



AUG 01 2002

4661 '02 AUG -5 P1:18

Alan Minsk, Esq.
Arnall Golden Gregory, LLP
1201 West Peachtree Street
Suite 2800
Atlanta, GA 30309-3450

Re: Docket No. 01P-0585/CP1

Dear Mr. Minsk:

This letter responds to your citizen petition ("Petition") dated December 26, 2001, in which you ask the Food and Drug Administration (FDA) to require that an abbreviated new drug application (ANDA) for mixed salts of a single entity amphetamine product (mixed amphetamine salts) contain evidence of certain testing. In particular, to ensure that the safety profile of the ANDA product, including its dependence and abuse characteristics, is the same as the reference listed drug Adderall, you request that FDA require an ANDA applicant to include an assessment of in vivo bioequivalence to ensure strict equivalence with certain key pharmacokinetic parameters. For both the dextro- and levo-isomers of amphetamine, you state that the maximum plasma drug concentration (C_{max}), the total drug exposure represented by the area under the plasma drug concentration versus 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 those of Adderall. You maintain that variation from the reference listed drug's characteristics poses a potential risk to the public health associated with drug dependence and abuse. You also assert that a drug covered by an ANDA that fails to provide these assurances fails to satisfy the "same as" statutory and regulatory requirements for approval. For the reasons described below, your petition is denied.

Decision Summary

FDA must approve a generic mixed amphetamine salts product if the ANDA applicant provides, among other things, sufficient information to show that the generic mixed amphetamine salts drug product is bioequivalent to Adderall. FDA has discretion in determining what constitutes sufficient information to show that a generic mixed amphetamine salts product is bioequivalent to Adderall.

FDA requests that an ANDA applicant conduct a single-dose in vivo fasting bioequivalence study and assess the pharmacokinetic parameters of d-amphetamine and l-amphetamine separately. In reviewing bioequivalence studies for a generic mixed amphetamine salts product, FDA expects that the 90 percent confidence interval of the geometric ratios of the means for test to reference products for the pharmacokinetic parameters of AUC and C_{max} will fall within the appropriate acceptance limits (i.e., 0.8 - 1.25). If a generic mixed amphetamine salts drug product is bioequivalent and pharmaceutically equivalent and therefore therapeutically

OIP-0585

PDN 1

equivalent to Adderall, then FDA does not expect that there will be any clinically significant differences in rate of absorption or abuse potential.

FDA currently does not expect a proposed generic mixed amphetamine salts drug product to show that the rate of rise of plasma concentration is not greater than that characteristic of Adderall. Similarly, a generic mixed amphetamine salts product is not required to show that T_{max} is no shorter than that of Adderall. In addition, FDA does not find the studies cited in your petition to be persuasive evidence that differences in certain amphetamine pharmacokinetic parameters affect abuse potential in a clinically significant way. Accordingly, FDA does not consider an ANDA applicant's strict adherence to the pharmacokinetic parameters associated with Adderall to be necessary for the approval of a generic mixed amphetamine salts drug product.

I. Adderall

Adderall is a central nervous system (CNS) stimulant indicated for the treatment of attention-deficit/hyperactivity disorder in children and for the treatment of narcolepsy. Adderall consists of the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro (d-) isomer of amphetamine saccharate and dextro-, levo-amphetamine aspartate (d-, l-amphetamine aspartate). The labeling for Adderall contains a boxed warning stating, in part: "AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED."

II. Summary of Statutory and Regulatory Basis for ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), which established the current ANDA approval process. The showing that must be made for an ANDA to be approved is different from what is required in a new drug application (NDA). An NDA applicant must prove that the drug product is safe and effective. An ANDA applicant does not have to prove the safety and effectiveness of the drug product because an ANDA relies on FDA's previous finding that the reference listed drug is safe and effective. In order to rely on this finding, however, an ANDA applicant must demonstrate, among other things, that its generic drug product is bioequivalent to the reference listed drug.¹ 21 U.S.C. 355(j)(2)(A)(iv). The scientific premise underlying the Hatch-Waxman Amendments is that drug products that are bioequivalent and pharmaceutically equivalent and, therefore, therapeutically equivalent, generally may be substituted for each other. A generic drug product is bioequivalent to the reference listed drug if

¹ A generic drug that establishes bioequivalence as well as pharmaceutical equivalence is rated as therapeutically equivalent to the reference listed drug in FDA's *Approved Products with Therapeutic Equivalence Evaluations*, commonly referred to as the Orange Book.

