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January 19, 2006

Shire

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U.S. Food and Drug Administration
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CITIZEN PETITION (DOCKET 2005-0420/CP1) - SUPPLEMENT

Reference is made to the pending Citizen Petition and corresponding docket number referenced above, originally filed on October 18, 2005. The purpose of this correspondence is to provide a supplement to this Citizen Petition (in quadruplicate) as per 21 C.F.R. §10.30(e)(4)(g). We also acknowledge comments submitted in reference to this Petition entered in the docket on December 21, 2005 and January 4, 2006 by Barr Laboratories, Inc. and Impax Laboratories, Inc., respectively.

A. Introduction:

The purpose of this Supplement is to provide additional relevant data obtained following submission of Shire's pending Citizen Petition (see **Section B herein**). These recently acquired data have prompted an in-depth review of information provided in the pending Petition from clinical trial SLI 381-201 as described in **Section C**. In addition, Shire has had recent dialogue with CDER's Division of Psychiatry Products that continues to demonstrate FDA's position that standard bioequivalence criteria are not sufficiently rigorous when assessing the potential impact of changes to extended-release formulations in which the pharmacokinetic profile is expected to have a meaningful impact on therapeutic effect. This dialogue is described in **Section D.**

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B. Results of Study SLI 381-111:

Shire has recently completed and submitted to the FDA a study (SLI 381-111) requested by the Agency entitled "A Phase 1 Study to Assess the Relative Bioavailability of Single 30mg Doses of ADDERALL XR® Capsules and ADDERALL® Tablets vs. an Oral Solution of Mixed Amphetamine Salts (MAS) in Healthy Adult Volunteers Aged 18-55." The main text of this study report is provided in **Exhibit A hereto.** This study examined three equal-strength, distinct formulations of mixed amphetamine salts: Adderall (immediate-release formulation), Adderall XR, and an oral solution to serve as a reference (i.e. maximally bioavailable) formulation. As expected, there was a significant difference in plasma concentration-time profiles obtained following administration of the two immediate-release formulations (Adderall and MAS oral solution) and the extended-release formulation of Adderall XR. Resulting plasma concentration-time profiles are provided below for d- and l-amphetamine in Figures 1 and 2, respectively.

Figure 1: Study SLI381-111: Plasma profiles of d-amphetamine over 8 hours following administration to normal volunteers

