DEPARTMENT OF HEALTH & HUMAN SERVICES

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

JUN 22 2012

Eliseo O. Salinas, M.D., M.Sc.
Shire Pharmaceuticals Group, plc
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Re: Docket No. FDA-2005-P-0120[1]

Dear Dr. Salinas:

This responds to your citizen petition dated October 12, 2005 (Petition), and the related supplements dated January 19, 2006 and March 22, 2012 (2012 Supplement). You request that the Food and Drug Administration (FDA or Agency) apply a more stringent bioequivalence requirement including additional partial area-under-the-concentration-time curve (partial AUC) measurements for approval of any abbreviated new drug application (ANDA) or any section 505(b)(2) new drug application (NDA) for generic[2] or "follow-on"[3] versions of Shire Pharmaceuticals Group's (Shire's) drug product, Adderall XR amphetamine extended-release capsules (Adderall XR). Alternatively, you request that the FDA require for approval of such applications a clinical efficacy study in each approved patient population.

For the reasons that follow, your petition and related supplements are granted in part and denied in part. Although we are not granting your specific requests for partial AUC measurements, we will require that ANDAs referencing Adderall XR demonstrate two partial AUC parameters to determine the bioequivalence of generic mixed amphetamine modified-release (MR) formulations.[4]

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[1] This citizen petition was originally assigned docket number 2005P-0420/CP1. The number was changed to FDA-2005-P-0120 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] *Generic* is not defined in the Food, Drug, & Cosmetic Act (FD&C Act) or in FDA regulations. As used in this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act (21 U.S.C. 355(j)).

[3] Your petition requests that that the FDA apply these requirements to 505(b)(2) applications for follow-on versions of Adderall XR. We note, however, that 505(b)(2) applications typically are not required to demonstrate bioequivalence to a listed drug. In addition, because 505(b)(2) applications can differ from the listed drugs in a variety of ways, we cannot address hypothetical requests for what demonstrations would be needed for a 505(b)(2) application. Therefore, this response focuses solely on your request with respect to ANDAs.

[4] We have also considered comments submitted to the docket. We note that your December 6, 2005, letter requests that the Center for Drug Evaluation and Research's (CDER's) Division of Psychiatry Products and Division of Neurology Products be consulted on this response. Pertinent FDA personnel, including those from what is now referred to as the Division of Psychiatry Products, have been consulted on this response.

I. BACKGROUND

A. ADHD Drug Products and Adderall XR

The stimulants used to treat Attention Deficit Hyperactivity Disorder (ADHD) fall into two general categories: amphetamine and methylphenidate containing products. In addition to several immediate-release (IR) formulations, several MR formulations exist to treat ADHD: Adderall XR, an amphetamine product, and Concerta, Metadate CD, and Ritalin LA, which are methylphenidate-containing products. Each product has a different time-activity curve with differing claims of efficacy. Amphetamine and methylphenidate have effects on multiple neurotransmitters, but both are considered to be dopamine agonists, which increase synaptic levels of dopamine by inhibiting uptake of catecholamines (primarily dopamine), and also by stimulating dopamine release.[5]

The shift in clinical practice to day-long treatment of ADHD symptoms led to the development of longer-acting medications that can be administered on a once-daily basis, such as Adderall XR.[6] Adderall XR is a once-daily MR amphetamine product indicated for the treatment of ADHD that can be taken with or without food. The Agency approved Shire's NDA for Adderall XR on October 11, 2001, and it is available in 5-milligram (mg), 10-mg, 15-mg, 20-mg, 25-mg, and 30-mg doses. Adderall XR was first approved for the treatment of ADHD in children ages 6-12 years, but was later approved for the treatment of ADHD in adults and adolescents. The drug combines the neutral sulfate salts of dextroamphetamine (d-amphetamine) and amphetamine with the dextro isomer of amphetamine saccharate and d,levo (l)-amphetamine aspartate monohydrate. Adderall XR contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from Adderall XR compared to the conventional Adderall (IR) tablet formulation. Adderall XR contains the same mixed amphetamine salts as the IR formulation, Adderall. The formulation is a 1:1 ratio of IR and delayed-release (DR) pellets in a gelatin capsule designed to deliver the drug in a pulsatile manner to mimic taking two equal doses of Adderall 4 hours apart, thereby extending clinical efficacy. The IR and DR pellets contain the same amount and mixture of amphetamine salts, with the d- and l-amphetamines in the ratio of 3:1. The only difference between the two kinds of pellets is that DR pellets have an enteric coating designed to release the drug at higher pH values of the small intestine, i.e., about 4 hours after ingestion.

