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December 28, 2005

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

Re: IMPAX Laboratories, Inc.'s Comments Regarding Docket No. 2005P-0420
Bioequivalence Criteria for Generic Versions of Adderall XR® (mixed salts of a
single-entity amphetamine product) Extended-Release Capsules

Dear Sir or Madam:

Reference is made to the October 17, 2005 correspondence from Shire Pharmaceuticals providing resubmission of an October 12, 2005 Citizen Petition (CP) pertaining to Adderall XR® Extended-Release Capsules. The CP was filed by the Division of Dockets Management, FDA, on October 18, 2005 and was assigned Docket No. 2005P-0420.

IMPAX Laboratories, Inc. (IMPAX) has reviewed the Shire CP and has substantial disagreement with the scientific arguments presented therein. Accordingly, we are submitting our comments to the Shire CP herewith and request that this correspondence be filed as part of the administrative record for Docket No. 2005P-0420.

Sincerely,
IMPAX Laboratories, Inc.

A handwritten signature in black ink, appearing to read 'Mark C. Shaw'.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

Enclosure

2005P-0420

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On October 17, 2005 Shire Pharmaceuticals Group plc (Shire) submitted a Citizen Petition (CP) requesting the Food and Drug Administration (FDA) to require that bioequivalence (BE) criteria for the *d*-amphetamine and *l*-amphetamine active moieties of Adderall XR® Extended-Release Capsules be applied separately to pediatric (ages 6-12) and adult (ages 18 and older) subjects under both fasting and fed conditions. According to Shire, the basis of the CP is to ensure therapeutic equivalence in two ADHD patient populations between any generic or follow-on 505(b)(2) products and Adderall XR® Extended-Release Capsules (MASP; Mixed Salts of a Single-Entity Amphetamine Product) :

- Demonstration of identical (superimposable) plasma concentration-time pharmacokinetic profile, and such an identical pharmacokinetic profile must be demonstrated by
 - BE for traditional pharmacokinetic parameters including C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$
 - BE for early absorption measurements (AUC_{pR}) following administration, where AUC_{pR} is per FDA's definition as the population median T_{max} of the reference formulation for an immediate-release product
 - BE for additional partial AUC measurements for each of the following time points, up to 4 hours: AUC_{0-1} , AUC_{1-2} , AUC_{2-3} , and AUC_{3-4}

Shire further demanded that if a generic or follow-on 505(b)(2) applicant fails to meet the above proposed BE criteria, FDA should require a clinical efficacy study in each currently approved population (i.e. children, adolescents and adults), and the design of each of these studies should be the same as the clinical studies described in the approved Adderall XR® MASP package insert, or a design of comparable rigor based on current FDA requirements.

Shire listed 10 grounds as forming the basis for its CP. These 10 grounds can be summarized into three main points. IMPAX's comments on each of these three points follow immediately after each point:

IMPAX Summary of Shire Point A:

When Shire was developing Adderall XR®, a new QD MASP product intended to replace the BID Adderall® IR tablet given 4 to 6 hours apart, FDA was concerned that the rate of input for this drug may be related to clinical efficacy, the plasma concentration time curves would have to be superimposable for both peaks, and the standard PK parameters will need to be assessed for both peaks.

In the correspondence dated May 4, 1999, FDA indicated that,

"Assuming that the time concentration profile for the modified release Adderall product will not be identical to that seen with bid dosing with immediate release Adderall, at least one adequate and well controlled clinical study in children with ADHD to demonstrate clinical efficacy for the product."

In the July 20, 1999 meeting, Shire presented 24-hour comparative PK data, presumably single-dose PK data, to provide support for the biopharmaceutical approach for development of Adderall® XR. Based on the data provided by Shire, FDA noted 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® formulations for the two plasma peaks. Since for this drug, the rate of input may be related to clinical efficacy, the plasma concentration time curves would have to be superimposable for both peaks, and the standard PK parameters will need to be assessed for both peaks.”

In the same meeting memo, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) outlined two possible development plans based on a biopharmaceutical approach.

Option 1 was to conduct all BA/BE studies in pediatric subjects, including demonstration of multiple-dose BE at the lowest dose, assessment of food/sprinkle effects at the lowest dose, and assessment of dosage strength equivalency (3X10 mg vs. 1X30 mg).

