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RESEARCH**

*APPLICATION NUMBER:*  
**202088Orig2s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

NDA: 202-088	Submission Date(s): 08/17/2010
Brand Name	<i>tbd</i>
Generic Name	Phentermine HCl
Reviewer	Immo Zdrojewski, Ph.D.
Clinical Pharmacology Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products
Sponsor	Citius Pharmaceuticals LLC.
Submission Type	505 (b)(2)
Formulation	Oral disintegrating tablet, 15 mg, 30 mg, 37.5 mg
Indication	Short term (a few weeks) adjunct in a regimen of weight reduction

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## 1. Executive Summary

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### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 202-088 and finds it acceptable, pending acceptability of inspection by division of scientific investigations (DSI).

### 1.2 PHASE IV REQUIREMENT

**Post Marketing Requirement:** Assessment of exposures of phentermine in subjects with varying degrees of renal impairment.

### 1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The sponsor, Citius Pharmaceuticals LLC., submitted a 505 (b)(2) new drug application (NDA 202-088) seeking a marketing approval for a phentermine oral disintegrating tablet (ODT) with 15 mg, 30 mg, and 37.5 mg dose strengths. The sponsor's rationale of developing an ODT formulation is to provide a more palatable means of dosing for patients who are unable to or have an aversion to swallowing conventional tablets or capsules. Phentermine HCl is indicated as short term (a few weeks) adjunct in a regimen of weight reduction. The sponsor references Phentermine HCl capsules from Sandoz for the 15 mg and 30 mg dose strengths and Adipex-P from Teva for the 37.5 mg dose strength.

The sponsor conducted three relative bioavailability trials with additional arms to evaluate the following labeling claims:

- I. [...] place the [...] tablet on top of the tongue where it will dissolve, then swallow with saliva or water. Administration with water is not necessary.
- II. [REDACTED] (b) (4)
- III. [REDACTED] (b) (4) can be administered with or without food.

The study designs were as follows:

1. **01806KH:** This study evaluated the following three treatment arms:
  - T1.** Phentermine ODT 15 mg (followed by water after disintegration) fasted
  - T2.** Phentermine ODT 15 mg (disintegration without water) fasted
  - Ref.** Phentermine HCl capsule Sandoz 15 mg (administered with water) fasted
2. **018089D:** This study evaluated the following three treatment arms:
  - T1.** Phentermine ODT 30 mg (administered with water, swallow without disintegration) fasted
  - T2.** Phentermine ODT 30 mg (swallow after disintegrated followed by water) fed
  - Ref.** Phentermine HCl capsule Sandoz 30 mg (administered with water) fasted

3. **01809PB:** This study evaluated the following three treatment arms:
- T1.** Phentermine ODT 37.5 mg (followed by water after disintegration) fasted
  - T2.** Phentermine ODT 37.5 mg (followed by water after disintegration) fed
  - Ref.** Adipex-P 37.5 mg tablet (administered with water) fasted

The results from the three studies, 01806KH (Figure 1), 018089D (Figure 2), and 01809PB (Figure 3) demonstrate that the geometric mean ratios (GMR) and the 90% confidence intervals (90% CI) of the GMR of Phentermine ODT administered under two different administration conditions compared to the reference product are contained within the bioequivalence boundaries of 80-125%. Additionally, GMR and 90% CI for comparisons of the test product (Phentermine ODT) under two different administration conditions are also contained within the bioequivalence boundaries of 80-125%.

Figure 1 Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine (15 mg) for 01806KH (Geometric mean ratio (GMR) and 90% confidence interval (90% CI))

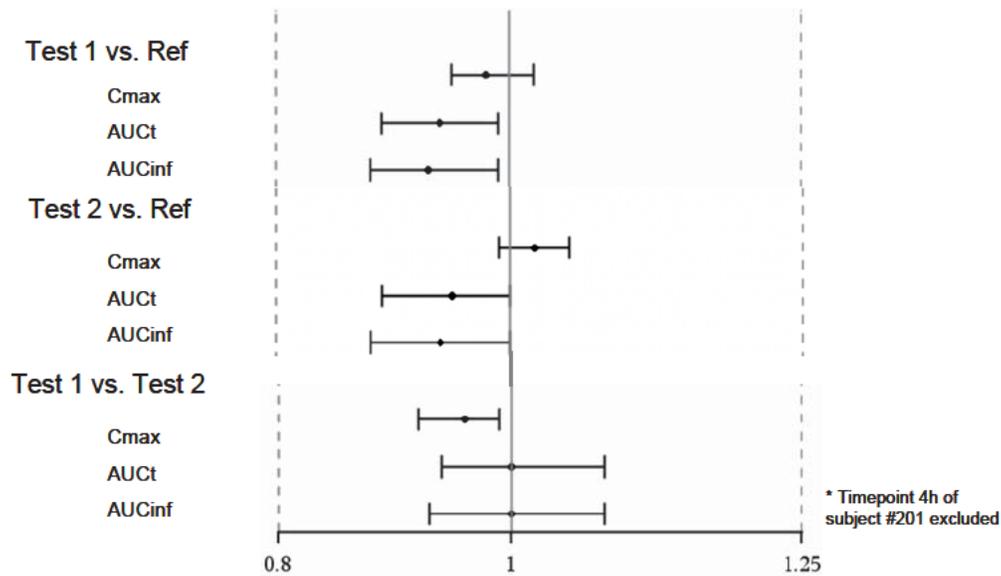


Figure 2 Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine (30 mg) for 018089D (Geometric mean ratio (GMR) and 90% confidence interval (90% CI))

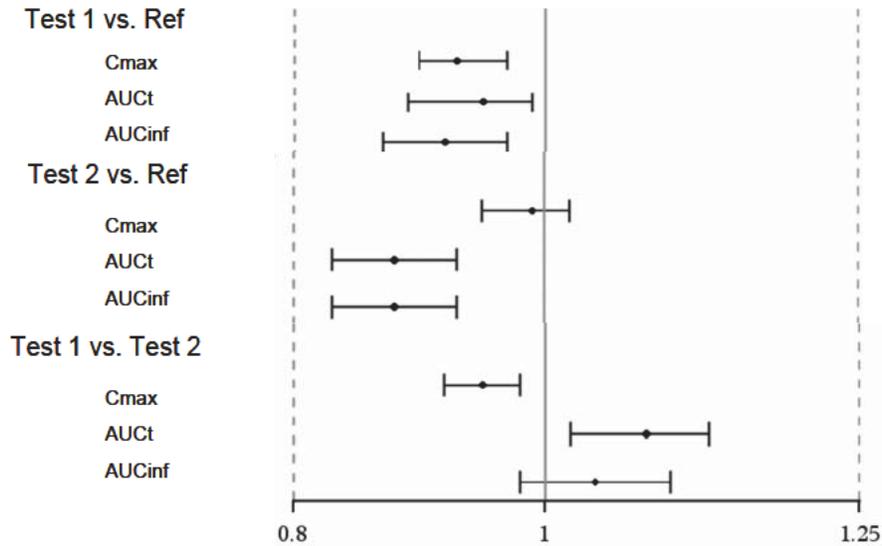
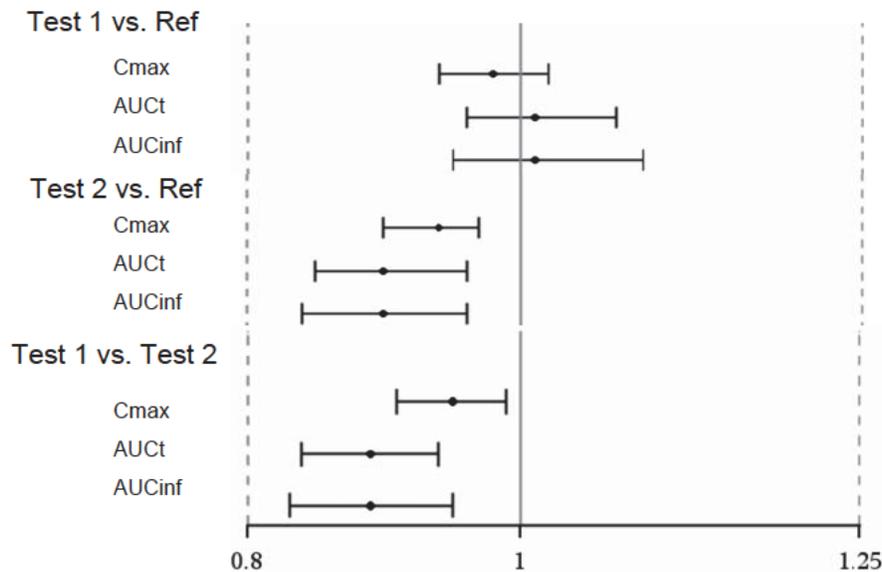


Figure 3 Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine (37.5 mg) for 01809PB (Geometric mean ratio (GMR) and 90% confidence interval (90% CI))



**Labeling claims:**

The labeling claim “[...] place the [...] tablet on top of the tongue where it will dissolve, then swallow with saliva or water. Administration with water is not necessary.” is acceptable. This was demonstrated in study 01806KH. Administration after disintegration with water (T1) was bioequivalent to administration after disintegration followed by

saliva (T2). The geometric mean ratios for  $C_{\max}$ ,  $AUC_{(0-t)}$ , and  $AUC_{(0-inf)}$ , as well as the 90 % confidence interval (CI) were contained within the boundaries of 80% to 125%.

