

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**ANDA 65-089**

**BIOEQUIVALENCE REVIEW(S)**

**Amoxicillin and Clavulanate Potassium  
For Oral Suspension USP,  
200 mg/28.5 mg/5 mL and 400 mg/57 mg/5 mL  
ANDA 65-089**

**Teva Pharmaceuticals, USA  
North Wales, PA 19454  
Submission Date: 04/12/2001**

**Reviewer: Chandra S. Chaurasia**  
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### Review of Two Bioequivalence Studies and Dissolution Data

**Introduction:** *Augmentin*® (Amoxicillin and Clavulanate Potassium) is an oral antibacterial combination consisting of the antibiotic amoxicillin and the (beta)-lactamase inhibitor, clavulanate potassium.

**First Generic:** No

**Indication:** *Augmentin*® is indicated in the treatment of infections caused by susceptible strains of the designated organisms.

**Type of Submission:** Original

#### **Contents of Submission:**

1. Fasting and non-fasting studies on the 400 mg/ 57 mg/5 mL Amoxicillin and Clavulanate Potassium for Oral Suspension.
2. Dissolution data on the 400 mg/ 57 mg/5 mL and 200 mg/ 28.5 mg/5 mL Amoxicillin and Clavulanate Potassium for Oral Suspension. Waiver request on the 200 mg/ 28.5 mg/5 mL strength.
3. A repeat fasting study in 4 subjects.

**Reference Listed Drug:** The reference-listed drug for Amoxicillin and Clavulanate Potassium for Oral Suspension is *Augmentin*® Powder for Reconstitution 400 mg/5 mL; EQ 57 mg Base/5 mL (NDA #50725, May 31, 1996) manufactured by Smith Kline and Beecham. The innovator also markets; 200 mg/5 mL; EQ 28.5 mg Base/5 mL under the same NDA. In addition, the following *Augmentin* products are also listed in the Orange Book (Electronic 2001)

Augmentin Powder for Reconstitution:  
250 mg/5 mL; EQ 62.5 mg Base/5 mL, and  
125 mg/5; EQ 31.25 mg Base/5 mL

Augmentin Oral Tablets:  
875 mg; EQ 125 mg Base  
500 mg; EQ 125 mg Base  
250 mg; EQ 125 mg Base

Augmentin Oral Chewable Tablets:  
400 mg; EQ 57 mg Base  
250 mg; EQ 62.5 mg Base  
200 mg; EQ 28.5 mg Base  
125 mg; EQ 31.25 mg Base

#### **Recommended Dose:**

Based on the amoxicillin component, *Augmentin* should be dosed as follows (PDR 2001):  
Neonates and infants aged < 12 weeks (3 months)

The recommended dose of *Augmentin* is 30 mg/kg/day divided q12h, based on the amoxicillin component.

Pediatric patients weighing 40 kg and more should be dosed according to the following adult recommendations: The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours. For more severe infections, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours.

### Pharmacokinetics and Metabolism:

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of *Augmentin*. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While *Augmentin* can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when *Augmentin* was dosed at 30 and 150 minutes after the start of a high fat breakfast.

Oral administration of single doses of 400 mg *Augmentin* chewable tablets and 400 mg/5 mL suspension to 28 adult volunteers yielded comparable pharmacokinetic data:

Dose	AUC <sub>0-∞</sub> (µg.hr./mL)		C <sub>max</sub> (µg/mL)	
	amoxicillin (±S.D.)	clavulanate potassium (±S.D.)	amoxicillin (±S.D.)	clavulanate potassium (±S.D.)
400 mg/57 mg (5 mL of suspension)	17.29 ±2.28	2.34 ±0.94	6.94 ±1.24	1.10 ±0.42
400mg/57 mg (one chewable tablet)	17.24 ±2.64	2.17 ±0.73	6.67 ±1.37	1.03 ±0.33

The reported half-life of amoxicillin after the oral administration of *Augmentin* is 1.3 hours and that of clavulanic acid is 1.0 hour

