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Division of Dockets Management (HFA-305)  
U.S. Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20852

**CITIZEN PETITION**

The undersigned hereby submits this Citizen Petition in quadruplicate, pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355, and FDA regulations 21 C.F.R. §§ 10.20, 10.30, 314.54, 314.94 and 320.21(b)(1).

Petitioner Shire Pharmaceuticals Group plc ("Shire") respectfully requests that the U.S. Food and Drug Administration (FDA) apply a more stringent bioequivalence requirement consistent with that FDA previously required of Shire, plus additional partial AUC measurements to demonstrate bioequivalence during early exposure, to any abbreviated new drug application (ANDA) or any Section 505(b)(2) new drug application (NDA) seeking regulatory approval of a generic or follow-on drug product that references Shire's drug product Adderall XR<sup>®</sup> (mixed salts of a single-entity amphetamine product) 5mg, 10mg, 15mg, 20mg, 25mg and/or 30 mg, indicated for the treatment of attention deficit hyperactivity disorder ("ADHD"). Alternatively, a clinical efficacy study in each approved patient population should be required for any such approval.

**A. ACTION REQUESTED**

As evidenced by clinical trial data provided subsequently in this petition, the plasma concentration-time curve for Adderall XR<sup>®</sup> MASP<sup>1</sup> is specifically related to clinical efficacy. Therefore, Shire petitions that FDA establish the following therapeutic equivalence requirements for any generic or follow-on drug product referencing Adderall XR<sup>®</sup> MASP:

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<sup>1</sup> In this petition, Adderall XR<sup>®</sup> will be described as "Adderall XR<sup>®</sup> MASP"; "MASP" is an abbreviation for "mixed amphetamine salts product".

- If an applicant attempts to demonstrate therapeutic equivalence by a bioequivalence study, the plasma concentration-time pharmacokinetic profile for any generic or follow-on drug product referencing Adderall XR<sup>®</sup> MASP must be shown to be identical to (*i.e.*, superimposable upon) the plasma concentration-time pharmacokinetic profile associated with Adderall XR<sup>®</sup> MASP under the once-daily dosing described in the reference product's approved package insert (attached as **Exhibit A**), as FDA required Shire to demonstrate when assessing the bioequivalence of Adderall XR<sup>®</sup> to immediate-release Adderall<sup>®</sup>.
- Such an identical pharmacokinetic profile must be demonstrated not only by the traditional pharmacokinetic parameters of  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$ , but also by the pharmacokinetic parameter of  $AUC_{pR}$ , since Adderall XR<sup>®</sup> MASP is a drug for which early absorption measurements during the first four hours following administration are clinically important in determining therapeutic equivalence for the treatment of ADHD.
- Additional partial AUC measurements must be conducted for each time point up to four hours (*i.e.*  $AUC_{0-1}$ ,  $AUC_{1-2}$ ,  $AUC_{2-3}$ ,  $AUC_{3-4}$ ), to more completely characterize the respective plasma concentration-time profile between a generic or follow-on drug product and Adderall XR<sup>®</sup> MASP during the clinically important first four hours of absorption.
- Demonstration of bioequivalence by the above standards must be established in both pediatric (ages 6-12) and adult (ages 18 and older) subjects, to ensure identical pharmacokinetic performance of a generic or follow-on drug product in these distinct ADHD patient populations.
- If a generic or follow-on drug sponsor is unable or unwilling to meet these criteria for establishing bioequivalence, the only reasonable alternative is the performance of at least one adequate and well-controlled clinical investigation demonstrating

the safety and effectiveness of the generic or follow-on drug product in the treatment of ADHD in the approved patient populations for Adderall XR<sup>®</sup> MASP: children, adolescents and adults.

The relevant data supporting the requirements petitioned for are described in the approved package insert for Adderall XR<sup>®</sup> MASP, and by the additional data and information provided in this petition.

**B. STATEMENT OF GROUNDS**

Adderall XR<sup>®</sup> MASP is an approved new drug indicated for the treatment of children, adolescents and adults with ADHD, available in the above dosage strengths as a capsule dosage form. It is an extended-release formulation of Adderall<sup>®</sup>. The NDAs for both drug products are held by Shire Development, Inc., a related company of petitioner.