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[5] Swanson JM, Lerner M, Wigal T, Steinhoff K, Greenhill L, Posner K, Freid J, and Wigal S, 2002, The Use of a Laboratory School Protocol to Evaluate Concepts About Efficacy and Side Effects of New Formulations of Stimulant Medications. *J. Attention Disorders* 6(1):S73-S88.

[6] McGough JJ, Biederman J, Greenhill LL, McCracken JT, Spencer TJ, Posner K, Wigal S, Gornbein J, Tulloch S, and Swanson JM, 2003, Pharmacokinetics of SLI381 (Adderall XR) an Extended Release Formulation of Adderall. *J. Am. Acad. Child Adolesc. Psychiatry* 42(6):684-691.

B. Statutory and Regulatory Background

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 (FD&C Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act). In addition, an ANDA must contain, with certain exceptions not relevant here, information to show that the proposed drug has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD (section 505(j)(2)(A) of the FD&C Act). FDA must approve an ANDA unless the information submitted in the ANDA is insufficient to meet the requirements delineated in section 505(j)(2)(A) of the FD&C Act, including a demonstration of bioequivalence (section 505(j)(4) of the FD&C Act). The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet the following criteria are therapeutically equivalent and may be substituted for each other: (1) contain identical amounts of the same active ingredient(s) in the same route of administration and dosage form; (2) meet applicable standards of strength, quality, purity, and identity; (3) are manufactured in compliance with current good manufacturing practices regulations; and (4) are adequately labeled.[7]

FDA regulations at 21 CFR part 320 list acceptable methodologies for determining the bioequivalence of drug products. These methodologies include pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, comparative clinical trials, and *in vitro* studies. The selection of the method used depends on the purpose of the study, the analytical methods available, and the characteristics of the drug product under consideration (21 CFR 320.24). The courts have expressly upheld FDA's regulatory implementation of the FD&C Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995) and *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994)).

FDA's general recommendation for bioequivalence testing of extended-release, orally administered, and systemically absorbed drug products is a single-dose fasting study and a single-dose food-effect study.[8] FDA recommends administration of single doses of the

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[7] See section 505(j) of the FD&C Act.

[8] See the FDA guidance for industry *Bioavailability and Bioequivalence for Orally Administered Drug Products – General Considerations* (BA/BE guidance) (available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

test and reference drug products to subjects during the respective treatment phases, with measurement of the plasma concentrations of the test and reference drugs over time.

To evaluate the rate and extent of test drug absorption, the measured plasma concentrations for each subject should be plotted graphically against time of measurement. The graph depicts the plasma sampling time on the horizontal (x) axis and corresponding plasma drug concentration on the vertical (y) axis. The relevant PK parameters calculated from these data include the area under the plasma concentration *curve vs. time* (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity ($AUC\infty$). These parameters represent the *extent* of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant PK parameters are the maximum or *peak* drug concentration (C_{max}), and the time required to reach the peak drug concentration after administration (T_{max}), which reflect the rate of absorption. FDA recognizes that, under certain circumstances, it may be appropriate to use a partial AUC parameter to ensure comparable therapeutic effects. In the BA/BE guidance, FDA recommends using partial AUC to assess early exposure, for example, when rapid onset is critical to the safety and/or efficacy of the drug product.