The labeling claim [REDACTED] (b) (4) [REDACTED] has not been evaluated in any of the submitted studies and is thus not acceptable.

The labeling claim “[...] can be administered with or without food” is acceptable. The geometric mean ratios for  $C_{\max}$ ,  $AUC_{(0-t)}$ , and  $AUC_{(0-inf)}$ , as well as the 90 % CIs fall within the bioequivalence criteria of 80-125%, for fasted (T1) administration compared to fed (T2) administration respectively.

**Intrinsic factor: renal impairment**

The sponsor mentions in the product background information, that about 30% of phentermine is excreted unchanged in urine and that the excretion is highly variable and dependent on urinary pH. Literature information (published by Delbeke & Debackere *Arzneim-Forsch* 36:134-7 (1986)) reports cumulative urinary excretion of phentermine under uncontrolled urinary pH conditions to be between 63% to 85%.

Increases in exposure due to renal impairment are likely considering urinary excretion of phentermine and may be of significant importance for patient safety. Thus, this reviewer recommends conducting a specific population PK study in subjects with varying degree of renal impairment as Post Marketing Requirement (PMR) to assess exposure changes with renal impairment.

## 2. Question Based Review

### 2.1 What is the pertinent regulatory background?

The sponsor, Citius Pharmaceuticals LLC., submitted a 505 (b)(2) new drug application (NDA 202-088) seeking a marketing approval for a phentermine oral disintegrating tablet with 15 mg, 30 mg, and 37.5 mg dose strengths. The sponsor's rationale of developing an ODT formulation is to provide a more palatable means of dosing for patients who are unable to or have an aversion to swallowing conventional tablets or capsules. The sponsor references Phentermine HCl capsules from Sandoz for the 15 mg and 30 mg dose strengths and Adipex-P from Teva for the 37.5 mg dose strength. Phentermine HCl ODT drug product is proposed at three strengths Phentermine HCl ODT 15 mg, 30 mg and 37.5 mg.

The quantitative and qualitative compositions of phentermine HCl ODT at different strengths are summarized in Table 1.

Table 1 Composition of phentermine ODT drug product

Components	Phentermine HCl 15 mg strength	Phentermine HCl 30 mg strength	Phentermine HCl 37.5 mg strength
	mg/tablet		
Phentermine HCl	15.00*	30.00*	37.50*
Mannitol powder (b) (4)	(b) (4)		
(b) (4)			
Citric Acid powder			
Povidone CL (b) (4)			
Povidone K 30 (b) (4)			
Sucralose			
Magnesium Stearate			
Peppermint flavour			
Talc			
Sodium Lauryl Sulfate			
Mannitol pregranulated (b) (4)			
FD&C Blue # 1 lake (b) (4)			
FD&C Yellow # 5 lake (b) (4)			

Since composition of the 15 mg and 30 mg dose strength is proportional, and the reference products for the 30 mg and 37.5 mg dose strength are different, DSI inspection was requested for the studies that used the 30 mg and 37.5 dose strength (study 018089D and 01809PB). The results from the DSI inspections are pending.

## 2.2 Are the labeling claims regarding bioavailability and dosage and administration acceptable?

Yes, the ODT formulation is bioequivalent to the reference products at all dose strengths. The labeling claims regarding “IMMEDIATELY place the [...] tablet on top of the tongue where it will dissolve, then swallow with saliva or water. Administration with water is not necessary.” and “[...] can be administered with or without food.” are also acceptable.” The labeling claim that [REDACTED] (b) (4) is not acceptable.

The sponsor conducted three relative bioavailability trials to evaluate the bioavailability and the labeling claims.

### **Trial 01806KH:**

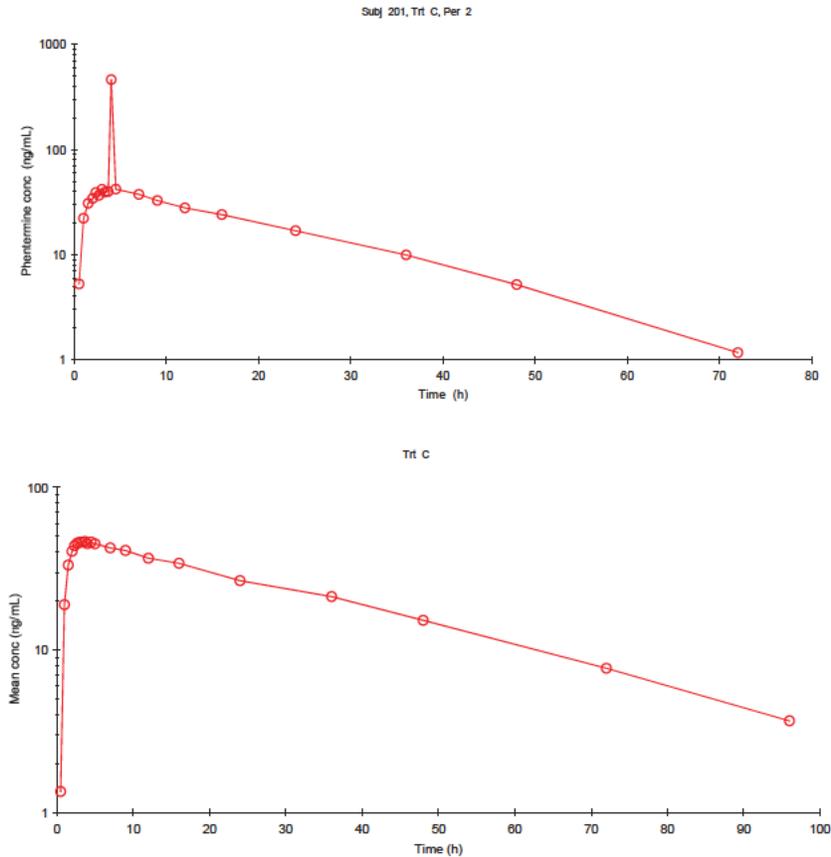
Fifteen healthy subjects of either sex, aged between 18 to 45 years and with a body mass index (BMI) ranging from 18.3 to 28.1 kg/m<sup>2</sup> were enrolled. The objective of this study was to compare the bioavailability of the ODT formulation swallowed after disintegration with water (T1) and swallowed after disintegration without water (T2) to the reference product.

The following treatments were administered in a crossover fashion with a 10 day washout between treatments:

- Test Formulation (T1)
  - Phentermine HCl, 15 mg ODT, swallowed after oral disintegration with water
- Test Formulation (T2)
  - Phentermine HCl, 15 mg ODT, swallowed after disintegration without water
- Reference Product: Phentermine HCl USP, 15 mg Capsule [Sandoz, Inc.]

During the analysis of the bioanalytical results, one subject (#201) demonstrated a high concentration at a single timepoint (t=4h) this concentration was approximately 6.5-fold greater than the next highest concentration during this trial (463.5 ng/mL vs. 71.5 ng/mL). This high concentration was observed after administration of the reference product. The concentration time profile for subject #201 after reference product administration and the mean concentration time profile of all other subjects receiving reference product are illustrated in Figure 4.

Figure 4 Log-linear concentration time profile for phentermine for subject #201 after reference drug administration (top) and mean phentermine concentration-time profile for all subjects excluding #201 (bottom) in study 01806KH.



The sponsor reanalyzed the sample both at original and 10-fold dilution and the results confirmed the original concentration. The sponsor conducted a Grubbs-Test for outlier, determined that this timepoint was an outlier, and excluded the subject from the analysis. The sponsor's statistical analysis plan did not provision for an outlier analysis and data from subjects who completed two of three treatments (test and reference) was to be included in the pharmacokinetic dataset.

However, the determination of bioequivalence is particularly sensitive to the concentration observed in subject #201 at timepoint 4h. Without excluding subject #201's 4h concentration, the lower boundaries of the 90% confidence interval (CI) of the ratio for  $C_{max}$  (test/reference) would lie outside the 80-125% bioequivalence range (lower CI of 66.6 and 69.3 for T1 and T2, respectively vs. Reference). Consequently, the approach regarding subject #201's concentrations becomes pivotal for the determination of bioequivalence.

In contrast to excluding all data from subject #201 as proposed by the sponsor, it is adequate to exclude the 4 hour timepoint in subject #201 after reference drug administration due to the following reasons:

1. The aberrant concentration occurred in the reference product, whereas the test product under both administration conditions (T1 and T2) has performed similarly.
2. Previous and subsequent concentrations of the 4 hour timepoint showed no significant deviation, indicating that the 4 hour timepoint is truly an outlier.
3. 6 out of 15 subjects reported 11 treatment related adverse events. None of these reported adverse events was reported by subject #201.

Additionally, the AUC met the BE criteria of 80-125% for both T1 and T2 even after inclusion of timepoint 4 hour of subject #201, indicating there is no overall change in bioavailability.

The relative bioavailability of the test product under different administration conditions, and after excluding subject #201's 4h concentration in the reference product is illustrated in Table 2 and Table 3.

