, insoluble oils, chemicals to make insufflation painful, or transdermal patch dosage form technology.

Although we support and encourage development of abuse-deterrent formulations of all prescription drugs with potential for abuse, including CNS stimulant drugs, we do not believe that a general reformulation requirement for all drugs in this class, as the petition requests, is appropriate at this time. The science of abuse deterrence is relatively new. Both the drug and formulation technologies involved, as well as the clinical, epidemiological, and statistical methods for evaluating those technologies, are rapidly evolving. As your petition acknowledges, there are drawbacks or limitations to each of the abuse-deterrent technologies that you mention. For example, although adding a chemical to the drug product might make it unpleasant to insufflate, it might also have the unintended consequence of making the tablet unpalatable or causing allergic reactions in susceptible patients. Your petition also acknowledges that transdermal patches, while not readily subject to abuse by insufflation or injection, are not an appropriate therapeutic choice in many instances.

FDA will continue to assess the benefit-risk profile of each CNS stimulant drug product, including the risk of abuse, on a case-by-case basis. Imposing a general reformulation requirement as you have requested would be inconsistent with this approach.

III. CONCLUSION

In summary, FDA encourages the development of abuse-deterrent formulations of controlled drugs. For the reasons described above, however, we do not think that it is appropriate at this time to require reformulation of CNS stimulant products as requested in the petition.

Accordingly, the petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[7] We note that these drugs can also be abused by taking them orally, i.e., without converting them to a different form. Since the Petition does not discuss oral abuse, we do not address it in this response.