> For orally administered immediate-release drug products, BE [bioequivalence] can generally be demonstrated by measurements of peak and total exposure. An early exposure measure may be informative 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. We recommend that the partial area be truncated at the population median of T_{max} values for the reference formulation.[9]

FDA considers products bioequivalent when the 90 percent confidence intervals for test/reference PK parameter ratios are entirely within an 80 to 125 percent acceptance interval.[10] The choice of the 80 to 125 percent acceptance interval reflects decades of scientific data on the variability of product characteristics (such as potency) within and between batches, as well as biological variability in patients. From these data, FDA concluded that the variability in PK values allowed under this acceptance interval would

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[9] BA/BE guidance at 8. If there are considerable differences in T_{max} between a test product and a reference product, FDA's Office of Generic Drugs generally consults with the Office of New Drugs to determine whether the difference might have clinical significance.

[10] See FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence*, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

not adversely affect clinical outcomes because this variability is within the range of differences that can arise from other product-specific and biological factors.[11]

II. Discussion

In your Petition, you claim that the d- and l-amphetamine plasma concentration-time curves for Adderall XR are specifically related to clinical efficacy (Petition at 1). As a result, you request that FDA establish the following therapeutic equivalence requirements for ANDAs referencing Adderall XR (Petition at 2-3):

- ANDAs seeking to demonstrate therapeutic equivalence to Adderall XR by a bioequivalence study must demonstrate d- and l-amphetamine concentration-time profiles identical to (superimposable upon) those of Adderall XR under the once-daily dosing described in the reference listed drug's package insert.

- The identical pharmacokinetic profiles must be demonstrated by the traditional pharmacokinetic parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, plus the pharmacokinetic parameter AUC_{pR} (area under concentration-time curve truncated at the population median T_{max}).

- Additional partial AUC measurements must be conducted for each time point up to 4 hours (AUC_{0-1}, AUC_{1-2}, AUC_{2-3}, AUC_{3-4}).

- Bioequivalence must be established in both pediatric (ages 6-12) and adult (ages 18 and older) subjects.

You request that if the ANDA applicant is unable or unwilling to meet the above criteria, FDA require one adequate and well-controlled clinical investigation demonstrating safety and effectiveness in each currently approved population (children, adolescents, and adults) (Petition at 2-3). You maintain that the relevant data supporting the requirements that you are requesting are described in the Adderall XR package insert as well as the petition (Petition at 3).

In your 2012 Supplement, you request an additional partial AUC metric of 1.5 hours ($AUC_{0-1.5}$ and $AUC_{1.5-t}$) (2012 Supplement at 2). Alternatively, you request a partial AUC metric of 3 hours (AUC_{0-3} and AUC_{3-t}) (2012 Supplement at 2). You request that the partial AUC metric be applied under fasting, sprinkled, and fed conditions with appropriate adjustments to the partial AUC intervals. You also request that generic

[11] Dighe SV, and WP Adams, 1991, Bioequivalence: A United States Regulatory Perspective. In: PG Welling, LS Tse, and S Dighe, eds. Pharmaceutical Bioequivalence, Marcel Dekker, Inc., New York, 347-380.

sponsors be required to conduct a deconvolution study to demonstrate comparability of the bimodal drug absorption profile of the generic product and Adderall XR (2012 Supplement at 3).

It is unclear whether the requests in your 2012 Supplement replace your original requests in the Petition or are offered in the alternative. Therefore, we will address the requests contained in both the Petition and the 2012 Supplement.