**1. FDA Imposed an "Identical" Plasma Concentration-Time Pharmacokinetic Profile Requirement for Adderall XR<sup>®</sup> MASP**

While in the process of developing and testing Adderall XR<sup>®</sup> MASP, Shire was informed by FDA, in comments on Shire's proposed clinical development plan, that the plasma concentration-time pharmacokinetic profile for extended-release Adderall<sup>®</sup> (i.e., Adderall XR<sup>®</sup> MASP) had to be identical to the plasma concentration-time profile demonstrated from BID dosing with Adderall<sup>®</sup> immediate-release ("IR"); otherwise, a bioequivalence-based approval would not be possible. (See letter to Shire from Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products, May 4, 1999, p. 1, attached as **Exhibit B**, emphasis added). FDA stated that if the plasma concentration-time profiles of Adderall<sup>®</sup> IR and Adderall XR<sup>®</sup> MASP were not identical, a bioequivalence study would not suffice to support approval of a once-daily, extended-release formulation of Adderall<sup>®</sup> and, in the words of the agency: "at least one adequate and well controlled clinical study would be needed to support efficacy." *Id.*

At a subsequent development plan meeting on July 20, 1999, FDA reiterated the "identical" pharmacokinetic profile requirement, and stated that "seeking approval through the bioequivalence route may be difficult since the comparative PK profile indicated a slightly different kinetic pattern between the IR and ER Adderall<sup>®</sup> formulations for the two plasma peaks." The agency went on to note: "Since for this drug [Adderall XR<sup>®</sup> MASP] the rate of input may be **related to clinical efficacy**, the plasma concentration-time curves would have to be **superimposable** for both peaks." (See FDA's Minutes of Clinical Development Meeting with Shire Laboratories, page 2, copy attached as **Exhibit C**, emphasis added).

It is evident that FDA based its requirement for an identical plasma concentration-time pharmacokinetic profile in a bioequivalence study comparing Adderall XR<sup>®</sup> MASP to Adderall<sup>®</sup> IR administered BID on the following factors:

- It is established that symptoms of ADHD occur over the course of a child's daily schedule. Accordingly, clinical effectiveness at particular time periods is clinically important.<sup>2</sup>
- Clinical trial data for both Adderall XR<sup>®</sup> MASP and extended-release methylphenidate products have demonstrated that the rate of input (absorption) of an extended-release drug indicated for management of ADHD symptoms impacts clinical efficacy (see Section B.3 below).
- Different technologies for extending drug release, and potentially varying fractions of amphetamine salts provided in different extended-release formulations, may result in an inferior product such that dissimilar pharmacokinetic profiles may result in therapeutic non-equivalence.

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<sup>2</sup> American Academy of Pediatrics Committee on Quality Improvement/Subcommittee on Attention-Deficit/Hyperactivity Disorder. Treatment of the School-Aged Child with Attention- Deficit/Hyperactivity Disorder. *Pediatrics*. 2001; 108: 1033-1044.

## **2. Pharmacokinetic and Clinical Studies Conducted on Adderall XR<sup>®</sup> MASP**

In the initial development of Adderall XR<sup>®</sup> MASP, Shire conducted a bioequivalence study between Adderall XR<sup>®</sup> MASP and Adderall<sup>®</sup> IR administered BID. The study results, illustrated in the Adderall XR<sup>®</sup> MASP package insert, show an “inflection point” between the plasma concentration-time curves approximately four hours following administration, indicating that these profiles are not identical. The study did, however, demonstrate bioequivalence within FDA’s traditional bioequivalence confidence limit of 80-125% between test and reference products for AUC and C<sub>max</sub> pharmacokinetic parameters.

Nevertheless, due to the slight difference in pharmacokinetic profiles, FDA would not accept Shire’s bioequivalence study as the basis for regulatory approval for Adderall XR<sup>®</sup> MASP. The agency required that Shire conduct at least one clinical efficacy study. Shire thereupon performed two double-blind, randomized, placebo-controlled clinical efficacy studies in children aged 6-12 (Studies SLI 381.201 and SLI 381.301). The results from both trials showed clinical efficacy significantly favoring Adderall XR<sup>®</sup> MASP over placebo in the primary efficacy endpoints. Shire’s NDA for Adderall XR<sup>®</sup> MASP was subsequently approved on October 11, 2001 based primarily upon these clinical data. Additionally, Shire received approval for Adderall XR<sup>®</sup> MASP for use in adults with ADHD on August 11, 2004 and in adolescents on July 21, 2005. These approvals were similarly based on a well-controlled clinical trial in each of these populations.