Table 2 Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation Administered with Water (T1) to the Reference Product with Water (Primary Analysis n=14, excluding subject 201's 4h concentration)					
Dependent Variable	Geometric Mean <sup>a</sup>		Ratio(%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>	
	Test	Ref		Lower	Upper
ln(C <sub>max</sub> )	46.7895	47.5819	98.33	95.09	101.69
ln(AUC <sub>last</sub> )	1565.6351	1663.7368	94.10	88.78	99.74
ln(AUC <sub>inf</sub> )	1664.6820	1781.3413	93.45	87.74	99.53

<sup>a</sup> Geometric Mean for the Test Formulation with water, T1 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values  
<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)  
<sup>c</sup> 90% Confidence Interval  
Source: Reviewer analysis

Table 3 Statistical Analysis of the Log- Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation Administered without Water (T2) to the Reference Product with Water (Primary Analysis n=14, excluding subject 201's 4h concentration)					
Dependent Variable	Geometric Mean <sup>a</sup>		Ratio(%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>	
	Test	Ref		Lower	Upper
ln(C <sub>max</sub> )	48.7198	47.5819	102.39	99.01	105.89
ln(AUC <sub>last</sub> )	1575.4703	1663.7368	94.69	89.34	100.37
ln(AUC <sub>inf</sub> )	1680.9236	1781.3413	94.36	88.60	100.50

<sup>a</sup> Geometric Mean for the Test Formulation without water, T2 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values  
<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)  
<sup>c</sup> 90% Confidence Interval  
Source: Reviewer analysis

Comparison of T1 with T2 allows for evaluation of the labeling claim that phentermine ODT can be administered with water or saliva and administration with water is not necessary. Administration after disintegration with water (T1) was bioequivalent to administration after disintegration followed by saliva (T2). The geometric mean ratios for  $C_{max}$ ,  $AUC_{(0-t)}$ , and  $AUC_{(0-inf)}$ , as well as the 90 % confidence interval (CI) were contained within the boundaries of 80% to 125%.

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation Administered with Water (T1) to Test Formulation Administered without Water (T2) (n=15)					
Dependent Variable	Geometric Mean <sup>a</sup>		Ratio(%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>	
	Test	Ref		Lower	Upper
ln( $C_{max}$ )	48.7198	46.7895	96.04	92.69	99.50
ln( $AUC_{last}$ )	1575.4703	1565.6351	99.38	92.87	106.34
ln( $AUC_{inf}$ )	1680.9236	1664.6820	99.03	92.40	106.14
<sup>a</sup> Geometric Mean for the Test Formulation without water, T2 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values <sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref) <sup>c</sup> 90% Confidence Interval Source: Reviewer analysis					

### **Trial 018089D:**

Fifteen healthy subjects of either sex, aged between 18 to 45 years and with a BMI ranging from 18.9 to 29.1 kg/m<sup>2</sup> were enrolled. The objective of this study was to compare the bioavailability of the ODT formulation when swallowed without disintegration with water or swallowed after disintegration with water to the reference.

- Test Formulation (T1):
  - Phentermine HCl, 30 mg ODT, administered orally with water, fasted
- Test Formulation (T2):
  - Phentermine HCl, 30 mg ODT, administered by oral disintegration followed by water, fed
- Reference Product:
  - Phentermine HCl USP, 30 mg capsule [Sandoz, Inc.] administered with water, fasted

Relative bioavailability was determined comparing both T1 and T2 to the reference product. The results are illustrated in Table 4 and Table 5

Table 4 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation-Swallowed with Water (T1) to the Reference Product with Water

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	92.1244	98.6089	93.42	90.35	96.61	1.0000	5.38
ln(AUC <sub>last</sub> )	3430.0518	3625.4359	94.61	89.74	99.75	1.0000	8.51
ln(AUC <sub>inf</sub> )	3685.5871	4012.1922	91.86	86.89	97.11	1.0000	8.95

<sup>a</sup> Geometric Mean for the Test Formulation swallowed with water, T1 (Test) and Reference Product with water (Ref) based on

Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

Source: Table 11.4.3.6, page 56, of the sponsors study report for 018089D

Table 5 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation-Disintegrated followed by Water (T2) to the Reference Product with Water

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	97.3409	98.6089	98.71	95.46	102.08	1.0000	5.38
ln(AUC <sub>last</sub> )	3182.3721	3625.4359	87.78	83.26	92.55	1.0000	8.51
ln(AUC <sub>inf</sub> )	3540.2612	4012.1922	88.24	83.46	93.29	1.0000	8.95

<sup>a</sup> Geometric Mean for the Test Formulation disintegrated followed by water, T (Test) and Reference Product with water (Ref) based on

Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

Source: Table 11.4.3.7, page 57, of the sponsors study report for 018089D

The geometric mean ratios as well as the 90 % CIs fall within the bioequivalence criteria of 80-125%, for both T1 and T2 compared to reference. This reviewer analyzed the data using WinNonlin and obtained comparable results. However, determination of the bioequivalence between T2 and reference is confounded by administration under different food conditions (fed vs. fasted), which demonstrated an approximated 10% difference in exposure in study 01809PB (see trial 01809PB below). Thus, it is difficult to differentiate between the food effect and the effect of swallowing after disintegration followed by water. The effect of disintegration followed by water however can be determined from study 01806KH by comparing T1 with reference. Comparing T1 to reference in study 01806KH demonstrates that rate and extend of exposures, as well as 90% CI are within the bioequivalence criteria of 80-125%.

### **Trial 01809PB:**

Eighteen healthy subjects of either sex, aged between 18 to 45 years and with a BMI from 21.1 to 29 kg/m<sup>2</sup> were enrolled. The objective of this study was to compare the bioavailability of the ODT formulation under fasting (T1) and fed (T2) conditions to the reference.

The following treatments were administered in a crossover fashion with a 10 day washout between treatments:

- Test Formulation (T1):
  - Phentermine HCl, 37.5 mg ODT, swallowed after oral disintegration with saliva followed by water, fasted
- Test Formulation (T2):
  - Phentermine HCl, 37.5 mg ODT, swallowed after oral disintegration with saliva followed by water, fed
- Reference Product:
  - Phentermine HCl, 37.5 mg Capsule [Adipex-P] administered with water, fasted

Relative bioavailability was determined comparing both T1 and T2 to the reference product. The results are illustrated in Table 6 and Table 7.

Table 6 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation under Fasting Conditions (T1) to the Reference Product under Fasting Conditions

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	116.4055	118.4320	98.29	94.40	102.33	1.0000	6.70
ln(AUC <sub>last</sub> )	4099.3519	4054.3170	101.11	95.59	106.95	1.0000	9.34
ln(AUC <sub>inf</sub> )	4467.8094	4394.7729	101.66	94.99	108.80	0.9997	11.30

<sup>a</sup> Geometric Mean for the Test Formulation with water, T1 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

Source: Table 11.4.3.6, page 56, of the sponsors study report for 01809PB

Table 7 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation under Fed Conditions (T2) to the Reference Product under Fasting Conditions

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	110.7577	118.4320	93.52	89.82	97.37	1.0000	6.70
ln(AUC <sub>last</sub> )	3661.5895	4054.3170	90.31	85.38	95.53	1.0000	9.34
ln(AUC <sub>inf</sub> )	3956.0526	4394.7729	90.02	84.11	96.34	0.9997	11.30

<sup>a</sup> Geometric Mean for the Test Formulation with water, T1 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

Source: Table 11.4.3.7, page 57, of the sponsors study report for 018089D

The geometric mean ratio as well as the 90 % CI fall within the bioequivalence criteria of 80-125%, for T1 and T2 respectively. T1 and T2 are thus bioequivalent to the reference product.

Additionally, the sponsor compared the influence of administration conditions by comparing the exposures of the two test products. This comparison of the geometric mean ratios also demonstrated that the 90 % confidence interval of the GMR of rate and extend of exposure between the two methods of administration were within 80-125% (Table 8).

Table 8 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation under Fed Conditions (T2) to Test Formulation under Fasting Conditions (T1)

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	110.8916	116.3979	95.27	90.72	100.05	1.0000	7.81
ln(AUC <sub>last</sub> )	3663.9929	4100.3847	89.36	84.80	94.16	1.0000	8.34
ln(AUC <sub>inf</sub> )	3957.4255	4469.1860	88.55	83.05	94.41	0.9996	10.23

a Geometric Mean for the Test Formulation-Fed, T2 (Test) and Test Formulation-Fasting, TI (Ref) based on Least Squares Mean of log-Transformed parameter values

b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

c 90% Confidence Interval

Source: Table 11.4.3.9, page 59, of the sponsors study report for 01809PB

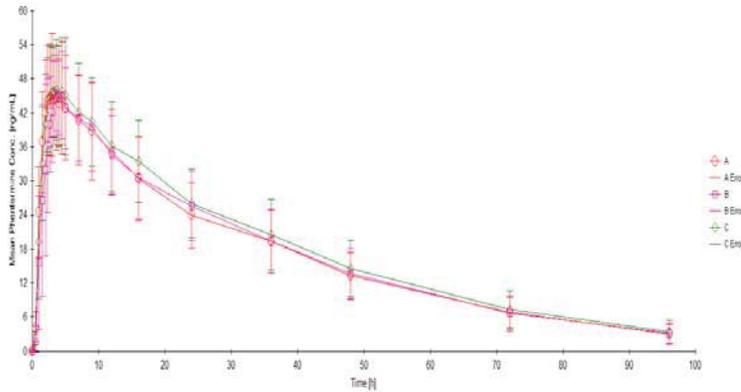
This reviewer analyzed the data using WinNonlin and obtained comparable results. The sponsor's claim of administration regardless of meals is acceptable.