Option 2 was to demonstrate multiple-dose BE at the highest dose and assess food effect/sprinkle effects at the highest dose in adult subjects, while assessing dosage strength equivalency (3X10 mg vs. 1X30 mg) in pediatric subjects.

IMPAX Comments on Shire Point A:

Based on IMPAX's review of the SBA, Shire apparently decided to demonstrate the efficacy of Adderall® XR MASP in children with ADHD (Study SLI381.301) using a placebo-controlled trial design. In addition, Shire also conducted a 5-way (10 mg IR Adderall®, 10, 20, and 30 mg Adderall XR®, and placebo), crossover PK/PD study (Study SLI381.201), presumably to investigate the correlation between concentrations and clinical effects for mixed amphetamine salts product.

Although FDA was originally concerned that

“Since for this drug, the rate of input may be related to clinical efficacy, the plasma concentration time curves would have to be superimposable for both peaks, and the standard PK parameters will need to be assessed for both peaks.”

the results of Shire's SLI381.201 PK/PD study clearly demonstrated that therapeutic equivalence of mixed amphetamine salts product does not require superimposable/identical plasma concentration-time profiles.

Specifically, the results of Shire's Study SLI381.201 showed that even with substantially different initial input rates, hence non-superimposable plasma concentration-time profiles between Adderall® 10 mg tablet and Adderall XR® 10 mg capsule (Figure 1), the clinical

effects over a 12-hour period were essentially the same between the two formulations (Table 1). These results directly address FDA's concern on the effect of input rate of mixed amphetamine salt products on the clinical effects, and indicate that superimposable/identical plasma concentration-time profiles are not required in order for mixed amphetamine salt products to yield similar clinical effects.

IMPAX Summary of Shire Point B:

Shire stated that,

“Clinical data for both Adderall XR[®] 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”.

Shire also stated that,

“FDA recommends that, for drugs such as Adderall XR[®] MASP in which early exposure measures are relevant for determining therapeutic equivalence, assessment of partial AUC also be conducted.”

Shire cited Study SLI381.201 and a publication by Swanson *et al.* in 2004 on methylphenidate to support the presence of clinically relevant early exposures and PK/PD relationship for Adderall XR[®] MASP, and the need for a BE requirement during early exposure (AUC_{pR}). Shire observed an inflection point at 4 hours after dosing of Adderall XR[®] MASP based on Figure 1 in the package insert of Adderall XR[®] MASP, and further demanded the need for BE requirements for AUC_{0-1} , AUC_{1-2} , AUC_{2-3} , and AUC_{3-4} to ensure “superimposable” pharmacokinetic profiles of follow-on generic products.

IMPAX's Comments on Shire Point B :

First, IMPAX is not aware of any recommendation from FDA for ANDAs of Adderall[®] XR that for drugs such as Adderall XR[®] MASP in which early exposure measures are relevant for determining therapeutic equivalence, assessment of partial AUC also be conducted”

On the contrary, Shire Study SLI381.201 actually provided clear evidence that a large range of initial exposure to mixed salts of *d*-amphetamine and *l*-amphetamine will produce similar clinical effects. Therefore, there is no need to require ANDA applicants to demonstrate BE for AUC_{0-4} , AUC_{0-1} , AUC_{1-2} , AUC_{2-3} , and AUC_{3-4} as requested by Shire.

As illustrated in Figure 1, the concentration-time profiles of *d*- and *l*-amphetamine between the 10 mg Adderall IR and XR[®] MASP formulations were not identical at all time points except at one time point (approximately 10 hours post-dose) where two curves crossed. However, as summarized in Table 2, the two formulations had comparable steady-state C_{max} and AUC values at the 10 mg dose level. Based on Figure 1 using IR as the reference, the mean differences between the two formulations (Table 3) were estimated to range from approximately -35% to +32% for *d*-amphetamine and from

approximately -32% to +10% for *l*-amphetamine from pre-dose to 4.5 hours post-dose. The differences were estimated to range from approximately -35% to +49% for *d*-amphetamine, and from approximately -32% to +40% for *l*-amphetamine over a 24-hr period (Table 3).