A. Identical Plasma Concentration-Time Profile

You state that to obtain regulatory approval by a bioequivalence study (i.e., an approval based only on bioequivalence data and not on clinical data or an adequate and well-controlled study to support efficacy) for Adderall XR, FDA required Shire to demonstrate that the drug's d- and l-amphetamine plasma concentration-time profiles were identical to those of Adderall IR (Petition at 3, 6). You further state that if the plasma concentration-time profiles of Adderall IR and Adderall XR were not identical, the Agency indicated at least one adequate and well-controlled clinical study would be needed to support efficacy of the drug product (Petition at 3). You state that the bioequivalence study results showed that following dosing with Adderall IR both the d- and l-amphetamine plasma concentration-time profiles showed an inflection point.[12] In contrast, following dosing with Adderall XR an inflection point in the d- and l-amphetamine plasma concentration-time curves was not observed. You cite these observations as evidence that Adderall IR and Adderall XR do not produce identical plasma profiles. You claim that despite this difference in inflection point, the study did demonstrate bioequivalence using FDA's traditional pharmacokinetic parameters, AUC and C_{max}. You maintain that as a result of what you refer to as a slight difference in pharmacokinetic profiles, FDA would not accept Shire's bioequivalence study as a basis for regulatory approval of Adderall XR and required at least one clinical efficacy study. Consequently, you argue ANDAs for generic versions of Adderall XR should be held to the same standard for a bioequivalence study, i.e., they should be required to demonstrate identical (superimposable) plasma concentration-time pharmacokinetic profiles (Petition at 6). You further state that given this standard of superimposability for therapeutic equivalence purposes there appears to be no valid clinical or regulatory rationale for dispensing with this standard for ANDA applicants (Petition at 6).

In considering new drug applications for modified-release dosage forms such as Adderall XR, FDA makes a judgment as to how similar the modified- and immediate-release

[12] The pivotal bioequivalence study submitted for NDA 21-303, Study SLI381-102 (Study 102), was a relative bioavailability study in which d- and l-amphetamine pharmacokinetic profiles were compared in healthy normal adult subjects receiving either a single 20-mg dose of Adderall XR or two 10-mg doses of Adderall IR given 4 hours apart. The inflection point is the point where the increases in plasma d- and l-amphetamine are first observed after administration of the second 10-mg dose of Adderall IR.

products must be to conclude that an adequate and well-controlled study would not be needed to demonstrate safety and efficacy. In the case of a new drug application for a drug indicated for the treatment of ADHD, it was considered essential to assess clinical performance of the proposed new modified-release product (Adderall XR) throughout the day. It should also be emphasized that the purpose of a bioequivalence study is different for NDAs and ANDAs. For an NDA, the purpose of a bioequivalence study would be to demonstrate safety and efficacy. For an ANDA, the purpose of a bioequivalence study is to show that the generic product is the same as the innovator and is therefore substitutable.

We disagree with your argument that generic versions of Adderall XR must demonstrate a plasma concentration-time profile that is identical to, or superimposable upon, that of the RLD. Although we agree that the shape of the curve can be important for drugs that treat ADHD and have multiple peaks from the IR and MR components, we do not agree that identical (i.e., superimposable) PK curves are necessary to approve an ANDA referencing Adderall XR as the RLD. Although the effect of different time-concentration profiles on the clinical efficacy of mixed amphetamine salts products needed to be ascertained during the development of Adderall XR, identical or superimposable profiles are not necessary for the approval of a generic drug product, because it already has been established that products with different PK profiles, such as IR products taken twice daily and controlled release products with varying PK release profiles, can be equally effective for their indicated use. For example, the plasma concentration-time profiles for a single dose of Adderall XR and two doses of Adderall given 4 hours apart are different. However, both formulations are effective. Adderall given twice a day is likely to be more effective in controlling behavior and improving performance over the course of the day than a single dose of Adderall,[13] and a once-a-day dose of Adderall XR has a longer duration of action than a once-a-day dose of Adderall.[14]

B. Pharmacokinetic Parameter of AUC_{pR} and Partial AUC Measurements up to T_{max}

The Petition requests that FDA require ANDAs for generic versions of Adderall XR to demonstrate, in addition to the traditional pharmacokinetic parameters of C_{max}, AUC_{0-t},

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[13] Greenhill LR, Swanson JM, Steinhoff K, Fried J, Posner K, Lerner M, Wigal S, Clausen SB, Zhang Y, and Tulloch S, 2003, A Pharmacokinetic/Pharmacodynamic Study Comparing a Single Morning Dose of Adderall to Twice-Daily Dosing in Children With ADHD. *J. Am. Acad. Adolesc. Psychiatry*, 42(10): 1234-2141.