In all three trials, the effect of ODT on mucosal area was examined to evaluate the potential of mucosal irritation. The sponsor reports that no clinically significant abnormalities in oral (mucosal) examinations were observed. The Clinical Division will evaluate this claim.

### 2.3 What are the pharmacokinetic properties of the ODT formulation?

Following the administration of the oral disintegrating tablet (ODT) phentermine reaches peak concentrations (C<sub>max</sub>) after 3.0 to 4.5 hours (Table 9, Table 10, and Table 11). Swallowing the ODT after disintegration with water compared to saliva did not affect the extent (AUC) of phentermine exposure (Table 9). Concentration time profiles for phentermine after administration of the test product and the reference product are illustrated in Figure 5 for study 01806KH and Figure 6 for study 018089D and Figure 7 for study 01809PB.

Figure 5 Concentration-time profile of phentermine given as ODT T1(A, swallowed after oral disintegration with water) or T2 (B, swallowed after disintegration without water) or reference product (C, Phentermine HCl USP, 15 mg Capsule [Sandoz, Inc.]

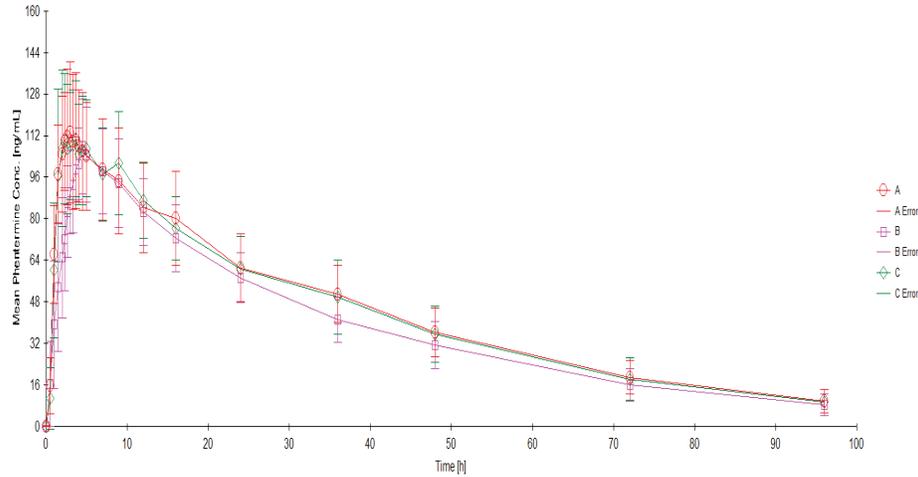


**Table 9 Pharmacokinetic parameters of 15 mg phentermine, given as ODT (T1 with water & T2 without water) or as capsule (Ref)**

Parameter	T1	T2	Ref
C <sub>max</sub> (SD)	47.66(9.9)	49.30 (8.06)	48.44 (9.55)
AUC <sub>last</sub> (SD)	1609.07 (384.37)	1614.90(383.80)	1711.17 (418.27)
AUC <sub>inf</sub> (SD)	1718.60 (439.65)	1730.99 (441.31)	1841.95 (485.24)
t <sub>max</sub> (Range)	3.0 (2.0-5.0)	3.67 (2.0-7.0)	4.0 (2.0-5.0)
t <sub>1/2</sub> (SD)	22.63 (5.8)	22.45 (6.42)	22.85 (6.96)

Swallowing the ODT without prior disintegration decreased the  $C_{max}$  of phentermine by approximately 7% and the AUC by approximately 8% (Table 10).

Figure 6 Concentration-time profile of phentermine given as ODT T1 (swallowed whole with water, fasted) or T2 (B, administered by oral disintegration followed by water, fed) or reference product (C, Phentermine HCl USP, 30 mg capsule [Sandoz, Inc.] administered with water, fasted)

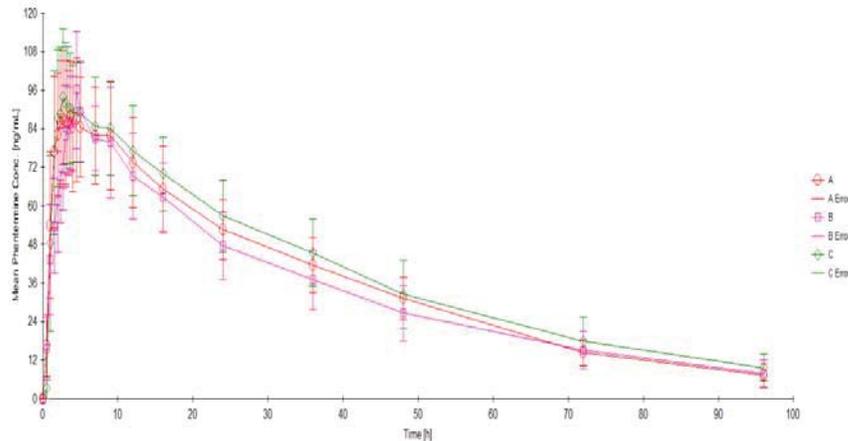


**Table 10 Pharmacokinetic parameters of 30 mg phentermine, given as ODT (T1 swallowed whole, fasted, & T2 swallowed after disintegration, fed) or as capsule (Ref, fasted)**

Parameter	T1	T2	Ref
$C_{max}$ (SD)	119.07 (24.99)	111.92 (16.11)	120.79 (22.77)
$AUC_{last}$ (SD)	4197.55 (873.20)	3719.06 (638.43)	4135.48 (855.93)
$AUC_{inf}$ (SD)	4595.45 (1058.28)	4033.29 (813.18)	4509.29 (1070.82)
$t_{max}$ (Range)	3.00 (2.00-5.00)	4.50 (3.67-5.00)	2.66 (1.53-9.00)
$t_{1/2}$ (SD)	25.81 (7.54)	27.29 (4.65)	25.12 (6.32)

Administration of the ODT after a high fat/high calorie breakfast decreased the  $C_{max}$  of phentermine by approximately 5% and the AUC by approximately 12% (Table 11). However, the geometric mean ratios as well as the 90 % CIs fall within the bioequivalence criteria of 80-125%, for T1 and T2.

Figure 7 Concentration-time profile of phentermine given as ODT T1 (A, swallowed after oral disintegration with saliva followed by water, fasted) or T2 (B, swallowed after oral disintegration with saliva followed by water, fed) or reference product (C, Phentermine HCl, 37.5 mg Capsule [Adipex-P] administered with water, fasted)



**Table 11 Pharmacokinetic parameters of 37.5 mg phentermine, given as ODT (T1 fasted & T2, fed) or as tablet (Ref, fasted)**

Parameter	T1	T2	Ref
$C_{max}$ (SD)	93.98 (20.22)	98.84 (18.22)	100.13 (18.20)
$AUC_{last}$ (SD)	3477.04 (155.84)	3236.57(635.36)	3698.56 (787.35)
$AUC_{inf}$ (SD)	3746.09 (183.19)	3632.30(871.24)	4113.99 (978.37)
Median $t_{max}$ (Range)	3.67 (1.5-7.0)	4.5 (3.0-5.0)	3.67 (2.0-5.0)
$t_{1/2}$ (SD)	23.41 (5.80)	27.63 (6.94)	25.91 (5.47)

#### 2.4 What is the influence of renal impairment of Phentermine ODT pharmacokinetics?

The sponsor mentions in the product background information, that about 30% of phentermine is excreted unchanged in urine and that the excretion is highly variable and dependent on urinary pH. Delbeke and Debackere [Delbeke & Debackere *Arzneim-Forsch* **36**:134-7 (1986)] investigated the influence of diuretics on phentermine excretion and demonstrated that under uncontrolled urinary pH conditions cumulative urinary excretion ranges from 62% to 85%. Similarly, Beckett and Brooks [Beckett & Brooks. *J*

*Pharm Pharmacol* **23**:288-94 (1971)] reported urinary phentermine excretion of 70% to 80% under acidic urinary control. Exposure increases in patients with renal impairment are currently unknown.

Additionally, the current approved label information state that “The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.” Increases in exposure due to renal impairment are likely considering urinary excretion of phentermine and may be of significant importance for patient safety. Thus, this reviewer recommends conducting a specific population PK study in subjects with varying degree of renal impairment as Post Marketing Requirement (PMR) to assess exposure changes with renal impairment.

