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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition under 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs require an applicant of an abbreviated new drug application (ANDA) submitted for mixed salts of a single entity amphetamine product to conduct the necessary testing, including assessment of in vivo bioequivalence, to assure strict equivalence with key pharmacokinetic parameters of the reference listed drug (RLD), ADDERALL®, so that the safety profile, including dependence and abuse characteristics of the ANDA product, are the same as the RLD. The safety profile of a drug product also has bearing on its efficacy.

For both the d- and l-isomers of amphetamine, the maximum plasma drug concentration (C_{max}), the total drug exposure represented by the area under the plasma drug concentration vs. time curve (AUC), and the rate of rise of plasma concentration should be no greater, and the time to maximum concentration (T_{max}) no shorter, than the RLD. Variation from the reference drug's characteristics poses a potential risk to public health associated with drug dependence and abuse. In addition, an ANDA that fails to provide the aforementioned assurances fails to satisfy the "same as" statutory and regulatory requirements and, thus, must be rejected.

A. Action Requested

The undersigned requests that the Commissioner require an applicant for an ANDA for mixed salts of a single entity amphetamine product to conduct the necessary testing, including assessment of bioequivalence, to assure strict equivalence with

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key pharmacokinetic parameters of the RLD, ADDERALL®, so that the safety profile, including dependence and abuse characteristics of the ANDA product are the same as the RLD.

B. Statement of Grounds

Background: Attention Deficit/Hyperactivity Disorder (ADHD) is among the most prevalent chronic health conditions affecting school-age children and it often persists into adolescence and adulthood. The American Academy of Pediatrics has estimated the prevalence of ADHD to be up to 10% in school-age populations. *See* "American Academy of Pediatrics, Clinical Practice Guideline: Diagnosis and Evaluation of the Child with Attention-Deficit/Hyperactivity Disorder." *Pediatrics* 2000;105:1158–1170. This disorder causes significant impairment across multiple settings, including home, school, work, and social environments. The prevalence, chronic nature, and functional impairments associated with ADHD make it a major public and professional health concern.

Stimulant medications are highly efficacious in ameliorating the symptoms of ADHD and remain first-line agents for treatment. *See* MTA Cooperative Study Group, "Fourteen-month randomized clinical trial of treatment strategies for attention deficit hyperactivity disorder." *Arch Gen Psychiatry* 1999;56:1073–1086; Pliszka SR, et al, "The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on medication treatment of childhood attention-deficit/hyperactivity disorder." *J Am Acad Child Adolesc Psychiatry* 2000;39:908–919; Conners CK, et al, "Treatment of attention-deficit/hyperactivity disorder: expert consensus guidelines." *Journal of Attention Disorders* 2001;4(suppl 1):S1–S128; "American Academy of Pediatrics, Clinical Practice Guideline: Treatment of the school-aged child with attention-deficit/hyperactivity disorder." *Pediatrics* 2001;108:1033–1044.

Abuse Potential: Stimulant medications are known to have a high potential for abuse that may lead to drug dependence. This information is clearly enunciated in product labeling warnings. Risk of diversion has been reduced by the recent introduction of once-daily dosage forms of stimulant medications. These formulations are the current state-of-the-art and allow control of storage and administration to remain with the parent or primary caregiver. However, with any stimulant medication, several factors are associated with an increased risk of dependence and abuse.

The abuse potential of a drug is mainly determined by five factors: the intrinsic pharmacological action of the drug; the availability or market exposure; the recommended and prescribed dose; patient-related factors; and the pharmacokinetic profile of the drug in question. *See* Busto UE, Sellers EM, "Pharmacokinetic

determinants of drug abuse and dependence. A conceptual perspective." *Clin Pharmacokinet* 1986;11:144–153; Busto UE, Lanctot KL, Bremner KE, Sellers EM. "Benzodiazepine kinetics contribute to their differential abuse." *Can J Clin Pharmacol* 1995;2:23–28. International and national criteria for scheduling and control of drugs with abuse liability and dependence potential consider pharmacokinetics to be important in the review process. *See* "World Health Organization EB85/1990/REC/1, Annex 7."

Pharmacokinetic factors partially explain different abuse liabilities of drugs within the same class. Rapid delivery of the drug to the brain (by rapid absorption or intravenous injection) provides the optimal conditions for reinforcing properties and drug readministration. Intravenous drugs consistently show higher abuse liability than oral drugs. Volkow et al investigated the brain pharmacokinetics of intravenous methylphenidate (Ritalin) and cocaine in the human brain. *See* "Volkow ND, et al., "Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain." *Arch Gen Psych*;52:456–463. They found that the fast uptake in the striatum of the drugs studied paralleled the experience of the "high." Shorter time to peak plasma levels also explains the greater abuse liability and physical dependence associated with illicit drugs taken intravenously as compared to when taken orally (e.g., methamphetamine).