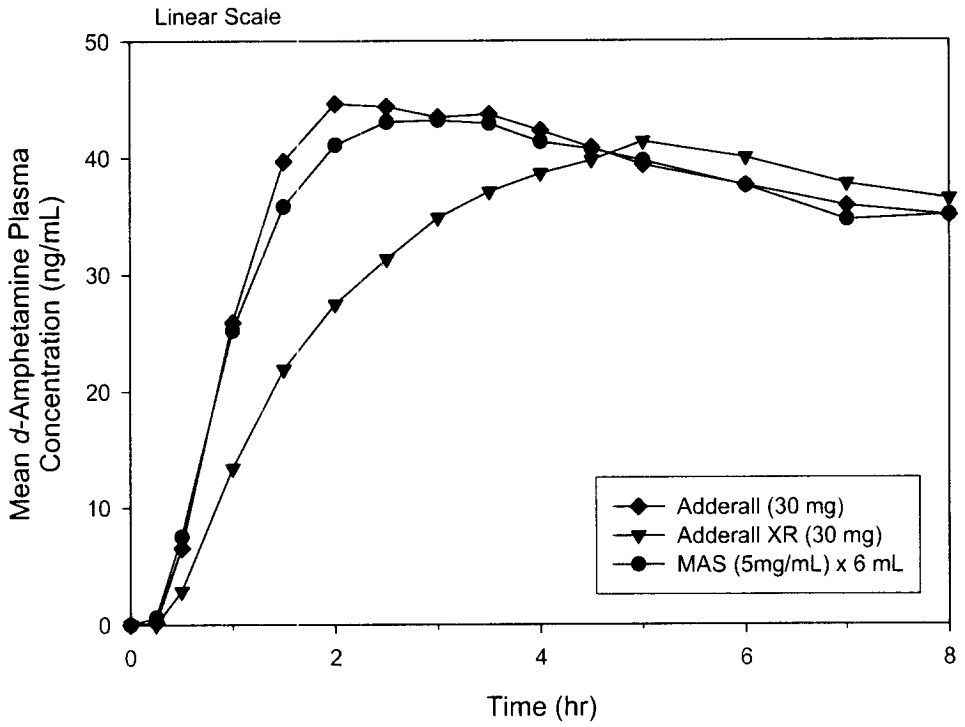
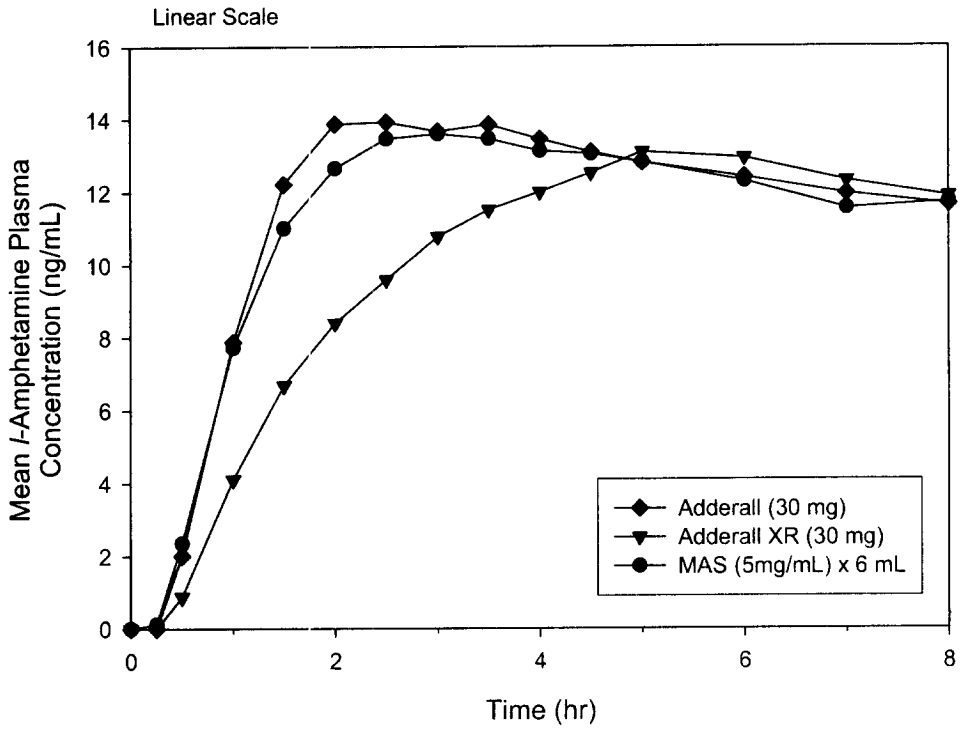


Figure 2: Study SLI381-111: Plasma profiles of l-amphetamine over 8 hours following administration to normal volunteers



Summarized in Tables 1 through 4 below are the relevant statistical parameters associated with the above plasma profiles:

Table 1: *d*-Amphetamine Plasma Pharmacokinetic Parameters Following a Single 30mg Amphetamine Dose to Healthy Subjects

Parameter	Statistic	Treatment		
		Adderall XR (A)	Adderall (B)	MAS (C)
	N*	18	17	17
C_{max} (ng/mL)	Mean (SD)	44.0 (7.3)	46.2 (10.4)	45.4 (8.7)
T_{max} (hr)	Median (Min, Max)	5.0 (2.5, 10.0)	2.5 (2.0, 4.0)	3.0 (2.0, 4.5)
$AUC_{0-\infty}$ (hr*ng /mL)	Mean (SD)	843.8 (120.0)	844.1 (102.3)	838.8 (136.3)
AUC_{0-t} (hr*ng /mL)	Mean (SD)	821.7 (118.4)	825.1 (100.7)	820.4 (135.5)