### 2.5 Is the bioanalytical method validation acceptable?

Yes, the bioanalytical method validation is acceptable. The validation titled “Determination of Phentermine in Human K<sub>2</sub>-EDTA Plasma by LC-MS-MS Validation of the Analytical Method” was conducted by (b) (4). Concentrations of phentermine in human plasma (EDTA) were determined using high performance liquid chromatography (HPLC) with mass spectrometric detection. Human plasma containing phentermine and the internal standard, (b) (4) was extracted using a solid phase extraction cartridge and analyzed on a Sciex API 5000 LC-MS-MS equipped with an HPLC column. The peak area of the m/z 150→91 phentermine product ion was measured against the peak area of the m/z 156→92 (b) (4) internal standard product ion.

Calibration standards were prepared to yield 0.500, 1.00, 5.00, 20.0, 60.0, 100, 135, 150 ng/mL by fortifying 0.200 mL of blank plasma with 10.0 µL of the appropriate spiking solution immediately prior to each analysis. QC samples were prepared by fortifying blank plasma with intermediate solution at the appropriate concentrations. High, medium, and low QC samples were prepared at 120, 30.0, and 1.50 ng/mL. The QC samples were stored at approximately -20 °C. Additionally, a very high dilution QC pool was prepared with an ampoule at 600 ng/mL.

Samples were benchtop stable for 25 h and extract stability was determined for 68 h.

Samples were stable over four freeze/thaw cycles. The bias for the effect of analytical matrix on recovery ranged from -7.5% to 4.5%. No interferences were observed at any retention time.

**Table 12** Results of Quality Control from the bioanalytical method validation

Analyte / Parameter	Curve range (ng/mL)	Calibration		Quality control (between batch)	
		LLOQ (ng/mL)	%CV	%CV	%Bias
Phentermine	0.500-150	0.500	1.6-4.2%	2.7-4.9%	0.0-2.0%

## 2.6 Is the bioanalytical analysis acceptable?

Yes, the bioanalytical; analysis was acceptable. Concentrations of phentermine in human plasma (EDTA) were determined using high performance liquid chromatography (HPLC) with mass spectrometric detection. Human plasma containing phentermine and the internal standard, (b) (4) was extracted using a solid phase extraction cartridge and analyzed on a Sciex API 5000 LC-MS-MS equipped with an HPLC column. The peak area of the m/z 150→91 phentermine product ion was measured against the peak area of the m/z 156→92 (b) (4) internal standard product ion. A set of 8 non-zero calibration standards, ranging from 0.500 ng/mL to 150 ng/mL for phentermine were included in each run.

QC samples at 3 different concentrations: 15.0 ng/mL, 30 ng/mL and 120 ng/mL were prepared. Additional QCs for study:

- 01806KH 48 ng/mL and 600 ng/mL
- 01809PB: 600 ng/mL
- 018089D: 4X dilution QC (120 ng/mL)

**Table 13** Results of Quality Control from the bioanalytical method for Phentermine

Study	Calibration Curve range (ng/mL)	LLOQ (ng/mL)	Quality control (between batch)		
			%CV	%CV	%Bias
01806KH	0.500-150	0.500	2.1-6.9%	4.1-5.6%	3.3 to -7.8%
01809PB	0.500-15.0	0.500	25.-7.7%	6.8-8.2%	-1.3 to -5.0%
018089D	0.500-150	0.500	2.5-7.6%	7.9-8.8%	-5.0 to 1.3%

### 3. Preliminary labeling comments

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Labeling statements to be removed are shown in ~~red strikethrough~~ and suggested labeling to be included is shown in underline blue font. The following main labeling recommendations based on this submission should be considered during labeling negotiations:



(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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IMMO ZADEZENSKY  
05/18/2011

SALLY Y CHOE  
05/18/2011

CHANDRAHAS G G SAHAJWALLA  
05/18/2011

## ONDQA (Biopharmaceutics) Review

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**NDA:** 202-088 (000)  
**Submission Date:** 08/11/2010, 11/29/2010  
**Product:** (b) (4)® (Phentermine HCl) Orally Disintegrating Tablets (15, 30 and 37.5 mg)  
**Type of Submission:** Original NDA Submission  
**Sponsor:** Citius Pharmaceuticals LLC  
**Reviewer:** Tapash K. Ghosh, Ph.D.

---

**Background:** This is a paper NDA for an orally disintegrating tablet with 15, 30, and 37.5 mg phentermine HCl to treat obesity. This review will discuss the dissolution method and dissolution specification of this immediate release product.

### **Recommendation:**

The sponsor's choice of USP dissolution method as outline below for product quality control purposes is acceptable.

#### Dissolution test conditions

- **Apparatus:** Paddle
- **Speed of rotation:** 50 rpm
- **Dissolution medium:** 900 mL purified water for tablet with MT 15 mg of API for vessel or 500 mL purified water for tablet with NMT 15 mg of API for vessel.

with the sampling time changed from the sponsor's proposed (b) (4) to the Agency's proposed 15 minutes.

Also, based on the dissolution data, the Agency proposes the specification of "NLT (b) (4) in 15 minutes"

Tapash K. Ghosh, Ph. D.  
Biopharmaceutics Primary Reviewer  
Office of New Drugs Quality Assessment

RD/ FT Initialed by Patrick Marroum, Ph. D. \_\_\_\_\_

Table 2.3.P.1-1. Composition of Phentermine HCl ODT Drug Product.

Components	Phentermine HCl 15 mg strength	Phentermine HCl 30 mg strength	Phentermine HCl 37.5 mg strength
	mg/tablet		
Phentermine HCl	15.00*	30.00*	37.50*
Mannitol powder (b) (4)	(b) (4)		
Citric Acid powder			
Povidone CL (b) (4)			
Povidone K 30 (b) (4)			
Sucralose			
Magnesium Stearate			
Peppermint flavour			
Talc			
Sodium Lauryl Sulfate			
Mannitol pregranulated (b) (4)			
FD&C Blue # 1 lake (b) (4)			
FD&C Yellow # 5 lake (b) (4)			

**Dissolution:**

The dissolution test was carried out using the USP method. The following description provides an overview of the method for the proposed ODT drug product:

Dissolution test conditions

- Apparatus: Paddle
- Speed of rotation: 50 rpm
- Dissolution medium: 900 mL purified water for tablet with MT 15 mg of API for vessel or 500 mL purified water for tablet with NMT 15 mg of API for vessel.
- Temperature: 37 ± 0.5 °C
- Sampling time: (b) (4)
- Sample volume: 5 mL

Test procedure

Place the mentioned volume of dissolution medium in each test vessel to be utilized. Wait for reaching temperature set-point. Add one tablet to each vessel and turn on rotation. After exactly (b) (4) sample 5 mL from each vessel.

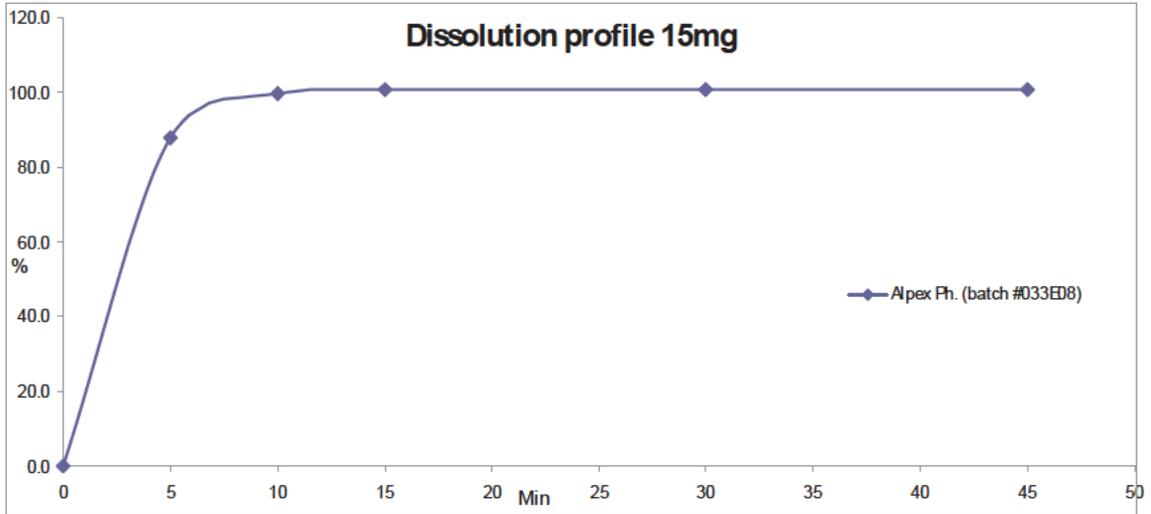
Chromatographic operating conditions

Instrument: HPLC system  
Column: Waters Symmetry C<sub>18</sub>; 250 x 4.6mm  
Mobile phase: Methanol:Ion pair solution (volume ratio 21:19)  
Correct the pH at 2.5 ±0.1 with phosphoric acid 85%.  
*Ion pair solution:* Dissolve 1.1 g of 1-heptanesulfonic acid sodium salt in 1.0 L of purified water. Add 3.5 mL of glacial acetic acid and mix.  
Flow: 1.0 mL/min isocratic  
Injection volume: 25 µL  
Detection: UV 208 nm  
Analysis time: 15 min  
Retention time: 5 min