[14] SLI 381.201: A Randomized, Double-Blind, Placebo- and Active-Controlled, Crossover Study of SLI 381 in children with Attention Deficit Hyperactivity Disorder. Vol. 1.100-1.104, NDA 021303; McCracken JT, Biederman J, Greenhill LL, Swanson JM, McGough JJ, Spencer TJ, Posner K, Wigal S, Pataki C, Zhang Y, and Tulloch S, 2003, Analog Classroom Assessment of a Once-Daily Mixed Amphetamine Formulation, SLI381 (ADDERALL XR), in Children With ADHD. *J. Am. Acad. Adolesc. Psychiatry*, 42(6): 673-683.

and $AUC_{0-\infty}$, the pharmacokinetic parameter of AUC_{pR}, as well as AUC measurements for each hour up until 4 hours (AUC_{0-1h}, AUC_{1h-2h}, AUC_{2h-3h}, AUC_{3h-4h}). You maintain that Adderall XR is a drug for which early absorption measurements during the first 4 hours following administration are clinically important and that AUC_{pR} should be required based on the BA/BE guidance (Petition at 6-7).

In the 2012 Supplement, you state that results of a PK/PD modeling analysis demonstrate the relationship between drug concentrations in plasma and drug effects, and support the need for additional partial AUC bioequivalence metrics for generic formulations of Adderall XR (2012 Supplement at 2). You request an additional partial AUC metric of 1.5 hours ($AUC_{0-1.5}$ and $AUC_{1.5-t}$) based on results of a clinical response analysis (2012 Supplement at 2). Alternatively, you request a partial AUC metric of 3 hours (AUC_{0-3} and AUC_{3-t}) to capture the effects supported by the results of a drug concentration - clinical effect analysis. You request that the partial AUC metric be applied under fasting, sprinkled, and fed conditions with appropriate adjustments to the partial AUC intervals.

FDA's BA/BE regulations (21 CFR 320) require applicants seeking approval of systemically available generic products to compare only two PK parameters statistically. These are C_{max} in plasma, serum, or whole blood, and AUC in plasma, serum, or whole blood, unless some other approach is more appropriate for valid scientific reasons. FDA does not agree that we should require the PK parameter AUC_{pR}, as defined in the BA/BE guidance (AUC truncated at the population median T_{max}), as a criterion for determining bioequivalence of generic drug products referencing Adderall XR. The BA/BE guidance discussion of a possible use for AUC_{pR} in certain circumstances does not apply to Adderall XR because AUC_{pR} is not sensitive to differences in the amphetamine absorption profile and onset of clinical effect resulting from the formulation of Adderall XR.

However, because Adderall XR is a complex formulation, we find that requiring sampling times for a partial AUC[15] determination based on the pharmacokinetic/pharmacodynamic properties of the active ingredient (the mixed amphetamines), rather than using the T_{max} corresponding to the highest observed amphetamine plasma concentration, is appropriate for determining bioequivalence. We think it is important to use partial AUC for some specialized dosage forms, because our current acceptance criteria as set forth in the BA/BE guidance may not be adequate for certain drugs formulated as multiphasic MR products. Furthermore, because the mixed amphetamine salts MR dosage form (1) contains IR and DR components; (2) is designed to achieve both rapid onset of activity and sustained activity throughout the day; and (3) does not show unusual accumulation at steady state, the additional metrics may be appropriate to ensure that generic versions are therapeutically equivalent to the reference

[15] Partial AUC refers to the AUC between two specified time points (clinically relevant time interval). The clinically relevant time interval is identified based on a clear link between drug concentration and pharmacokinetic/pharmacodynamic effect.

product.

Adderall XR contains IR and DR components in its formulation and exhibits rapid initial absorption similar to that of the mixed amphetamine IR formulation of Adderall, followed by a delayed release of amphetamines approximately 4 hours after the initial dose. The rapid absorption phase is demonstrated by a consistent shoulder[16] at 2-4 hours in the mean plasma concentration-time PK profiles of Adderall XR (30 mg) which corresponds to the mean T_{max} (3 hours) of Adderall (the IR mixed amphetamine salts product). This shoulder is followed by peak plasma concentrations between 6 to 7 hours, representing the DR phase of the drug product.