Table 2: Statistical Analysis Results of Plasma *d*-Amphetamine Following a Single 30mg Amphetamine Dose to Healthy Subjects

Parameter	N	Exponentiated LS Means			Ratio of LS Means		90% CI of LS Mean Ratio	
		Adderall XR (A)	Adderall (B)	MAS (C)	A/C	B/C	A/C	B/C
C_{max} (ng/mL)	18	43.4	45.2	44.7	97.1	101.0	92.5, 101.9	96.2, 106.0
$AUC_{0-\infty}$ (hr*ng /mL)	18	836.4	839.2	830.9	100.7	101.0	96.3, 105.2	96.6, 105.6
AUC_{0-t} (hr*ng/mL)	18	814.4	820.7	813.1	100.2	100.9	95.9, 104.6	96.7, 105.4

Table 3: *l*-Amphetamine Plasma Pharmacokinetic Parameters Following a Single 30mg Amphetamine Dose to Healthy Subjects

Parameter	Statistic	Treatment		
		Adderall XR (A)	Adderall (B)	MAS (C)
	N*	18	17	17
C_{max} (ng/mL)	Mean (SD)	14.0 (2.5)	14.6 (3.2)	14.3 (2.8)
T_{max} (hr)	Median (Min, Max)	5.0 (3.0, 10.0)	2.5 (2.0, 10.0)	3.0 (2.5, 4.5)
$AUC_{0-\infty}$ (hr*ng /mL)	Mean (SD)	315.2 (51.9)	318.5 (49.1)	318.0 (61.3)
AUC_{0-t} (hr*ng /mL)	Mean (SD)	297.6 (49.6)	302.2 (46.6)	302.3 (59.7)

Table 4: Statistical Analysis Results of Plasma *l*-Amphetamine Following a Single 30mg Amphetamine Dose to Healthy Subjects

Parameter	N	Exponentiated LS Means			Ratio of LS Means		90% CI of LS Mean Ratio	
		Adderall XR (A)	Adderall (B)	MAS (C)	A/C	B/C	A/C	B/C
C_{max} (ng/mL)	18	13.8	14.3	14.1	97.7	101.6	92.8, 102.9	96.5, 106.9
$AUC_{0-\infty}$ (hr*ng /mL)	18	311.6	314.2	312.4	99.7	100.6	94.9, 104.8	95.7, 105.7
AUC_{0-t} (hr*ng/mL)	18	294.2	298.5	297.3	99.0	100.4	94.3, 103.9	95.6, 105.4

The statistical data presented in Tables 2 and 4 above serve to illustrate the relative insensitivity of routine bioequivalence measures to determine differences in formulations of this nature. According to the bioequivalence criteria of C_{max} and AUC currently accepted by FDA, the differences in these formulations are virtually meaningless, in that a maximally available oral solution is mathematically demonstrated to be bioequivalent to both an immediate-release tablet formulation (which one would expect) as well as an extended-release, multiple-particulate formulation such as that contained in Adderall XR® (which one would not expect). This mathematical agreement underscores the lack of adequate scientific rigor standard bioequivalence criteria provide in determining meaningful differences in formulations that would reasonably be expected to result in differences in therapeutic effect. We believe this further

substantiates Shire's position that additional and more stringent bioequivalence parameters such as those proposed in our pending Petition must be required for an adequate assessment of the potential for therapeutic equivalence of a generic version of Adderall XR® to the innovator product.