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses ...

21 U.S.C. 355(j)(8)(B)(i)); see also 21 CFR 320.1(e) and 320.23(b).

FDA regulations at 21 CFR part 320 establish acceptable methodologies for determining the bioequivalence of drug products. The courts have expressly upheld FDA's regulatory implementation of the Act's bioequivalence requirements. See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

III. Standard Bioequivalence Testing²

The standard bioequivalence (pharmacokinetic) study is conducted using a two-treatment crossover study design in a small number of volunteers, usually 24-36 healthy normal adults. Single doses of the test and reference drug products are administered to these volunteers, and the blood, plasma, or serum levels of the drug are measured over time. The pharmacokinetic parameters characterizing the rate and extent of absorption are examined by statistical procedures. The pharmacokinetic parameters of interest are the area under the plasma concentration vs. time curve (AUC) calculated to the last measured concentration time (AUC_{0-t}), AUC extrapolated to infinity (AUC_{∞}), which represents the extent of absorption of the drug, and the maximum or peak drug concentration (C_{max}). C_{max} is affected by the rate of absorption and is considered to be a surrogate for the rate of absorption.

The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference), is significantly less bioavailable. The second of the two one-sided tests determines whether the reference product, when substituted for the test product, is significantly less bioavailable. Based on the opinions of FDA medical experts, a difference of greater than 20 percent for each of the above tests has been determined to be significant and, therefore, undesirable. Numerically, this is expressed as a limit of test-product average/reference-product average of 80 percent for the first statistical test and a limit of reference-product average/test-product average of 80 percent for the second statistical test. By convention, all data are expressed as a ratio of the average response (AUC and C_{max}) for test and reference, so the limit expressed in the second statistical test is 125 percent (reciprocal of 80 percent).

For statistical reasons, all data are log-transformed prior to statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90 percent confidence interval for both C_{max} and AUC. The confidence interval for both AUC

² The description of standard bioequivalence testing is taken generally from the Orange Book at ix-x.

and C_{max} should be entirely within the 80 percent to 125 percent boundaries described above. Because the mean of the study data lies in the center of the 90 percent confidence interval, the mean of the data is usually close to 100 percent (a test/reference ratio of 1).

The pharmacokinetic parameter T_{max} is defined as the time to peak plasma drug concentration following dosing. T_{max} is also used as a general index of the rate of drug absorption. T_{max} can be statistically analyzed by nonparametric methods but, due to the highly variable nature of T_{max} data, this parameter cannot be analyzed by the same ANOVA methodology used to construct the 90 percent confidence intervals. Thus, statistical criteria are not applied to T_{max} . FDA considers T_{max} as supportive data in determining whether two products are bioequivalent.

IV. Analysis – Issues Related to Bioequivalence Evaluation Methods

- A. FDA must approve a generic mixed amphetamine salts drug product if the ANDA applicant provides, among other things, sufficient information to show that the generic mixed amphetamine salts drug product is bioequivalent to Adderall.³

FDA has discretion with respect to what constitutes sufficient information to show that a mixed amphetamine salts drug product is bioequivalent to Adderall. As noted by the Third Circuit, "[a]lthough the Act mandates a showing of bioequivalence for generic drug approvals, there is no evidence that Congress intended to limit the discretion of FDA in determining when drugs are bioequivalent for purposes of ANDA approvals." *Schering Corp. v. FDA*, 51 F.3d at 399.

To support marketing approval of a generic mixed amphetamine salts drug product, FDA requests that applicants conduct a single-dose in vivo fasting bioequivalence study and determine the plasma levels of the enantiomers d-amphetamine and l-amphetamine separately. The geometric ratios of the means of the test to reference products for AUC and C_{max} should pass the 90 percent confidence interval criteria for both enantiomers. If a generic mixed amphetamine salts drug product is bioequivalent and pharmaceutically equivalent and therefore therapeutically equivalent to Adderall, then any differences in rate of absorption and abuse potential are not expected to be clinically significant. FDA recently approved Barr Laboratories, Inc.'s generic mixed amphetamine salts drug products (Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets) that met the necessary standards of approval, including bioequivalence to Adderall.