However, as shown in Table 1, of the 4 clinical effects (SKAMP attention, SKAMP deportment, PERMP number attempted and PERMP Number Correct) monitored over a 12-hr period, only 3/32 PD measurements showed statistically significant differences at the 10 mg dose level. However, of these three significant differences, the two differences observed in PERMP-Numbers Attempted and Number Correct at 10.5 hours were no longer present at 12 hours after dosing as would be expected based on Figure 1, suggesting the statistically significant differences may be due to randomness related to multiple comparisons. Therefore, differences in early exposure to amphetamine when the C_{max} and AUC are comparable between two formulations do not translate to therapeutic in-equivalence.

Furthermore, in the same study (SLI381.201), when comparing Adderall XR[®] MASP 20 mg using Adderall IR 10 mg as the reference, clinical effects between these two regimens during the initial 4 hours were not statistically significantly different, even though the concentration differences can be estimated to range from approximately +30% to +164% for *d*-amphetamine and from approximately +37% to +120% for *l*-amphetamine from pre-dose to 4.5 hours post-dose, assuming dose-linearity between Adderall XR[®] MASP 10 and 20 mg (Table 3).

In fact, FDA's assessment of Study 381.201, by Dr. Hong Zhao, indicated that,

"Plasma concentrations of amphetamine are neither highly nor directly correlated with pharmacodynamic measure."

A publication based on Study 381.201 also stated that,¹

"This study did not identify a clear relationship between drug concentration levels and behavioral response."

Therefore, the results from Shire's Study SLI381.201 actually indicate that a wide range of exposures/concentrations from mixed amphetamine salts will result in similar clinical effects. As such, there is no need to demonstrate superimposable plasma concentration-time profiles for generic Adderall XR[®] MASP. Similarly, a BE requirement based on 0-4 hour AUC or a point-to-point BE match in terms of AUC₀₋₁, AUC₁₋₂, AUC₂₋₃, and AUC₃₋₄ are not necessary for Adderall XR[®] MASP.

Shire also stated that,²

¹ McGough JJ, Biederman J, et al. Pharmacokinetics of SLI381 (ADDERALL XR), an extended-release formulation of Adderall. *J Am Acad Child Adolesc Psychiatry* 2003;42:684-691.

² Swanson JM, Wigal SB, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics* 2004;113:e206-216.

“Swanson et al. (2004) described substantially similar results as those generated in SLI 381.201 for two extended-release methylphenidate products.”

However, it should be pointed out that Swanson’s study compared products with similar dose levels for three dose levels in three parallel arms, while the only comparison at similar dose levels in Shire’s Study SLI381.201 is Adderall IR and Adderall XR® at a 10 mg dose level, which was analyzed in detail in the above discussion. The conclusion of the above analysis was that differences in early exposure to amphetamine when the C_{max} and AUC are comparable between Adderall IR and Adderall XR® at 10 mg dose level do not translate to therapeutic in-equivalence.

In fact, various studies of methylphenidate products have also shown that a large range of exposures will produce similar clinical effects for methylphenidate.^{3,4,5} In particular, an analysis of the results of the Lopez study (2003)³ also showed that Concerta at 18 and 36 mg produced statistically similar effects over an 8-hour period in a randomized, crossover study.

Most importantly, according to the package insert of Adderall XR®, intake of food does not affect the extent of absorption, but prolongs T_{max} by 2.5 hours for *d*-amphetamine and 2.1 hours for *l*-amphetamine. This indicates that plasma concentration-time profiles of Adderall XR® are not superimposable during the early exposure time period, and AUC_{pR} , AUC_{0-4} , AUC_{0-1} , AUC_{1-2} , AUC_{2-3} , and AUC_{3-4} likely are also not BE under fed and fasting conditions. However, the package insert of Adderall XR® indicates that

“Adderall XR® may be taken with or without food”

under the DOSAGE AND ADMINISTRATION section. This usage instruction clearly indicates that Shire **BELIEVES** that the variations in plasma concentrations or in early exposures will have no clinically relevant effects on the efficacy or safety of Adderall XR®.