It is important to carefully select the appropriate partial AUC sampling times for a multiphasic MR formulation because, for some of these formulations, the T_{max} associated with the highest plasma concentration may occur as drug is released from the DR component of the formulation, and thus be influenced by the elimination of drug released from the IR portion of the formulation. Thus, the traditional BE metrics, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (even including T_{max}) will not provide information on the initial onset of activity. For the same reason, AUC_{pR} is not likely to be a relevant metric for assessing early onset of activity from mixed amphetamine salts MR formulations because it may not relate to the onset of action resulting from release of amphetamine from the IR portion of the Adderall XR formulation.

We do not agree that the multiple partial AUCs requested in the Petition or the 2012 Supplement are necessary to characterize the initial absorptive phase of the plasma concentration-time profile for ANDAs referencing Adderall XR. We agree that the onset of the IR phase of Adderall XR occurs at around 3 hours for *d*- and *l*-amphetamines. Nevertheless, we believe that the use of a partial AUC sampling time 2× standard deviations (SD) beyond the mean T_{max} of the IR component is appropriate and consistent with the partial AUC approaches recommended for other MR products (e.g., zolpidem extended release tablets and methylphenidate hydrochloride).[17] We find that using two partial AUCs, AUC_{0-5h} and AUC_{5h-t}, would be sufficiently sensitive to determine the bioequivalence of generic mixed amphetamine MR formulations. We would require these two partial AUC metrics, in addition to C_{max}, and $AUC_{0-\infty}$, for both d- and l-amphetamines in fasting, fasting sprinkle-in-applesauce, and fed bioequivalence studies of generic mixed amphetamine salts MR products referencing Adderall XR. The 90% confidence intervals of the geometric mean of the test-to-reference ratios for all four

[16] A shoulder is a region in the plasma concentration versus time profile where the rate of increase or decrease in drug plasma concentrations slows or flattens for a time.

[17] The guidance for zolpidem can be found on the Internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf. The draft guidance for methylphenidate hydrochloride can be found on the Internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf.

metrics for plasma d- and l-amphetamines should fall within the BE acceptance limits of 80-125%.

As mentioned above, the shoulder in the plasma concentration-time profile following a single dose of Adderall XR (30 mg) corresponds to the T_{max} of the amphetamine profiles of the mixed amphetamine salts IR formulation. The timing of the shoulder concurs with the mean time to peak PD effect for 15 mg of Adderall (2.6 hours), which corresponds to the strength of the IR component of Adderall XR (30 mg).[18]

The partial $AUC_{0\text{-}5hr}$ is sufficiently sensitive, and has relatively low variability for both *d*- and *l*-amphetamines under fasting and fed conditions. The rationale for selecting the sampling time of 5 hours for the partial AUCs in the fasting study is based on the following:

- The initial absorption and early onset of response of the mixed amphetamine salts MR product is similar to those of the mixed amphetamine salts IR products.
- The T_{max} for the mixed amphetamine salts IR products is about 3 hours.
- The SD around the mean T_{max} for the mixed amphetamine IR product is about 1 hour; two SDs correspond to 2 hours. Approximately 95% of observations should fall within two SDs of the mean.
- Therefore, time of 5 hours (i.e., mean + 2 * SD = 3 hours + 2 hours) corresponds to the time at which 90-95% of subjects are likely to achieve optimal early onset of response.

Accordingly, because T_{max} occurs at 3 hours for the IR portion of the Adderall XR formulation under fasted conditions, the partial AUC truncated at 5 hours (i.e., $AUC_{0\text{-}5h}$) in a fasting BE study captures the early responses of 95% of the subjects.