The results above indicate that, according to the currently accepted bioequivalence assessment methodology, a generic manufacturer would only be required to formulate a generic version of Adderall XR® that has the correct amount of mixed amphetamine salts in the capsule formulation in order to have a bioequivalent version of the innovator product, with no consideration of the extended-release technology employed. We believe that FDA would agree that a generic version of a widely prescribed medication that lacks the intrinsic properties of the extended-release, once-daily formulation comprising Adderall XR® would be contrary to the expectation that generic formulations be therapeutically equivalent to a reference listed drug product. Shire fully supports the need for high-quality generic products, but not at the expense of the basic premise that a generic product is expected to perform the same therapeutically as the innovator product. While standard bioequivalence criteria are adequate to establish this therapeutic equivalence for many products, in the case of Adderall XR® it is clear that, at a minimum, additional and more rigorous pharmacokinetic agreement in the indicated patient populations – or the generation of confirmatory clinical data – must be required for a generic version of Adderall XR® to be adequately assured to be therapeutically equivalent to this extended-release, once-daily product.

C. Clinical Impact of Different Release Rates Obtained from Bioequivalent Formulations – Retrospective Review of Study SLI381-201:

Once the data from Study SLI381-111 above were obtained, information from study SLI381-201 (submitted in our pending Citizen Petition) was reviewed in detail for differences in pharmacodynamic measurements resulting from administration of Adderall® and Adderall XR®. This review indicates there is a clear difference in the pharmacodynamic effect during the efficacy onset period. Although the main purpose of this study was to detect differences between active treatments and placebo and was not designed to detect differences between dose groups, we believe that this information is relevant and clinically meaningful as presented.

As illustrated in figures 4 through 7 below, there are clinically meaningful differences observed in SKAMP and PERMP measures (primary endpoints) resulting from administration of these two fundamentally different, yet bioequivalent, formulations:

Figure 4: Comparison of PERMP (Correct) Following Administration of Adderall 10 mg or Adderall XR 10mg over 8 hours following dosing (Study SLI381-201)

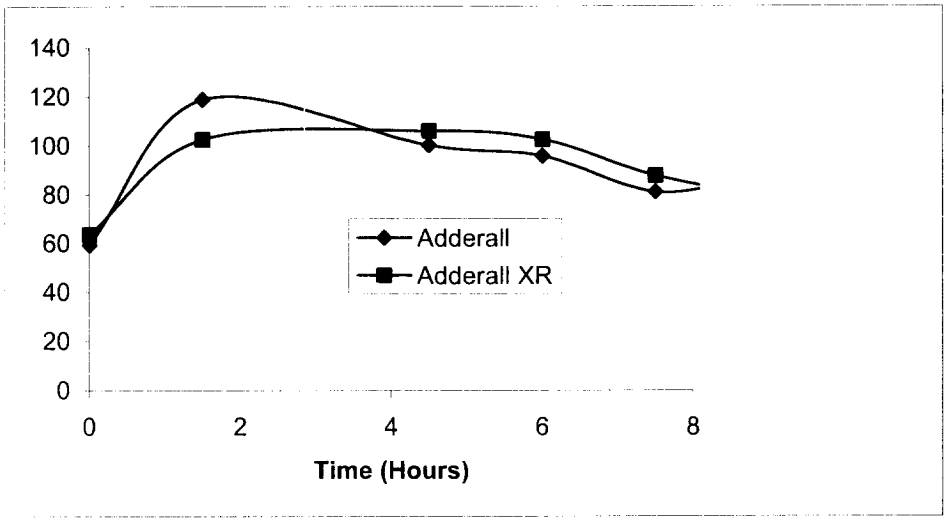


Figure 5: Comparison of PERMP (Attempted) Following Administration of Adderall 10mg or Adderall XR 10mg over 8 hours Following Dosing