## **3. Plasma Concentration-Time Course Relationship to Clinical Efficacy: Adderall XR<sup>®</sup> MASP**

Study SLI 381.201 referenced above, entitled “A Randomized, Double-Blind, Placebo and Active-Controlled, Crossover Study of SLI 381 in Children with Attention Deficit Hyperactivity Disorder”, provided detailed evidence in support of a pharmacokinetic/pharmacodynamic relationship for Adderall XR<sup>®</sup> MASP by measuring the primary efficacy endpoints at 0.5, 1.5, 4.5, 6.0, 7.5, 9.0, 10.5 and 12 hours post dosing. The primary efficacy endpoints in this trial were the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) Rating Scale and the

Permanent Product (PERMP) derived measures. The main text of the clinical study report for trial SLI 381.201 (with related tables and figures) is provided as **Exhibit D**. It should also be noted that Swanson, et al. (2004) described substantially similar results as those generated in SLI 381.201 for two extended-release methylphenidate products. A reprint of this publication is provided as **Exhibit E**.

**4. Generic and Follow-On Versions of Adderall XR<sup>®</sup> MASP Must Meet FDA's "Identical" Plasma Concentration-Time Profile Requirement**

FDA was clearly concerned with the rate of drug input and its potential effects on clinical efficacy when it required Shire to demonstrate an identical plasma concentration-time profile to obtain regulatory approval of Adderall XR<sup>®</sup> MASP via any bioequivalence-based approach. Since FDA has determined that only a bioequivalence study producing identical or "superimposable" plasma concentration-time curves is sufficiently predictive of desired ADHD clinical patient outcomes to permit such a study to substitute for a clinical efficacy trial to support regulatory approval of Adderall XR<sup>®</sup> MASP, other applicants who seek to obtain regulatory approval of generic or follow-on versions of Adderall XR<sup>®</sup> MASP via ANDAs or Section 505(b)(2) NDAs should reasonably be held to the same requirement.

To reiterate, given that a superimposable plasma concentration-time profile standard was applied by FDA when Adderall XR<sup>®</sup> MASP was compared to Adderall<sup>®</sup> IR for therapeutic equivalence purposes, there appears to be no valid clinical or regulatory rationale for dispensing with this standard when subsequent applicants attempt to demonstrate therapeutic equivalence of a generic or follow-on version of Adderall XR<sup>®</sup> MASP to the reference product.

**5. Additional Partial AUC Measurements Required**

**5.1 AUC<sub>pR</sub>**

As provided in its *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (March 2003)*, FDA describes pharmacokinetic parameters appropriate for assessing peak exposure ( $C_{max}$ ) and total exposure

( $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ) when attempting to demonstrate bioequivalence between test and reference drug products. Additionally, the FDA recommends that, for drugs such as Adderall XR<sup>®</sup> MASP in which early exposure measures are relevant for determining therapeutic equivalence, an assessment of partial AUC also be conducted. The partial AUC measure described is the population median of  $T_{max}$  values for the reference formulation ( $AUC_{pR}$ ). As the cited *Bioavailability and Bioequivalence Studies* Guidance states in section III(A)(8)(a):

“a. Early Exposure

For orally administered immediate-release drug products, BE may 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. The partial area should be truncated at the population median of  $T_{max}$  values for the reference formulation. At least two quantifiable samples should be collected before the expected peak time to allow adequate estimation of the partial area.”

Given the demonstrated clinical relevance of early drug exposure in administering Adderall XR<sup>®</sup> MASP, the tenets of FDA's guidance apply directly to this situation. It is strongly recommended that the pharmacokinetic measure  $AUC_{pR}$  also be required in any bioequivalence studies comparing a generic version of Adderall XR MASP<sup>®</sup> to the reference product in an ANDA or Section 505(b)(2) NDAs referencing Adderall XR<sup>®</sup> MASP. Thus bioequivalence, for both dextro- and levo- isomers of amphetamine, should be determined in fed and fasted states by  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $AUC_{pR}$  in all ANDAs and Section 505(b)(2) NDAs referencing Adderall XR<sup>®</sup> MASP.