Taken together, there is absolutely no justification to require that generic products meet BE requirements (90% confidence interval of 80% to 125%) for AUC_{0-4} , AUC_{0-1} , AUC_{1-2} , AUC_{2-3} , and AUC_{3-4} for Adderall XR® MASP as requested by Shire.

IMPAX Summary of Shire Point C:

Due to differences observed in pharmacokinetics of Adderall XR® MASP in children and adults, Shire demanded that all the BE requirements described above be met for both pediatric (ages 6-12) and adult (ages 18 and older) subjects,

³ Lopez F, Silva R, et al. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. *Paediatr Drugs* 2003;5:545-555.

⁴ Pelham WE, Gnagy EM, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics* 2001;107:E105.

⁵ Swanson JM, Gupta S, et al. Efficacy of a new pattern of delivery of methylphenidate for the treatment of ADHD: effects on activity level in the classroom and on the playground. *J Am Acad Child Adolesc Psychiatry* 2002;41:1306-1314

“to ensure identical pharmacokinetic performance of a generic or follow-on drug product in these distinct ADHD patient populations”

IMPAX's Comments on Shire Point C :

Due to differences in intrinsic physiological differences (e.g., body size and metabolism rate, etc), the pharmacokinetic profiles of ***all drugs*** have been reported to be different and are expected to differ between children and adults. However, when two formulations are bioequivalent in healthy adults using a randomized crossover design, these two formulations are expected to be also bioequivalent in pediatric or any special populations following randomized, crossover studies.

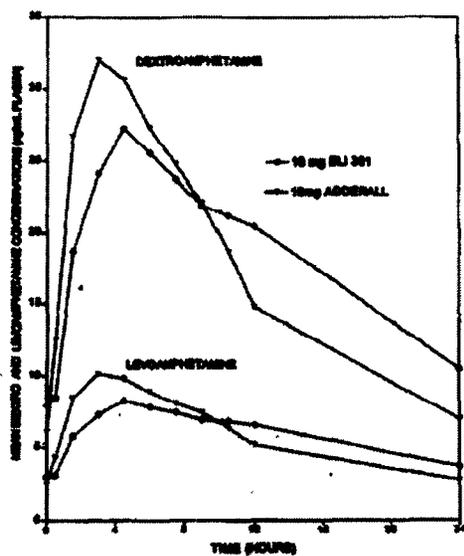
For example, Shire's Study SLI 381.404 showed that Adderall XR® 10 mg and Adderall IR 10 mg were bioequivalent in terms of rate and extent of absorption (AUC and C_{max}) in 8 healthy adult subjects and Shire's Study SLI 381.201 also showed that these two formulations yield similar AUC and C_{max} in pediatric subjects at steady state (Table 2).

In fact, one of the two biopharmaceutical development options that FDA provided to Shire (see Option 2 proposed by FDA OCPB discussed above under Summary Point A) recommended that Shire demonstrate multiple dose BE at the highest dose and assess food effect/sprinkle effects at the highest dose in ***adult*** subjects. The only pediatric study required of Shire was to assess dosage strength equivalency (3 X 10 mg vs. 1 X 30 mg) for Adderall XR® capsules in ***pediatric*** subjects, which is necessary for an NDA in order to provide dosage strength equivalency information for Adderall XR® MASP in a pediatric population.

Conclusions

Based on the review of the SBA of Adderall XR®, package insert of Adderall XR®, and the data presented in the CP for Adderall XR® MASP, IMPAX concludes that demonstration of BE in terms of C_{max} , AUC_{0-t_1} , and $AUC_{0-\infty}$ in healthy adults under fed and fasting conditions is adequate to ensure therapeutic equivalence for generic products of Adderall XR® MASP.