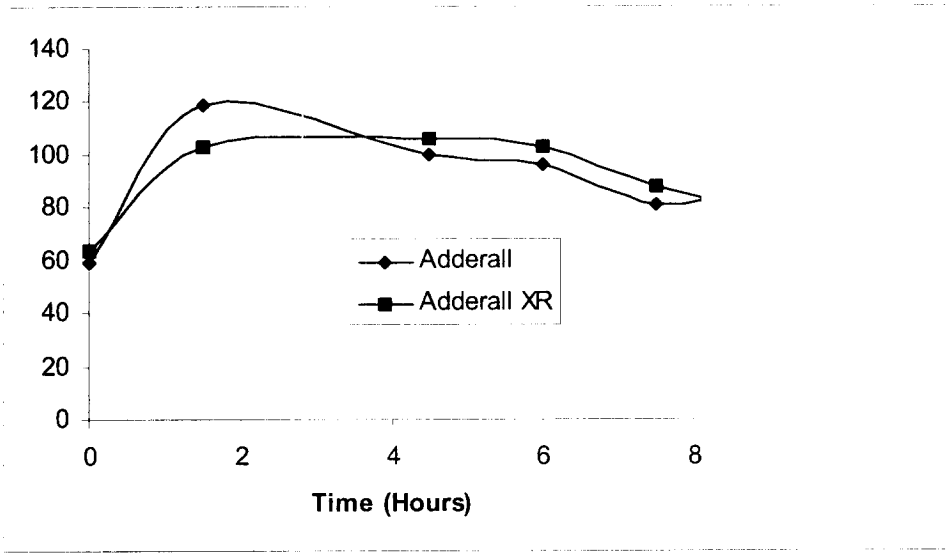


Figure 6: Comparison of SKAMP-Deportment Scores Following Administration of Adderall 10 mg or Adderall XR 10mg Measured Over 8 hours Following Dosing

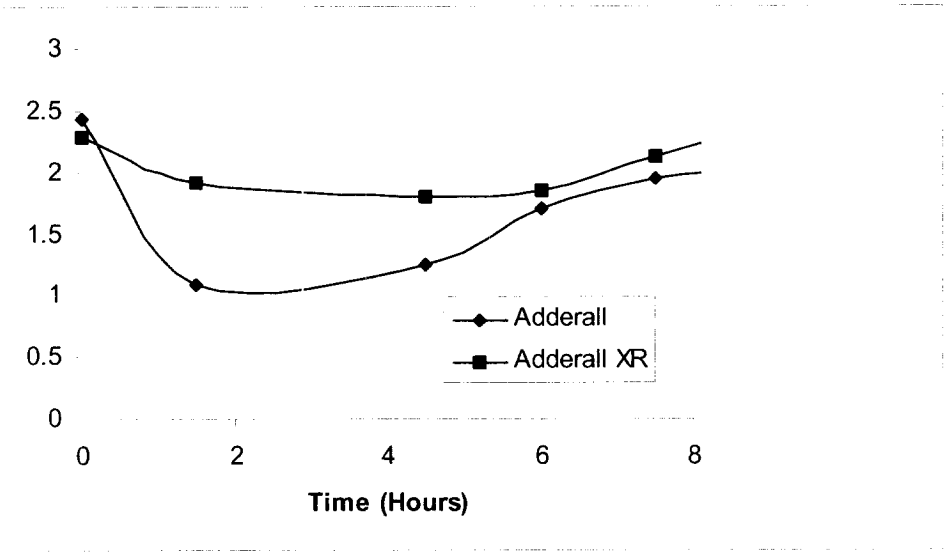
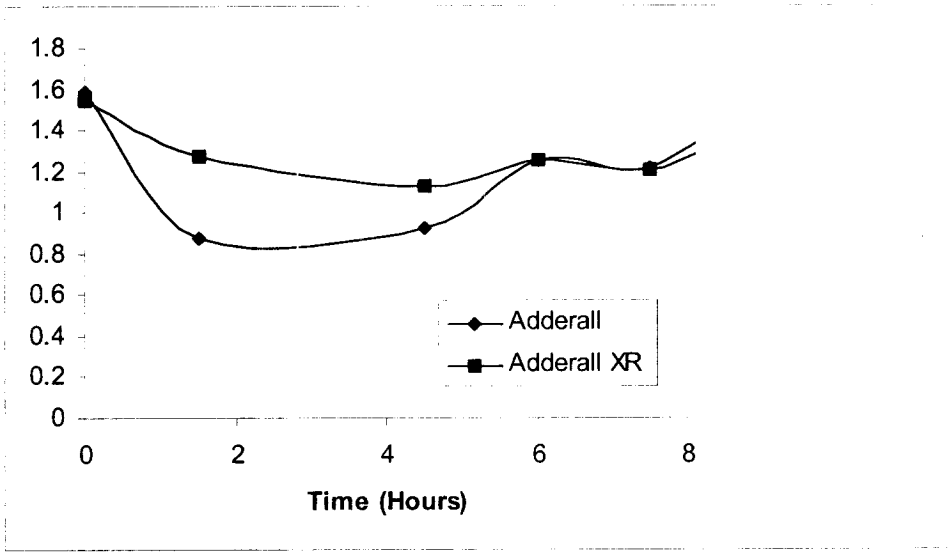