With respect to fed and fasting bioequivalence studies, although we agree that the BE studies for generic products referencing Adderall XR should be demonstrated under fasting, fed and fasting sprinkle-in-applesauce conditions, we believe that the same partial AUC metrics should apply under these various conditions. According to the product labeling, Adderall XR Capsules can be taken whole or the entire contents of the capsule can be sprinkled on apple sauce. FDA's food effect guidance recommends a fasting sprinkle bioequivalence study when the label indicates that the drug product can be sprinkled on soft foods.[19] Also, the amphetamine concentration-time profiles of

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[18] Swanson JM, Wigal S, Greenhill LL, Browne R, Waslik B, Lerner M, Williams L, Flynn D, Agler D, Crowley K, Fineberg E, Maren M, and Cantwell DP, 1998, Analog Classroom Assessment of Adderall in Children with ADHD. *J. Am. Acad. Child Adolesc. Psychiatry* 37(5):519-526).

[19] Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies (January, 2003): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf

Adderall XR under fasting and fasting sprinkle-in-applesauce conditions are similar. Therefore, we recommend fasting and fasting sprinkle-in-applesauce bioequivalence studies using the metrics C_{max}, $AUC_{0\text{-}5h}$ and $AUC_{5h\text{-}t}$, and $AUC_{0\text{-}\infty}$.

For the bioequivalence study under fed conditions, we would require the same metrics, i.e., C_{max}, $AUC_{0\text{-}5h}$, $AUC_{5h\text{-}t}$, and $AUC_{0\text{-}\infty}$, as the fasting bioequivalence studies. Although food prolongs the T_{max} of the mixed amphetamine salts MR product by about 2-2.5 hours, the RLD label states that Adderall XR can be administered with or without food. Additionally, there is some evidence suggesting that food may not affect the time to peak plasma amphetamine concentration following administration of mixed amphetamine salts IR products, which is a component of Adderall XR.

C. Bioequivalence in Pediatric Population

Because the labeling for Adderall XR describes meaningful differences in the pharmacokinetics of Adderall XR in children and adults, you urge FDA to require that bioequivalence be established in both pediatric (ages 6-12) and adult (ages 18 and older) subjects (Petition at 8).[20] You state that this will ensure that the generic formulation and Adderall XR will be safe and effective in each of these populations (Petition at 8).

We agree that there may be differences in the pharmacokinetics of Adderall XR when administered to children and adults. However, bioequivalence studies (typically two-treatment crossover studies) are designed to demonstrate that drug products that contain identical amounts of the same active drug ingredient in the same dosage form and route of administration and meet compendial or other applicable standards of strength, quality, purity, and identity,[21] do not present a known or potential bioequivalence problem. If a drug product demonstrates bioequivalence to the RLD under the above conditions, then it is deemed therapeutically equivalent. Therapeutically equivalent products are expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. In addition, bioequivalence studies are generally conducted in healthy adult volunteers because these subjects typically exhibit less variability than those who have the disease or condition being treated, and thus small differences in formulations are easier to detect.[22] Furthermore, there are no current data for any approved generic drug product indicating that a generic drug product approved on the basis of bioequivalence testing in healthy adults (and meeting the other criteria for

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[20] You also state that this issue is particularly important because over 70% of the prescriptions written annually for Adderall XR are for children, and an adult indication will not be available in the generic drug labeling until expiration of the three-year Hatch-Waxman exclusivity period. This issue is moot, because the marketing exclusivity to which you refer expired on August 11, 2007.

[21] FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) at vi.

[22] BA/BE guidance.

ANDA approval) performs differently from the RLD when administered to the pediatric population. For these reasons, we deny your request to require applicants for generic versions of Adderall XR to conduct a bioequivalence study in both the adult and pediatric population.

D. Clinical Study

You suggest that if the ANDA applicant is unable or unwilling to demonstrate an identical plasma concentration-time profile, we should require one clinical effectiveness study in each currently approved population (children, adolescents, and adults) (Petition at 8). You propose that the design of these studies should be the same as the clinical studies described in the Adderall XR package insert.

Amphetamine is the active moiety of Adderall XR, and it can be detected and accurately measured in plasma over time. Therefore, it meets the criteria for the most sensitive, accurate, and reproducible method for the assessment of bioavailability and bioequivalence described above. Accordingly, we do not find it necessary or in the interest of the public health to require ANDA applicants to conduct clinical efficacy studies. To require such studies would be contrary to one of the guiding principles for *in vivo* bioavailability studies—that no unnecessary human research should be conducted (21 CFR 320.25). It is important to note that the ANDA pathway for the approval of generic drug products is designed, in part, to avoid such necessary studies when bioequivalence to the RLD has been demonstrated.