Figure 1 : Steady-state mean *d*-amphetamine and *l*-amphetamine plasma concentrations following multiple dose administration of 10 mg Adderall XR® and 10 mg Adderall IR to pediatric subjects



Note: Figure taken from Clinical Pharmacology Biopharmaceutics Section in Shire NDA filing of Adderall XR (Study 381.201)

Table 1: Comparison of efficacy between SLI381 (Adderall XR®) 10 mg or 20 mg QD vs. Adderall 10 mg QD based on Shire Study 381.201

	Time (hr)							
Assessment (N=40-45)	0	1.5	4.5	6	7.5	9	10.5	12
SLI381 (Adderall XR®) 10 mg QD vs. Adderall IR 10 mg QD								
SKAMP Attention	NSD	NSD	NSD	NSD	NSD	NSD	NSD	SD
SKAMP Department	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
PERMP Number Attempted	NSD	NSD	NSD	NSD	NSD	NSD	SD	NSD
PERMP Number Correct	NSD	NSD	NSD	NSD	NSD	NSD	SD	NSD
SLI381 (Adderall XR®) 20 mg QD vs. Adderall IR 10 mg QD								
SKAMP Attention	NSD	NSD	NSD	NSD	NSD	SD	SD	SD
SKAMP Department	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
PERMP Number Attempted	NSD	NSD	NSD	SD	SD	NSD	SD	SD
PERMP Number Correct	NSD	NSD	NSD	SD	SD	SD	SD	SD

NSD=No statistical significant difference

SD=Statistically significant difference

Note: Data summarized based on SBA of Shire Adderall XR® MASP NDA, Clinical Pharmacology Biopharmaceutics Section.

Table 2: Steady-State pharmacokinetic parameters after SLI381 (Adderall XR®) 10 mg, SLI381 20 mg, and Adderall 10 mg, given once daily in pediatric subjects in Shire Study 381.201*

<i>d</i> -amphetamine	SLI381 (Adderall XR®) 10 mg (N=8)	SLI381 (Adderall XR®) 20 mg (N=9)	Adderall IR 10 mg (N=9)
C_{max}	28.82 ± 6.18	54.63 ± 18.76	33.80 ± 11.07
C_{min}	7.4 ± 3.0	12.3 ± 10.9	5.4 ± 3.1
AUC ₀₋₂₄	431.88 ± 123.01	777.24 ± 304.32	422.51 ± 138.27
T_{max}	6.38 ± 3.47	5.83 ± 1.75	3.33 ± 1.25
<i>l</i> -amphetamine	SLI381 (Adderall XR®) 10 mg (N=8)	SLI381 (Adderall XR®) 20 mg (N=9)	Adderall IR 10 mg (N=9)
C_{max}	8.82 ± 1.85	17.15 ± 6.80	10.64 ± 3.49
C_{min}	2.8 ± 1.0	4.9 ± 4.3	2.2 ± 1.2
AUC ₀₋₂₄	138.34 ± 40.25	261.63 ± 120.15	142.82 ± 46.82
T_{max}	6.38 ± 3.47	5.67 ± 2.22	3.22 ± 1.46

*Data obtained from SBA of Shire NDA filing of Adderall XR®

Note: Study SLI381.201 was a 5-way crossover study, but the pharmacokinetic data presented above were obtained during the last period only

Table 3: Percentage differences, defined as (XR-IR)/IRx100, in amphetamine concentration at various time points between SLI381 (Adderall XR®) 10 mg^a or SLI381 20 mg^b and Adderall 10 mg^a for *d*-amphetamine and *l*-amphetamine based on Shire Study 381.201

Time (hr)	Adderall XR® 10 mg vs. Adderall 10 mg		Adderall XR® 20 mg vs. Adderall 10 mg	
	<i>d</i> -amphetamine	<i>l</i> -amphetamine	<i>d</i> -amphetamine	<i>l</i> -amphetamine
0	32.4	10.0	164.9	120.0
0.5	-33.8	-27.2	32.3	45.5
1.5	-34.9	-31.6	30.1	36.8
3	-24.9	-29.6	50.2	40.8
4.5	-11.3	-15.6	77.5	68.9
6	-6.2	-13.0	87.6	74.1
7.5	-4.5	-9.4	90.9	81.3
9	-1.3	-7.1	97.5	85.7
10.5	14.1	8.0	128.1	115.9
12	38.8	23.6	177.6	147.3
24	48.9	39.7	197.9	179.3

^a Concentration-time data at 10 mg dose level for both formulations were digitized from Clinical Pharmacology Biopharmaceutics Section in Shire Adderall XR® NDA filing.

^b Concentration-time data Adderall XR® at 40 mg were estimated assuming dose proportionality between 10 and 20 mg strength of Adderall XR®