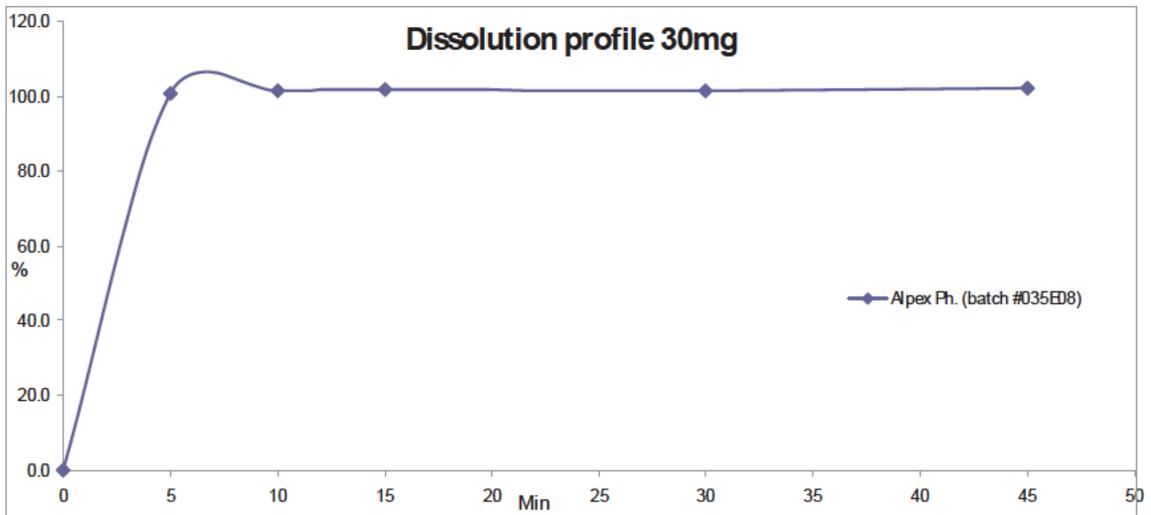
**Results:**

Dissolution data from the one stability batch of each strength are presented below:

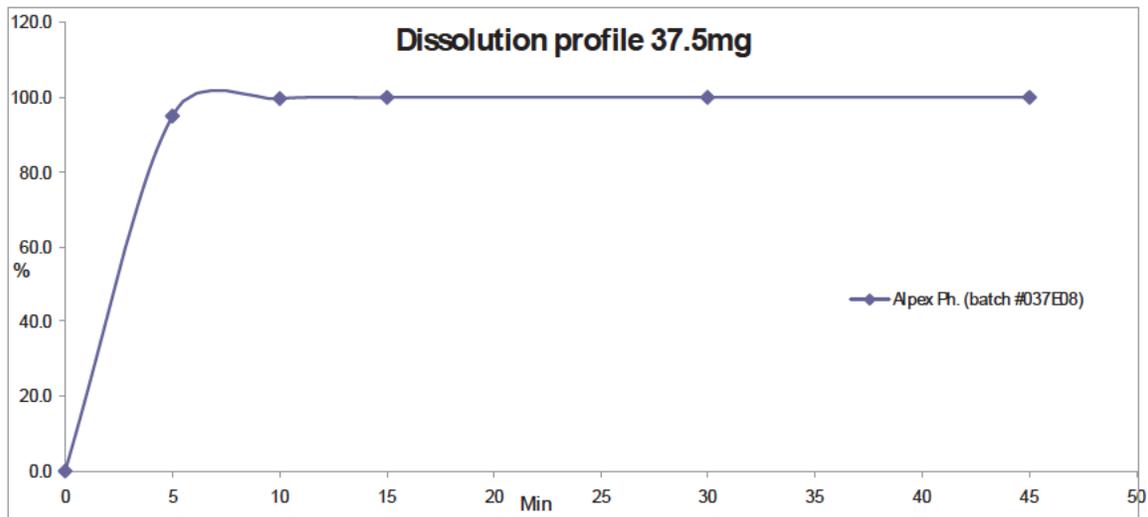
Phentermine HCl 15mg (batch # 033E08)	
Time (min)	% dissolved (mean of 12 tbl)
0	0.0
5	87.7
10	99.7
15	100.6
30	100.8
45	100.7



Phentermine HCl 30 mg (batch # 035E08)	
Time (min)	% dissolved (mean of 12 tbl)
0	0.0
5	100.6
10	101.5
15	101.6
30	101.3
45	102.0



Phentermine HCl 37.5 mg (batch # 037E08)	
Time (min)	% dissolved (mean of 12 tbl)
0	0.0
5	95.0
10	99.6
15	99.9
30	99.9
45	100.0



**Sponsor’s Proposed Specification:** The sponsor proposed “NLT (b) (4) in (b) (4) for the ODT product.

**Reviewer’s Conclusion:** The sponsor’s choice of dissolution method is acceptable. However, based on the dissolution data, the Agency proposes the specification of “NLT (b) (4) in 15 minutes”

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TAPASH K GHOSH  
01/25/2011

PATRICK J MARROUM  
01/26/2011

**Office of Clinical Pharmacology**  
**New Drug Application Filing and Review Form**

<b>General Information About the Submission</b>				
	Information		Information	
<b>NDA Number</b>	202088	<b>Brand Name</b>	(b) (4)	
		<b>Generic name</b>	Phentermine hydrochloride	
<b>Medical Division</b>	DMEP	<b>Drug Class</b>	Sympathomimetic amine	
<b>OCP Reviewer(s)</b>	Immo Zdrojewski, Ph.D.	<b>Indication(s)</b>	Short term (a few weeks) adjunct in a regimen of weight reduction	
<b>OCP Team Leader</b>	Sally Choe, Ph.D.	<b>Dosage Form</b>	Oral disintegrating tablet	
		<b>Proposed Dosing Regimen</b>	One tablet daily (15 mg, 30 mg, 37.5 mg) without regards to food, water intake or prior disintegration, administered (b) (4)	
<b>Date of Submission</b>	08/17/2010	<b>Route of Administration</b>	Oral	
<b>Estimated Due Date of OCPB Review</b>	<i>tdb</i>	<b>Sponsor</b>	Citius Pharmaceuticals LLC.	
<b>PDUFA Due Date</b>	06/16/2011	<b>Priority Classification</b>	Standard	
<b>Division Due Date</b>	Approx. mid to end 05/2011	<b>Submission Type</b>	505 (b) (2)	
<b>Clin. Pharm. and Biopharm. Information</b>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
<b>HPK Summary</b>				
<b>Labeling</b>	X			Label available in paper
<b>Reference Bioanalytical and Analytical Methods</b>	X			
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
In-vitro permeability:				
In-vitro metabolism:				
<b>Subpopulation studies -</b>				

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	3		Single dose relative BA studies with additional arms to evaluate labeling claims
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>	X			Food effect was included as a separate arm in relative BA study (01809PB)
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		3		
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
<b>Application filable?</b>	X	Yes, it is filable.		
<b>Comments sent to firm?</b>		1. Please submit the datasets for all three bioavailability studies in electronic format		
<b>QBR questions (key issues to be considered)</b>		<ul style="list-style-type: none"> <li>What is the relative bioavailability of the proposed ODT to the reference product?</li> <li>Are the labeling claims acceptable?</li> </ul>		
<b>Other comments or information not included above</b>	DSI inspection is requested for pivotal BE studies 018089D and 01809PB. Clinical site: CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217 Bioanalytical site: (b) (4)			
<b>Primary reviewer Signature and Date</b>	Immo Zdrojewski, Ph.D.			
<b>Secondary reviewer Signature and Date</b>	Sally Choe, Ph.D.			

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	✓			
2	Has the applicant provided metabolism and drug-drug interaction information?			✓	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	✓			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	✓			
5	Has a rationale for dose selection been submitted?			✓	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	✓			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	✓			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			✓	Paper NDA
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			✓	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			✓	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	✓			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			✓	505(b)(2)
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			✓	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			✓	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			✓	No pediatric studies proposed
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		✓		
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			✓	

<b>General</b>				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	✓		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		✓	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

The purpose of this document is to identify refuse to file and special issues, describe the materials needed for review but not included in the application, and summarize the application relevant to clinical pharmacology.

## **1. Identify refuse to file issues**

### **Are there any refuse to file issues?**

No, the application is filable from the Clinical Pharmacology perspective.

### **Does the applicant provide sufficient data to support the labeling claims?**

Yes, from a clinical pharmacology perspective, sufficient data is provided to perform appropriate evaluation of the label claims.

## **2. Identify special issues**

### **What are the specific issues regarding this application?**

- What is the relative bioavailability of the proposed ODT to the reference product?
- Are the labeling claims acceptable?

## **3. Identify materials needed for review but not included in the application**

### **What are the materials needed for review but not included in the application?**

The following data need to be requested:

1. Electronic datasets for all three relative bioavailability studies

## **4. Summary of the application relevant to clinical pharmacology**

The sponsor, Citius Pharmaceuticals LLC., is submitting a 505 (b)(2) new drug application (NDA 202-088) seeking a marketing approval for a phentermine oral disintegrating tablet with 15 mg, 30 mg, and 37.5 mg dose strengths. The sponsor's rationale of developing an ODT formulation is to provide a more palatable means of dosing for patients who are unable to or have an aversion to swallowing conventional tablets or capsules. The sponsor references Phentermine HCl capsules from Sandoz for the 15 mg and 30 mg dose strengths and Adipex-P from Teva for the 37.5 mg dose strength.