³ Section 505(j)(4) of the Act also requires an ANDA applicant to provide sufficient data and information on manufacturing, conditions of use, active ingredient(s), and labeling, and to meet other criteria necessary for approval. However, the focus of your petition is on issues related to pharmacokinetic parameters. FDA notes that you specifically defer to the Agency on other additional criteria that may be required to achieve "same as" status. Petition at 5.

- B. FDA does not believe it is preferable for an ANDA applicant to provide comparative clinical evidence (trials) showing that the generic product's safety profile is the same as that of Adderall.

You state that it would be preferable for an ANDA applicant to provide comparative clinical evidence showing that the generic product's safety profile is the same as that of Adderall. Petition at 5.

The Agency does not believe it would be preferable for an ANDA applicant to provide comparative clinical trials to demonstrate that the generic product's safety profile is the same as that of Adderall. FDA regulations at 21 CFR part 320 establish acceptable methodologies to determine the bioequivalence of drug products. Specifically, 21 CFR 320.24(a) ranks the types of evidence that may be used to establish bioequivalence in descending order of accuracy, sensitivity, and reproducibility, and requires applicants to conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach prescribed in the regulation.

The type of evidence that is ranked first is an in vivo test in humans in which the concentration of the active ingredient or active moiety, and when appropriate, its active metabolites, in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. Comparative clinical trials are ranked fourth. Comparative clinical trials are quite variable and often subjective and, therefore, may not be as sensitive to differences in drug formulations as comparisons that measure the active moiety in blood or plasma. Accordingly, for a generic mixed amphetamine salts product, FDA does not require an ANDA applicant to conduct comparative clinical trials that would involve more human subjects to assess bioequivalence when the standard two-way crossover bioequivalence study is more accurate and is sufficient for this purpose. A drug product that FDA has determined to be therapeutically equivalent is expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Orange Book at viii.

- C. A proposed generic mixed amphetamine salts drug product is not required to show that it is the "same as" Adderall with respect to the initial slope of the plasma concentration vs. time curve in human subjects, early partial AUC, and T_{max} .

You state that if FDA declines to require comparative clinical evidence showing that the generic product's safety profile is the same as that of the reference listed drug, in reviewing an in vivo bioequivalence study, the Agency should carefully compare the in vivo rate of absorption of Adderall and a proposed generic Adderall and pay specific attention to the initial slope of the plasma concentration vs. time curve in human subjects, early partial AUC, and T_{max} . Petition at 5.

FDA does not believe that comparing the initial slope of the plasma concentration vs. time curves of Adderall and of a proposed generic mixed amphetamine salts drug product would add

information beyond that already provided by statistically analyzing the comparisons of AUC and C_{max} and considering T_{max} . The inherent variability of the absorption rate limits the accuracy and usefulness of the initial slope as a reliable measure of absorption rate in bioequivalence studies. For these reasons, FDA relies on C_{max} as a surrogate for the rate of absorption. C_{max} is affected by the absorption rate and can be accurately derived from plasma profiles without model fitting and is sensitive to changes in drug formulation performance.

As noted in section III, T_{max} can be statistically analyzed by nonparametric methods but, due to the nature of the T_{max} data, this parameter cannot be analyzed by the same ANOVA methodology used to construct the 90 percent confidence intervals. Thus, statistical criteria are not applied to T_{max} . FDA considers T_{max} as supportive data in determining whether two products are bioequivalent.

Early partial AUC may be useful in certain limited situations. However, no data were provided to demonstrate that the measurement of early partial AUC (or even partial AUC) in this instance would prove meaningful. A CDER guidance for industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (issued 10/2000) (General BA/BE Guidance) discusses the use of partial AUC as follows:

For orally administered immediate-release drug products, BE may generally be demonstrated by measurements of peak and total exposure. An early exposure may be indicated on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this setting, the guidance recommends use of partial AUC as an early exposure measure. The partial area should be truncated at the population median of T_{max} values for the reference formulation.
General BA/BE Guidance at 9.