### Recent Correspondence and Reviews:

1. The DBE reviewed a control document on amoxicillin/clavulanate potassium powder for suspension, 250 mg/62.5 mg per 5 mL and 400 mg/57 mg per 5 mL (OGD# 00-368; \_\_\_\_\_, Submission Date 09/07/00; Review Date 10/11/00) and made the following recommendations regarding bioequivalence studies:
  - 1) To conduct fasting and non fasting bioequivalence studies for amoxicillin/clavulanate potassium powder for suspension, 250 mg/62.5 mg per 5 mL and 400 mg/57 mg per 5 mL.
  - 2) Amoxicillin/clavulanate potassium powder for suspension, 125 mg/31.25 mg per 5 mL and 200 mg/28.5 mg per 5 mL are eligible for a waiver of *in-vivo* bioequivalence studies if, the *in-vitro* dissolution profiles are comparable and formulations are proportional to amoxicillin/clavulanate potassium powder for suspension, 250 mg/62.5 mg per 5 mL and 400 mg/57 mg per 5 ml respectively.

**Financial Disclosure:** Form FDA 3454 was submitted. The firm certifies that it has not entered into any financial arrangement with clinical investigators and that its certification is in compliance with 21 CFR part 54 and 54.2(d) [Vol. 1.1, pp. 118].

**Protocol No. 00343:** A randomized two-way crossover study to determine the relative bioavailability of two combination oral suspension formulations of Amoxicillin/Clavulanate Potassium, 400 mg/57 mg/5 mL, in normal, healthy, non-smoking, male subjects under fasting conditions.

**Study Information**

**Clinical Facility:** \_\_\_\_\_

**Principal Investigator:** \_\_\_\_\_, M.D.

**Clinical Study Dates:** Period I: August 24, 2000, Period II: August 31, 2000

**Analytical Facility:** Novopharm Ltd., Toronto, Ontario, Canada

**Analytical Section Head:** Jean Maurice T-Onge

**Analytical Study Dates:** 10/27/00 to 11/17/00

**Storage Period:** 86 days

**Treatment Information**

<b>Treatment ID:</b>	A	B
<b>Test or Reference:</b>	T	R
<b>Product Name:</b>	Amoxicillin/Clavulanate Potassium Oral Suspension	Augmentin® Oral Suspension
<b>Manufacturer:</b>	Teva Pharmaceuticals	Smith Kline Beecham
<b>Manufacturing Date:</b>	06/26/00	N/A
<b>Expiration Date:</b>	N/A	06/2001
<b>ANDA Batch Size:</b>	_____	N/A
<b>Batch/Lot Number:</b>	10395P1	NA2976
<b>Potency: Amoxicillin:</b>	104.9 %	107.3%
<b>Clavulanic Acid:</b>	107.1%	106.7%
<b>Strength:</b>	400 mg/57 mg/5 mL	400 mg/57 mg/5 mL
<b>Dosage Form:</b>	Oral Suspension	Oral Suspension
<b>Dose Administered:</b>	400 mg/57 mg/5 mL	400 mg/57 mg/5 mL
<b>Study Condition:</b>	Fasting	Fasting
<b>Length of Fasting:</b>	Overnight	Overnight

**RANDOMIZATION**

**DESIGN**

<b>Randomized:</b>	Y	<b>Design Type:</b>	crossover
<b>No. of Sequences:</b>	2	<b>Replicated Treatment</b>	N
<b>No. of Periods:</b>	2	<b>Balanced:</b>	Y
<b>No. of Treatments:</b>	2	<b>Washout Period:</b>	7 days

**Randomization:** AB: 2,4,5,7,11,12,14,15,18,20,22,24,27,28,29,30,35,36,39,40

**Scheme:** BA: 1,3,6,8,9,10,13,16,17,19,21,23,25,26,31,32,33,34,37,38

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	40
Route of Administration:	Oral	No. of Subjects Completing:	36*
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	36
Number of Doses:	N/A	No. of Dropouts:	Four*
Loading Dose:	N/A	Sex(es) Included:	male
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	6

\*Subject #15 and 38 didn't report for Period II drug administration. Subject #28 was withdrawn prior to drug administration in Period II due to a positive laboratory result for cannabinoids. Subject #5 withdrew following the 1.5-hour blood sampling time point in Period II due to difficult blood draws.

**Blood Sampling:** One x 7 mL each before dosing (0-time) and at 0.33, 0.67, 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10, 12, and 14 hours collected in vacutainers containing Na-EDTA. The blood was centrifuged at 3000 rpm for 10 minutes at 4 °C, and all plasma samples were stored at -70 °C, pending assay.