Phentermine HCl ODT drug product is proposed at three strengths:

- Phentermine HCl ODT 15 mg: round, embossed tablets with AX4 on one side, yellow with blue spots, diameter 10 mm and weight 250 mg
- Phentermine HCl ODT 30 mg: round, embossed tablets with AX7 on one side, yellow, diameter 13 mm and weight 500 mg
- Phentermine HCl ODT 37.5 mg: round, scored, embossed tablets with AX8, white with blue spots, diameter 13 mm and weight 500 mg

The quantitative and qualitative compositions of phentermine HCl ODT with different strengths are summarized in Table 1.

Table 1 Composition of phentermine ODT drug product

Components	Phentermine HCl 15 mg strength	Phentermine HCl 30 mg strength	Phentermine HCl 37.5 mg strength
	mg/tablet		
Phentermine HCl	15.00*	30.00*	37.50*
Mannitol powder (b) (4)	(b) (4)		
(b) (4)			
Citric Acid powder			
Povidone CL (b) (4)			
Povidone K 30 (b) (4)			
Sucralose			
Magnesium Stearate			
Peppermint flavour			
Talc			
Sodium Lauryl Sulfate			
Mannitol pregranulated (b) (4)			
FD&C Blue # 1 lake (b) (4)			
FD&C Yellow # 5 lake (b) (4)			

(b) (4)

The sponsor conducted three relative bioavailability trials with additional arms (Appendix 1) to evaluate the following labeling claims and provided the following information:

**1. Water Effect:** (b) (4)

- This claim was evaluated in study 01806KH, a randomized, open-label, single dose, three-treatment, three-sequence, three-period, crossover study. This study evaluated the following three treatment arms:

- A. Phentermine ODT 15 mg (followed by water after disintegration) fasted
- B. Phentermine ODT 15 mg (administered without water) fasted
- C. Phentermine HCl capsule Sandoz 15 mg (administered with water) fasted

Comparisons were performed between A vs. C and B vs. C. Additionally, a comparison between A vs. B. was conducted. All comparisons (point estimate and 90% confidence interval) were contained in the 80-125% limits.

**2. Swallowing Effect:** (b) (4)

- This claim was evaluated in study 018089D, a randomized, open-label, single dose, three-treatment, three-sequence, three-period, crossover study. This study evaluated the following three treatment arms:

- A. Phentermine ODT 30 mg (administered with water, swallow without disintegration) fasted
- B. Phentermine ODT 30 mg (disintegrated followed by water) fed
- C. Phentermine HCl capsule Sandoz 30 mg (administered with water) fasted

Comparisons were performed between A vs. C and B vs. C. Additionally, a comparison between A vs. B. was conducted. All comparisons (point estimate and 90% confidence interval) were contained in the 80-125% limits.

**3. Food Effect:** (b) (4) **can be administered with or without food.**

- This claim was evaluated in Study 01809PB, a randomized, open-label, single dose, three-treatment, three-sequence, three-period, crossover study. This study evaluated the following three treatment arms:
  - A. Phentermine ODT 37.5 mg (followed by water after disintegration) fasted
  - B. Phentermine ODT 37.5 mg (followed by water after disintegration) fed
  - C. Adipex-P 37.5 mg tablet (administered with water) fasted

Comparisons were performed between A vs. C and B vs. C. Additionally, a comparison between A vs. B. was conducted. All comparisons (point estimate and 90% confidence interval) were contained in the 80-125% limits. Under fed conditions, the test product was administered 30 min after a high calorie / high fat breakfast (composition: 2 eggs fried in butter, 2 strips of bacon, 4 oz. hash brown potatoes, 2 slices of toast, 2 pats butter, 8 oz. whole milk)

Additionally, in each study the effect of ODT on mucosal area was examined to evaluate the potential of mucosal irritation. The sponsor reports that no clinically significant abnormalities in oral (mucosal) examinations were observed. The Clinical Division will evaluate this claim.

*Reviewer comment:*

- *During a prior review of the study protocols by this reviewer (Dr. Immo Zdrojewski, DARRTS dated 12/30/2008), a question emerged whether it is acceptable for the sponsor to evaluate the each extrinsic factor in only one dose strength. It seems that the proposed ODT formulations are sufficiently similar between strength 30 mg and 37.5 mg and proportional between 15 mg and 30 mg (Table 1). Therefore, it seems that the results of the extrinsic factor evaluation on the ODT in one dose strength can be applied to the two remaining dose strengths of the ODT.*
- *Since composition of the 15 mg and 30 mg dose strength is proportional, and the reference products for the 30 mg and 37.5 mg dose strength are different, DSI inspection is requested for the studies that used the 30 mg and 37.5 dose strength (study 018089D and 01809PB).*
  - *Clinical site: CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217*
  - *Bioanalytical site:* (b) (4)