## 5.2 Partial AUC Measurements up to $T_{max}$

To fully characterize the similarity of the plasma concentration-time curves between test and reference products in this context, it is further urged that additional partial AUC measurements be required up to  $T_{max}$  (approximately four hours with Adderall XR<sup>®</sup> MASP). Specifically,

AUC<sub>0-1</sub>, AUC<sub>1-2</sub>, AUC<sub>2-3</sub> and AUC<sub>3-4</sub> should also be demonstrated to be similar to such a degree, in fed and fasted states, as to further comply with FDA's stated requirement of pharmacokinetic profiles that are superimposable.

**6. Differences in Pharmacokinetics of Adderall XR<sup>®</sup> MASP in Children and Adults**

As described in the package insert, there are meaningful differences in the pharmacokinetics of Adderall XR<sup>®</sup> MASP in children and adults. Included in **Exhibit F** are data plots obtained from Shire pharmacokinetic trials SLI 381-103 (adult) and SLI 381-107 (pediatric). These plots show a 2-3x increase in C<sub>max</sub> and AUC for both d- and l-amphetamine in children as compared to adults. Please note that the main text of each of these clinical study reports are provided in **Exhibits G and H** for reference. These differences illustrate the need for any bioequivalence studies for purposes of generic or follow-on product approvals be conducted in **both children and adults**, with the data similarity requirements outlined previously applied to both populations. This will ensure a generic formulation of Adderall XR<sup>®</sup> MASP will be safe and effective in each of these clinically distinct populations. Additionally, since over 70% of the prescriptions written annually for Adderall XR<sup>®</sup> MASP are for children, and an adult indication will not be available in generic labeling until expiration of a three-year Hatch-Waxman exclusivity period for the adult indication, it is particularly appropriate to assess bioequivalence in the pediatric population.

**7. Alternative Clinical Study Requirement**

If an ANDA or Section 505(b)(2) applicant fails to show an identical plasma concentration-time profile in a bioequivalence study in the appropriate populations, FDA should require a clinical efficacy study be conducted in each currently approved population (i.e. children, adolescents and adults) to obtain regulatory approval. The design of each of these studies should be the same as the clinical studies described in the approved Adderall XR<sup>®</sup> MASP package insert, or a design of comparable rigor based on current FDA requirements.

Absent bioequivalence studies showing an identical plasma concentration-time profile to Adderall XR<sup>®</sup> MASP (as defined herein) conducted in both children and adults, or clinical studies demonstrating safety and efficacy in each of the approved populations, FDA should not grant regulatory approval of a generic or follow-on version of Adderall XR<sup>®</sup> MASP.

**8. Expert Consultation Obtained for this Petition**

Please note that independent experts Roger Porter, M.D. and Thomas Ludden, Ph.D. have been consulted in the development of this petition. Their professional qualifications to act in this capacity are summarized in **Exhibits I and J**, respectively.

**9. Copies Provided to CDER Offices**

Please note that copies of this Petition are being provided to CDER's Office of Generic Drugs (attention: G. Buehler, R.Ph.) as well as the CDER ODE I Divisions of Psychiatry Products (attention: T. Laughren, M.D.) and Neurology Drug Products (attention: R. Katz, M.D.).

**C. ENVIRONMENTAL IMPACT**

Under 21 CFR § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

**D. ECONOMIC IMPACT**

According to 21 CFR § 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

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includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

SHIRE PHARMACEUTICALS GROUP, plc

By:                     E. Salinas                    

Eliseo O. Salinas, M.D., M.Sc.

Executive Vice President, Global Research and  
Development, and Chief Scientific Officer

Exhibits A - J attached

cc: (w/attachments):

Gary J. Buehler, R.Ph. (OGD)  
Thomas P. Laughren, M.D. (ODE I - DPP)  
Russell G. Katz, M.D. (ODE I - DNP)