**Dietary Restrictions:** No alcohol-, xanthine-, containing beverages/foods for 48 hrs pre-dose and throughout sample collection period. No water 1 hr before/after dosing. Fasted overnight pre-dose and 4hrs post-dose.

**Activity Restrictions:** Subjects remained ambulatory or seated upright for the first 4 hours post-dose, except when warranted by medical events. No strenuous activity during the housing period.

**Drug Restrictions:** Subjects refrained from taking any prescription and over-the-counter medication from 14 and 7 days, respectively preceding the first drug administration until completion of the study.

## Study Results

### 1) Clinical

**Adverse Events:** During the study, 6 adverse events were reported by 6 of the 40 subjects. The adverse events are summarized in the table below:

Adverse Events	No of Adv. Events	Test/No. of sub.	Ref/No. of sub.	Severity	Resolution/Action taken	Relationship to study drugs
Headache	1	1	-	Mild	None	Unrelated
Feeling faint due to blood draw	1	1		Mild	Advised to lower head	Unrelated
Dislocated left shoulder	1	-	1	Mild	None	Unrelated
Elevated Creatinine	1	-	1	Mild	Test repeated, repeat test normal	Unlikely

Bruised and tender right arm	1	1	-	Mild	None	Unrelated
Diarrhea	1		1	Mild	None	Probably

**Protocol Deviations:** None other than minor sampling deviations.

## 2) Analytical (Not to be released under FOI)

**Analytes:** Amoxicillin and Clavulanic Acid

**Assay Method:** HPLC/UV (for Amoxicillin) and LC/MS MS (for Clavulanic Acid)

**Matrix:** plasma

Assay Validation – Pre-Study Analyte: Amoxicillin				
QC Conc. (ng/mL)	199.94 (LLOQ)	540.42 (LQC)	9006.98 (MQC)	18014.00 (HQC)
Intra day Precision (%CV)	8	8	2	4
Intra day Accuracy (% accuracy)	99.7	102.4	102.3	102.7
Inter day Precision (%CV)	Not provided	12	6	5
Inter day Accuracy (% accuracy)	Not provided	100.5	101.6	100.3
Stability in Plasma				
Room Temp.	Stable at nominal temperature of 20 °C for 23 hours			
Freeze-Thaw Cycles	Stable after three freeze-thaw cycles			
Long-term storage (Vol. 1.6, pp. 2342)	Stable at nominal temperature of -70 °C for at least 179 days			
Wet extract stability at 4 °C	98 hours			
Regression	weighted (1/x) linear regression			
Linearity (range of r <sup>2</sup> values)	0.9957-0.9997			
Linearity range (ng/mL)	9 points: 199.94, 399.87, 1249.61, 2499.22, 4998.43, 9996.86, 14995.30, 19993.70 and 24992.20			
Sensitivity/LOQ (ng/mL)	199.94 ng/mL			
Mean % recovery	LQC: 94.87%, MQC: 87.33% and HQC: 89.32%			
Specificity	No interfering peaks			

Assay Validation – Within Study Analyte: Amoxicillin									
Calibration Curve Standard Conc. (ng/mL)	199.18	398.35	1244.84	2489.69	4979.38	9958.75	14938.10	19917.50	24896.90
Inter day Precision (%CV)	17	9	7	11	7	6	4	3	2
Inter day Accuracy (% accuracy)	95	103	101	101	100	99	101	100	100
r <sup>2</sup> value of representative calibration curve	0.9977								
Linearity Range (ng/mL)	199.18-24896.90								

Assay Validation – Pre-Study Analyte: Clavulanic Acid				
QC Conc. (ng/mL)	50.02 (LLOQ)	108.64 (LQC)	1810.59 (MQC)	3621.18 (HQC)
Intra day Precision (%CV)	5	4	6	4
Intra day Accuracy (% accuracy)	113	98	99	104
Inter day Precision (%CV)	Not provided	4	4	6
Inter day Accuracy (% accuracy)	Not provided	95	96	98
Stability in Plasma				
Room Temp.	Stable at nominal temperature of 20 °C for 23 hours			
Freeze-Thaw Cycles	Stable after three freeze-thaw cycles			
Long-term storage (Vol. 1.8, pp.3567)	Stable at nominal temperature of -70 °C for at least 118 days			
Wet extract stability at 4 °C	23 hours			
Regression	weighted (1/x) linear regression			
Linearity (range of r <sup>2</sup> values)	0.9951-0.9996			