Appendix 1

Study Reference No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route)	Subjects (No. (M/F) type Age: mean (range))	Parameters	Study Report Locator																																																																												
01806KH	<p>Compare bioavailability of phentermine HCl 15 mg ODT when administered in each instance by oral disintegration and followed by water and swallowed after disintegration without water with phentermine HCl Reference 15 mg capsule when administered with water.</p> <p>Monitor safety including mucosal irritation</p>	<p>Randomized, balanced, open-label, single-dose, 3-treatment, 3-sequence, 3-period, crossover</p>	<p>Phentermine HCl 15 mg ODT by i) oral disintegration and followed by water and ii) swallowed after disintegration without water;</p> <p>Reference Phentermine HCl 15 mg Capsule when administered with water</p>	15	<p><b>Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation Administered with Water (T1) to the Reference Product with Water (Primary Analysis, n = 14).</b></p> <table border="1" data-bbox="1024 548 1850 786"> <thead> <tr> <th rowspan="2">Dependent Variable</th> <th colspan="2">Geometric Mean<sup>a</sup></th> <th rowspan="2">Ratio (%)<sup>b</sup> (Test/Ref)</th> <th colspan="2">90% CI<sup>c</sup></th> <th colspan="2">Power ANOVA</th> </tr> <tr> <th>Test</th> <th>Ref</th> <th>Lower</th> <th>Upper</th> <th></th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>ln(C<sub>max</sub>)</td> <td>47.2656</td> <td>47.8895</td> <td>98.70</td> <td>95.21</td> <td>102.31</td> <td>1.0000</td> <td>5.56</td> </tr> <tr> <td>ln(AUC<sub>last</sub>)</td> <td>1631.6223</td> <td>1729.1990</td> <td>94.36</td> <td>88.83</td> <td>100.22</td> <td>0.9999</td> <td>9.32</td> </tr> <tr> <td>ln(AUC<sub>inf</sub>)</td> <td>1742.6066</td> <td>1861.1115</td> <td>93.63</td> <td>87.67</td> <td>100.00</td> <td>0.9998</td> <td>10.17</td> </tr> </tbody> </table> <p><b>Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation Administered without Water (T2) to the Reference Product with Water (Primary Analysis, n = 14).</b></p> <table border="1" data-bbox="1024 954 1850 1192"> <thead> <tr> <th rowspan="2">Dependent Variable</th> <th colspan="2">Geometric Mean<sup>a</sup></th> <th rowspan="2">Ratio (%)<sup>b</sup> (Test/Ref)</th> <th colspan="2">90% CI<sup>c</sup></th> <th colspan="2">Power ANOVA</th> </tr> <tr> <th>Test</th> <th>Ref</th> <th>Lower</th> <th>Upper</th> <th></th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>ln(C<sub>max</sub>)</td> <td>49.1671</td> <td>47.8895</td> <td>102.67</td> <td>99.04</td> <td>106.43</td> <td>1.0000</td> <td>5.56</td> </tr> <tr> <td>ln(AUC<sub>last</sub>)</td> <td>1620.1964</td> <td>1729.1990</td> <td>93.70</td> <td>88.21</td> <td>99.52</td> <td>0.9999</td> <td>9.32</td> </tr> <tr> <td>ln(AUC<sub>inf</sub>)</td> <td>1736.8013</td> <td>1861.1115</td> <td>93.32</td> <td>87.38</td> <td>99.67</td> <td>0.9998</td> <td>10.17</td> </tr> </tbody> </table> <p><sup>a</sup> Geometric Mean for the Test Formulation without water, T2 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values  <sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)  <sup>c</sup> 90% Confidence Interval</p>	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power ANOVA		Test	Ref	Lower	Upper		CV%	ln(C <sub>max</sub> )	47.2656	47.8895	98.70	95.21	102.31	1.0000	5.56	ln(AUC <sub>last</sub> )	1631.6223	1729.1990	94.36	88.83	100.22	0.9999	9.32	ln(AUC <sub>inf</sub> )	1742.6066	1861.1115	93.63	87.67	100.00	0.9998	10.17	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power ANOVA		Test	Ref	Lower	Upper		CV%	ln(C <sub>max</sub> )	49.1671	47.8895	102.67	99.04	106.43	1.0000	5.56	ln(AUC <sub>last</sub> )	1620.1964	1729.1990	93.70	88.21	99.52	0.9999	9.32	ln(AUC <sub>inf</sub> )	1736.8013	1861.1115	93.32	87.38	99.67	0.9998	10.17	<p>Module 5 Volume 1 Page 7</p>
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018089D	Compare bioavailability of phentermine HCl 30 mg ODT when administered orally swallowed with water (T1) and disintegrated followed by water (T2) with phentermine HCl Reference 30 mg Capsule, swallowed with water under fasting conditions  Monitor safety including mucosal irritation	Randomized, balanced, open-label, single-dose, 3-treatment, 3-sequence, 3-period, crossover	Phentermine HCl 30 mg ODT when administered orally by i) swallowed with water and ii) disintegrated followed by water;  Reference Phentermine HCl 30 mg Capsule, swallowed with water under fasting conditions		<p><b>Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation-Swallowed with Water (T1) to the Reference Product with Water (Primary Analysis, n = 15).</b></p> <table border="1"> <thead> <tr> <th rowspan="2">Dependent Variable</th> <th colspan="2">Geometric Mean<sup>a</sup></th> <th rowspan="2">Ratio (%)<sup>b</sup> (Test/Ref)</th> <th colspan="2">90% CI<sup>c</sup></th> <th colspan="2">Power ANOVA</th> </tr> <tr> <th>Test</th> <th>Ref</th> <th>Lower</th> <th>Upper</th> <th></th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>ln(C<sub>max</sub>)</td> <td>92.1244</td> <td>98.6089</td> <td>93.42</td> <td>90.35</td> <td>96.61</td> <td>1.0000</td> <td>5.38</td> </tr> <tr> <td>ln(AUC<sub>last</sub>)</td> <td>3430.0518</td> <td>3625.4359</td> <td>94.61</td> <td>89.74</td> <td>99.75</td> <td>1.0000</td> <td>8.51</td> </tr> <tr> <td>ln(AUC<sub>inf</sub>)</td> <td>3685.5871</td> <td>4012.1922</td> <td>91.86</td> <td>86.89</td> <td>97.11</td> <td>1.0000</td> <td>8.95</td> </tr> </tbody> </table> <p><b>Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation-Disintegrated followed by Water (T2) to the Reference Product with Water (Primary Analysis, n = 15).</b></p> <table border="1"> <thead> <tr> <th rowspan="2">Dependent Variable</th> <th colspan="2">Geometric Mean<sup>a</sup></th> <th rowspan="2">Ratio (%)<sup>b</sup> (Test/Ref)</th> <th colspan="2">90% CI<sup>c</sup></th> <th colspan="2">Power ANOVA</th> </tr> <tr> <th>Test</th> <th>Ref</th> <th>Lower</th> <th>Upper</th> <th></th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>ln(C<sub>max</sub>)</td> <td>97.3409</td> <td>98.6089</td> <td>98.71</td> <td>95.46</td> <td>102.08</td> <td>1.0000</td> <td>5.38</td> </tr> <tr> <td>ln(AUC<sub>last</sub>)</td> <td>3182.3721</td> <td>3625.4359</td> <td>87.78</td> <td>83.26</td> <td>92.55</td> <td>1.0000</td> <td>8.51</td> </tr> <tr> <td>ln(AUC<sub>inf</sub>)</td> <td>3540.2612</td> <td>4012.1922</td> <td>88.24</td> <td>83.46</td> <td>93.29</td> <td>1.0000</td> <td>8.95</td> </tr> </tbody> </table> <p><sup>a</sup> Geometric Mean for the Test Formulation-Disintegrated followed by water, T2 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values  <sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)  <sup>c</sup> 90% Confidence Interval</p>	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power ANOVA		Test	Ref	Lower	Upper		CV%	ln(C <sub>max</sub> )	92.1244	98.6089	93.42	90.35	96.61	1.0000	5.38	ln(AUC <sub>last</sub> )	3430.0518	3625.4359	94.61	89.74	99.75	1.0000	8.51	ln(AUC <sub>inf</sub> )	3685.5871	4012.1922	91.86	86.89	97.11	1.0000	8.95	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power ANOVA		Test	Ref	Lower	Upper		CV%	ln(C <sub>max</sub> )	97.3409	98.6089	98.71	95.46	102.08	1.0000	5.38	ln(AUC <sub>last</sub> )	3182.3721	3625.4359	87.78	83.26	92.55	1.0000	8.51	ln(AUC <sub>inf</sub> )	3540.2612	4012.1922	88.24	83.46	93.29	1.0000	8.95	Module 5 Volume 9 Page 1
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01809PB	<p>Compare the bioavailability of phentermine HCl 37.5 mg ODT under fasting (T1) and fed (T2) with phentermine HCl Reference 37.5 mg tablets under fasting condition</p> <p>Monitor safety including mucosal irritation</p>	Randomized, balanced, open-label, single-dose, 3-treatment, 3-sequence, 3-period, crossover	<p>Phentermine HCl 37.5 mg ODT administered i) fasting and ii) fed;</p> <p>Reference Phentermine HCl 37.5 mg Tablet administered under fasting condition</p>		<p><b>Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation under Fasting Conditions, T1 to the Reference Product under Fasting Conditions.</b></p> <table border="1" data-bbox="1024 532 1845 764"> <thead> <tr> <th rowspan="2">Dependent Variable</th> <th colspan="2">Geometric Mean<sup>a</sup></th> <th rowspan="2">Ratio (%)<sup>b</sup> (Test/Ref)</th> <th colspan="2">90% CI<sup>c</sup></th> <th colspan="2">Power ANOVA</th> </tr> <tr> <th>Test</th> <th>Ref</th> <th>Lower</th> <th>Upper</th> <th>CV%</th> <th></th> </tr> </thead> <tbody> <tr> <td>ln(C<sub>max</sub>)</td> <td>116.4055</td> <td>118.4320</td> <td>98.29</td> <td>94.40</td> <td>102.33</td> <td>1.0000</td> <td>6.70</td> </tr> <tr> <td>ln(AUC<sub>last</sub>)</td> <td>4099.3519</td> <td>4054.3170</td> <td>101.11</td> <td>95.59</td> <td>106.95</td> <td>1.0000</td> <td>9.34</td> </tr> <tr> <td>ln(AUC<sub>inf</sub>)</td> <td>4467.8094</td> <td>4394.7729</td> <td>101.66</td> <td>94.99</td> <td>108.80</td> <td>0.9997</td> <td>11.30</td> </tr> </tbody> </table> <p><b>Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Phentermine Comparing Test Formulation under Fed Conditions, T2 to the Reference Product under Fasting Conditions.</b></p> <table border="1" data-bbox="1024 932 1845 1164"> <thead> <tr> <th rowspan="2">Dependent Variable</th> <th colspan="2">Geometric Mean<sup>a</sup></th> <th rowspan="2">Ratio (%)<sup>b</sup> (Test/Ref)</th> <th colspan="2">90% CI<sup>c</sup></th> <th colspan="2">Power ANOVA</th> </tr> <tr> <th>Test</th> <th>Ref</th> <th>Lower</th> <th>Upper</th> <th>CV%</th> <th></th> </tr> </thead> <tbody> <tr> <td>ln(C<sub>max</sub>)</td> <td>110.7577</td> <td>118.4320</td> <td>93.52</td> <td>89.82</td> <td>97.37</td> <td>1.0000</td> <td>6.70</td> </tr> <tr> <td>ln(AUC<sub>last</sub>)</td> <td>3661.5895</td> <td>4054.3170</td> <td>90.31</td> <td>85.38</td> <td>95.53</td> <td>1.0000</td> <td>9.34</td> </tr> <tr> <td>ln(AUC<sub>inf</sub>)</td> <td>3956.0526</td> <td>4394.7729</td> <td>90.02</td> <td>84.11</td> <td>96.34</td> <td>0.9997</td> <td>11.30</td> </tr> </tbody> </table> <p><sup>a</sup> Geometric Mean for the Test Formulation-Disintegrated followed by water, T2 (Test) and Reference Product with water (Ref) based on Least Squares Mean of log-transformed parameter values</p> <p><sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)</p> <p><sup>c</sup> 90% Confidence Interval</p>	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power ANOVA		Test	Ref	Lower	Upper	CV%		ln(C <sub>max</sub> )	116.4055	118.4320	98.29	94.40	102.33	1.0000	6.70	ln(AUC <sub>last</sub> )	4099.3519	4054.3170	101.11	95.59	106.95	1.0000	9.34	ln(AUC <sub>inf</sub> )	4467.8094	4394.7729	101.66	94.99	108.80	0.9997	11.30	Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power ANOVA		Test	Ref	Lower	Upper	CV%		ln(C <sub>max</sub> )	110.7577	118.4320	93.52	89.82	97.37	1.0000	6.70	ln(AUC <sub>last</sub> )	3661.5895	4054.3170	90.31	85.38	95.53	1.0000	9.34	ln(AUC <sub>inf</sub> )	3956.0526	4394.7729	90.02	84.11	96.34	0.9997	11.30	Module 5 Volume 17 Page 1
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IMMO ZDROJEWSKI  
10/22/2010

SALLY Y CHOE  
10/22/2010