If a drug with dependence liability is absorbed rapidly and completely, its effects appear more quickly, and are thus preferred to drugs that are more slowly absorbed. Absorption rate also affects the onset of drug metabolism and this is particularly important when metabolite(s) of the parent drug have intrinsic activity.

More rapid absorption is indicated on a kinetic profile by a more rapid rise of the plasma drug concentration per unit time during absorption, a shorter time to maximum concentration (T_{max}), a higher peak plasma drug concentration (C_{max}) or a higher area under the plasma drug concentration vs. time curve (AUC) during the absorption phase. The relationship between pharmacokinetic parameters and abuse risk or liability has been shown for stimulants, opiates, benzodiazepines and barbiturates. *See* Busto and Sellers. *Clin Pharmacokinet* 1986;11:144–153; Busto et al. *Can J Clin Pharmacol* 1995;2:23–28.

Among oral drugs, even small differences in absorption rate are associated with differences in abuse liability. For example, there is a strong correlation between abuse risk of selected benzodiazepines and absorption rate, where a shorter time to peak was associated with greater risk. *See* Busto et al. *Can J Clin Pharmacol* 1995;2:23–28. Kollins investigated acute behavioural effects of orally administered sustained-release (SR) methylphenidate (20 to 40 mg), immediate-release (IR) methylphenidate (20 to 40 mg), and placebo in healthy volunteers. *See* Kollins SH, Rush CR, Pazzaglia PJ, Ali JA, "Comparison of acute behavioral effects of sustained-

release and immediate-release methylphenidate." *Exp Clin Psychopharmacol* 1998;6:367–374. Using drug effect questionnaires and performance measures, the immediate-release formulation produced stimulant-like drug effects ("good effects") that, in general, varied as a function of dose and time. In contrast, the sustained-release formulation produced only transient effects on these measures. *These data demonstrate that absorption rate is an important determinant of abuse liability for orally administered stimulants.*

Adderall® is an immediate-release product, a mixture of d- and l- amphetamine isomers in a 3:1 ratio. The kinetics of the d- and l-isomers are well characterized and have been carefully studied. Because of the importance of absorption kinetics to the potential abuse liability of d- and l- amphetamine containing products, it is essential that all new products containing this active drug have a detailed, *in vivo* human pharmacokinetic study performed which compares the new product to the established standard. The study should focus on bioequivalence parameters and a careful comparison of the absorption profiles of the standard and test products. In vitro dissolution studies are not adequate or appropriate. Because both the d- and l-isomers are active, the kinetic comparisons should be for both isomers. See Smith RC, Davis JM, "Comparative effects of *d*-amphetamine and *l*-amphetamine, and methylphenidate on mood in man." *Psychopharmacology* 1997;53:1–12.

On the basis of evidence showing (1) a link between faster absorption and increased abuse risk, (2) the nature of the differences in dependence liability of drugs administered intravenously and orally, and (3) acute behavioral differences observed after administration of other immediate release and sustained/extended release stimulant formulations, *any new product which has a faster rate of rise of plasma concentration, higher C_{max}, greater AUC, or shorter T_{max} during the absorption phase than the RLD, Adderall®, will have a higher potential for abuse. Such an increase represents a public health risk as it may result in increased diversion and misuse in the general population. On an individual level, initiation or conversion of patients to such a formulation may also compromise patient safety. In addition, such differences can adversely affect efficacy because of the consequences to regimen compliance.*

Although conventional pharmacokinetic parameters do not correlate with the kinetics of reinforcement described here, the slope of the early rise in plasma concentration and the early partial AUC may provide an indication of the dependence risk and be additional tools for setting acceptable ranges for bioequivalence for this special class of medications. In the absence of established ranges for pharmacokinetic predictors of dependence, the kinetic profile of the current reference listed drug, Adderall®, should be considered as acceptable.

In summary, the purpose of this Citizen Petition is to request that FDA require the ANDA applicant to provide assurances that the safety profile, including the risk of dependence and abuse, are no greater than and are, in fact, the same as the RLD.

Preferably, the ANDA applicant should provide comparative clinical evidence showing that the product's safety profile is the same as that of the RLD. In the absence of such data, the petitioner recommends that specific attention be given to the *in vivo* rate of absorption as indicated by the initial slope of the plasma concentration vs. time curve in human subjects, as well as the early partial AUC and T_{max} when reviewing generic versions of the RLD. The petitioner will defer to FDA on other additional criteria that may be required to achieve "same as" status.

An ANDA product with differences in safety and efficacy from the RLD is not the "same as" the RLD and, thus, such an ANDA does not meet the statutory and regulatory requirements for FDA approval.

C. Environmental Impact

As provided in 21 C.F.R. § 25.31, neither an environmental assessment nor an environmental impact statement is required.

D. Economic Impact

As provided in 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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