In sum, you have not included in your petition data to demonstrate that either comparative clinical trials or the assessment of the initial slope of the plasma concentration vs. time curve and early partial AUC are needed to assess the bioequivalence of a generic mixed amphetamine salts drug product. Moreover, as discussed later in this response, you have failed to demonstrate that a generic mixed amphetamine salts product with a faster rate of rise of plasma concentration during the absorption phase than Adderall will have a greater potential for abuse.

- D. FDA agrees that ANDA applicants seeking approval of generic mixed amphetamine salts drug products should evaluate pharmacokinetic parameters for both d- and l-amphetamine enantiomers.

Adderall is a mixture of d- and l-amphetamine enantiomers in a 3 to 1 ratio. Because both enantiomers are active, you ask that FDA evaluate pharmacokinetic comparisons for both enantiomers. Petition at 4. FDA agrees, and asks ANDA applicants seeking marketing approval

of mixed amphetamine salts drug products to determine the plasma concentration of d-amphetamine and l-amphetamine separately in bioequivalence studies. The parameters AUC and C_{max} should pass the 90 percent confidence interval criteria for both enantiomers.

- E. FDA agrees that in vitro dissolution studies are not adequate to assess the bioequivalence of a generic mixed amphetamine salts drug product.

You state that in vitro dissolution studies are not adequate to assess the bioequivalence of a generic mixed amphetamine salts product. Petition at 4. The Agency agrees that an applicant for a generic mixed amphetamine salts product should conduct an in vivo bioequivalence study measuring the active moiety in blood or plasma. FDA asks the applicant to conduct the in vivo study on the highest strength the applicant proposes to market. As provided for in 21 CFR 320.22(d), the applicant may request waivers of in vivo testing on lower strengths of generic mixed amphetamine salts immediate-release tablets.

V. Relationship between Amphetamine Pharmacokinetics and Abuse Potential

You state that one of the factors that determines the abuse potential of a drug is its pharmacokinetic profile. Petition at 2. You assert that a generic mixed amphetamine salts product that has a faster rate of rise of plasma concentration, higher C_{max} , greater AUC, or shorter T_{max} during the absorption phase than Adderall will have a higher potential for abuse. Petition at 4. You claim that differences in these pharmacokinetic factors may result in increased diversion and misuse of these products. Petition at 2. To support your assertion that the pharmacokinetic profile of a mixed amphetamine salts product is related to abuse potential, you rely on the studies discussed below.

You state that pharmacokinetic factors partially explain different abuse liabilities of drugs in the same class. Petition at 3. You also state that rapid absorption of a drug by the brain provides the optimal condition for reinforcing properties and drug readministration. Petition at 3. In support of these propositions, you cite a study by N.D. Volkow, et al.,⁴ in which positron emission tomography was used to monitor uptake and clearance of cocaine and methylphenidate in the brain tissue of human subjects. This study does not support your thesis because the authors concluded that differences in the abuse potential of methylphenidate and cocaine are related to differences in drug clearance, not to differences in absorption rate.

You state that 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. Petition at 3. In support of your statement you cite the "World Health Organization EB85/1990/REC/1, Annex 7" (WHO Annex 7), which lists the revised guidelines for WHO review of dependence-producing psychoactive substances for international control, including a

⁴ "Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain," *Archives of General Psychiatry*, 1995; 52:456-463.

description of the review process and the critical review document used to assess the data on individual substances. Although one of the twelve headings in the critical review document under which the data should be organized is pharmacokinetics, WHO Annex 7 neither highlights pharmacokinetics nor discusses the relationship between pharmacokinetics and abuse potential.