Figure 7: Comparison of SKAMP-Attention Scores Following Administration of Adderall 10 mg or Adderall XR 10mg Measured Over 8 hours Following Dosing



When one reviews the mean PERMP (Correct and Attempted) as well as mean SKAMP (Deportment and Attention) scores over the first 8 hours following dosing of Adderall® and Adderall XR®, there is a consistent difference in pharmacodynamic profiles between the two formulations. There is approximately a 15% difference in clinical effect in both sets of PERMP scores. Pharmacodynamic differences are more pronounced in the SKAMP scores, where there is approximately a 30-40% difference between the two treatment groups over the same 8 hours. The SKAMP scores of the two treatments diverge at the first measured time point and are clearly separated until 6 hours post-dosing. Thus, the data from this study demonstrate that there are clinically meaningful pharmacodynamic differences between these immediate- and extended-release formulations over the absorption phase, despite the fact that these two formulations were shown to be bioequivalent according to standard bioequivalence rules. It is well established in clinical guidelines associated with the treatment of ADHD that short- and long-acting stimulant medications provide different benefits in a clinical setting. Therefore these marked clinical differences must be addressed by more than a standard bioequivalence approach, irrespective of any technical statistical considerations (see Impax comments on Shire Petition, Dec. 28, 2005, at 4).

As you are aware, the currently accepted bioequivalence parameters are intended to serve as a surrogate for the clinical demonstration of equivalent efficacy and safety of a generic product when compared to the reference listed drug. However, when evidence exists, such as in this case, that this surrogacy may not be valid, there is a requirement for such equivalency to be tested and proven through more clinically relevant means. This could be accomplished through a

confirmatory clinical trial in the indicated populations, or at a minimum through the use of additional and more stringent bioequivalence criteria as described in our pending Petition.

D. Shire/FDA Meeting Held on November 18, 2005:

During a meeting held with FDA on November 18, 2005 to discuss another extended-release amphetamine product Shire has in development, members of FDA provided extensive commentary stating their scientific opinion that standard bioequivalence criteria are inadequate to fully assess the potential impact of formulation changes made to extended-release drug products. In general, the FDA representatives felt strongly that for modified-release formulations in which plasma concentration-time relationships are meaningful for clinical efficacy during specific periods of exposure, scientific rigor beyond the standard surrogate measures of bioequivalence, including superposition of plasma profiles, should be employed to ensure that these changes do not have meaningful effects on a particular modified-release formulation's clinical performance. For reference, the minutes recording these comments were issued by FDA to Shire on December 22, 2005 under IND 66,329.

These comments including, but not limited to, those described above reaffirmed the scientific guidance provided to Shire in discussions with FDA in the original development of Adderall XR® as described previously in our pending Petition.

E. Conclusion:

Shire believes that the information provided in this Supplement provides additional significant support to the position presented in our pending Citizen Petition. Accordingly, we respectfully request that FDA consider this supplemental information, including a detailed review of the full FDA meeting minutes referenced above, in the consideration of this Petition

Please note that the information presented in this Supplement does not impact the Economic Impact, Environmental Impact or Certification statements made in our pending Petition.

Respectfully submitted,

SHIRE PHARMACEUTICALS GROUP, plc

By: _____

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Exhibit A attached

cc: (w/attachments):

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