E. Deconvolution Study

Because Adderall XR formulations have bimodal absorption profiles, you state that a generic applicant should conduct a deconvolution study to determine comparability of the bimodal absorption profile of the generic product and Adderall XR to account for the IR and DR components (2012 Supplement at 22). The 2012 Supplement summarizes results of your deconvolution analysis, which you claim shows input rates of the IR and DR phases, representing the bimodal absorption profile of Adderall XR.

We do not agree with your request for a deconvolution study because we believe that the bioequivalence studies using partial AUC metrics are sufficient to account for the IR and DR components of the drug product. Specifically, bioequivalence establishes the absence of significant difference between the rate and extent of absorption of a test formulation and the rate and extent of absorption of the reference drug when administered at the same molar dose (21 CFR 320.23(b)). Furthermore, bioequivalence evaluated using the partial AUC metrics determines comparability of IR and sustained release components of test formulations to those of the reference formulation for MR products.

In addition, an ANDA requires (with certain exceptions) that the proposed drug have the same active ingredient(s), indications, route of administration, dosage form, strength, and

labeling as the reference product, and be bioequivalent to the reference product. The dosage form does not refer to the drug's release mechanism; instead, it refers to the physical form of the drug product. Therefore, a generic drug will not necessarily release its drug substance in precisely the same manner as the reference drug. Your request to require ANDA applicants referencing Adderall XR to conduct a deconvolution study is therefore denied.

F. Advisory Committee

In your 2012 Supplement, you request that FDA obtain the recommendations of our Advisory Committee on Pharmaceutical Science and Clinical Pharmacology, in conjunction with the Office of Drug Evaluation/Division of Psychiatry Products, on your proposed partial AUC requirements before applying these standards to generic applicants and approving any ANDAs referencing Adderall XR (2012 Supplement at 3).

We deny your request to hold an advisory committee meeting on this issue. The Office of Generic Drugs has consulted with the relevant experts and divisions within the Agency, including the Division of Psychiatry Products, to determine the best approach for the partial AUC requirements for generic applicants referencing Adderall XR. At this point in time, recommendations from an advisory committee are unnecessary.

III. CONCLUSION

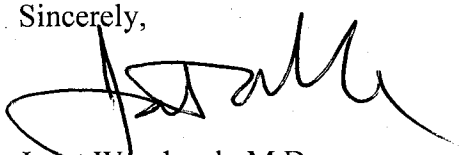
We have reviewed your petition, supplements, and other relevant information available to the Agency. For the reasons stated above, your petition and related supplements are granted in part and denied in part.

We deny your request that we require identical or superimposable plasma concentration-time profiles for ANDA applications for Adderall XR. We have found no convincing evidence that this requirement has any scientific value. Nevertheless, we will expect a comparable plasma profile, based on our evaluation of the pharmacokinetic parameters discussed in this citizen petition response.

We deny your request to require use of AUC_{pR} and do not agree that the multiple partial AUCs requested in the petition and supplements are necessary to compare the initial absorptive phase of the plasma concentration-time profile between generic mixed amphetamine MR formulations and Adderall XR. Furthermore, we do not think it is necessary to require ANDA applicants referencing Adderall XR to perform a deconvolution study, nor do we think it is necessary to seek the advice of an advisory committee regarding the partial AUC metrics for generic versions of Adderall XR. However, we will require generic applicants referencing Adderall XR to demonstrate $AUC_{0\text{-}5h}$ and $AUC_{5h\text{-}t}$, in addition to the standard parameters for determining bioequivalence.

Additionally, we do not agree that ANDAs for Adderall XR need to establish bioequivalence in the pediatric population. Finally, it is not in the interest of the public health to require ANDA applicants for Adderall XR to conduct clinical efficacy studies if they have not demonstrated an identical plasma concentration-time profile.

Sincerely,



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