You state that among oral drugs, even small differences in absorption rate are associated with differences in abuse liability. Petition at 3. In support of this proposition, you cite an article by U.E. Busto and E.M. Sellers⁵ that discusses the pharmacokinetics of addictive drugs in relation to their abuse properties. The authors admit that very little systematic, experimental work is available and that one purpose of the article is to discuss future directions for study by developing several testable hypotheses. The article only briefly discusses absorption rate as a factor in abuse potential, and the discussion and research cited relate solely to benzodiazepines. Benzodiazepines are sedatives, whereas amphetamines are stimulants. Moreover, at the molecular level, benzodiazepines and amphetamines elicit their effects through entirely different receptors. It cannot be assumed that the pharmacokinetic and pharmacodynamic relationships characteristic of benzodiazepines are relevant to amphetamines.

You cite another article by U.E. Busto et al. in support of your position that pharmacokinetic parameters contribute to differences in abuse potential.⁶ This article reports on a study that investigated a possible relationship between three pharmacokinetic parameters of ten different benzodiazepine drugs and abuse and dependence potential. For the ten drugs, the only statistically significant correlation (i.e., Pearson's correlation coefficient) was between benzodiazepine half-life and abuse rank. This study does not provide evidence to support your claim that drug absorption rate is correlated with amphetamine abuse liability. In fact, the study does not even support your conclusion that "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." Petition at 3. One statistical comparison used in the study found no correlation between benzodiazepine absorption rate and risk of abuse, and the second statistical analysis showed only a weak correlation between the two. Finally, since the study investigated benzodiazepines, it cannot be assumed that it has any relevance to amphetamines.

You also cite a study by S.H. Kollins et al.⁷ as support for the proposition that absorption rate is an important determinant of abuse liability for orally administered stimulants. This study administered various mood scales to subjects to compare the effects of d-amphetamine, l-amphetamine, and methylphenidate; it was not a pharmacokinetic study.

⁵ "Pharmacokinetic determinants of drug abuse and dependence, a conceptual perspective," *Clinical Pharmacokinetics*, 1986; 11:144-153.

⁶ See Busto et al, *Canadian Journal of Clinical Pharmacology*, 1995; 2:23-28.

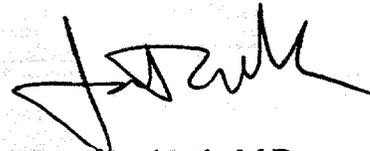
⁷ "Comparison of acute behavioral effects of sustained-release and immediate-release methylphenidate," *Experimental and Clinical Psychopharmacology*, 1998; 6:367-374.

In sum, the studies cited in your petition offer theoretical opinions, describe studies showing no clear relationship between indicators of abuse potential and psychostimulant kinetics or dose, or describe studies with neuroactive drugs that are not psychostimulants. They do not substantiate your claim that a generic mixed amphetamine salts product with a faster rate of rise of plasma concentration, higher C_{max} , greater AUC, or shorter T_{max} during the absorption phase will have a higher potential for abuse than Adderall.⁸ In fact, if a generic mixed amphetamine salts drug product is bioequivalent and pharmaceutically equivalent and therefore therapeutically equivalent to Adderall, then any differences in rate of absorption and abuse potential are not expected to be clinically significant.

VI. Conclusion

You have failed to demonstrate that the abuse potential of mixed amphetamine salts is different from that of other amphetamine-containing products and that a generic mixed amphetamine salts product must match exactly the pharmacokinetic profile of the reference listed drug Adderall. A generic mixed amphetamine salts product that meets FDA's statistical bioequivalence criteria is considered to be bioequivalent to the reference listed drug. For the reasons discussed above, your petition is denied.

Sincerely yours,



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

⁸ The Controlled Substances Act (CSA) also suggests that the abuse potential of Adderall and a generic mixed amphetamine salts product will be the same. The CSA schedules drugs based on the abuse potential of the active substance. Amphetamine and any material, compound, mixture, or preparation that contains any quantity of amphetamine, including its salts, optical isomers, and salts of its optical isomers (notwithstanding certain exceptions that are not applicable in this case) are listed in Schedule II of the CSA. 21 CFR 1308.12(d). Thus, Adderall is a Schedule II drug, and any generic mixed amphetamine salts product would also be a Schedule II drug. Under the CSA, the particular formulation of an amphetamine product is not the basis for determining its abuse potential because, for example, tablets may be crushed and extracted by solvents for administration by an intravenous, intramuscular, intranasal route, or other mode.