Linearity range (ng/mL)	9 points: 50.02, 100.04, 250.11, 500.22, 1250.54, 2000.86, 3001.30, 4001.73, 5002.16
Sensitivity/LOQ (ng/mL)	50.02 ng/mL
Mean % recovery	LQC: 91.42%, MQC: 89.26% and HQC: 79.76%
Recovery of Internal Standard	66.04%
Specificity	No interfering peaks

Assay Validation – Within Study Analyte: Clavulanic Acid for Study #00-343									
Calibration Curve Standard Conc. (ng/mL)	50.02	100.04	250.11	500.22	1250.54	2000.86	3001.30	4001.73	5002.16
Inter day Precision (%CV)	5	2	3	4	2	3	2	2	1
Inter day Accuracy (% Accuracy)	104	100	98	98	99	101	100	101	99
r <sup>2</sup> value of representative calibration curve	0.9995								
Linearity Range (ng/mL)	50.02-5002.16								

### Comments on Analytical Methodology:

The analytical method validations for amoxicillin and clavulanic acid are acceptable.

### 3) Pharmacokinetic and Statistical Analysis:

Mean Plasma Concentrations: Amoxicillin: Table 1

Clavulanic Acid: Table 4

Pharmacokinetics Measures: Amoxicillin: Tables 2, 3a-b and 7\*

Clavulanic Acid: Tables 5, 6a-b and 7\*

*\*Note 1: Tables 3b and 6b summarizes the PK measures for amoxicillin and clavulanic acid, respectively for 35 subjects (N=35) excluding subject 16. For details see below.*

*Note 2: Tables 7 and 8 summarizes the PK measures for amoxicillin and clavulanic acid, respectively for Subject 16 in comparison to those for all subjects (N=36) and excluding subject 16 (N=35). For details see below.*

Table 1. Fasting Single-Dose In Vivo Bioequivalence Study # 00343 Arithmetic Mean Plasma Amoxicillin Concentrations [ng/mL] ( $\pm$ S.D.) Vs. Time (N = 36)

Time	Test (treat A)		Ref (treat B)		A/B
	Conc.	S.D.	Conc.	S.D.	
0.0	0.00	-	0.00	-	-
0.33	1788.18	1169.86	1673.08	1016.10	1.07
0.67	5507.78	2140.06	5423.71	2319.50	1.02
1.0	7015.40	1986.96	7011.41	2329.03	1.00
1.25	6895.02	1582.27	7088.10	2061.11	0.97
1.5	6466.03	1449.16	6677.12	1708.57	0.97
1.75	5841.95	1364.72	6001.57	1354.61	0.97
2.0	5232.82	1326.97	5158.69	1211.41	1.01
2.33	4440.22	1217.35	4291.88	983.13	1.03
2.67	3646.13	1066.68	3547.06	921.98	1.03
3.0	2968.25	971.04	2851.40	840.56	1.04
3.5	2119.38	749.74	2060.01	711.59	1.03
4.0	1530.63	571.19	1498.70	575.78	1.02
5.0	786.99	336.15	780.65	340.07	1.01
6.0	469.32	228.89	464.23	246.68	1.01
7.0	246.26	179.35	233.61	199.37	1.05
8.0	83.29	131.47	97.87	135.86	0.85
10.0	0.00	-	0.00	-	-
12.0	0.00	-	0.00	-	-
14.0	0.00	-	0.00	-	-

Table 2. Fasting Single-Dose In Vivo Bioequivalence Study # 00343 Arithmetic Means ( $\pm$ SD) of Pharmacokinetic Parameters for **Amoxicillin (N = 36)**

PK Measures	Test (A)	Reference (B)
AUCt [ng•hr/mL]	18385.45 $\pm$ 3344.12	18236.38 $\pm$ 3518.38
AUCi [ng•hr/mL]	18883.70 $\pm$ 3398.64	18725.21 $\pm$ 3585.04
Cmax [ng/mL]	7459.47 $\pm$ 1810.70	7611.89 $\pm$ 2076.85
tmax [hr]	1.21 $\pm$ 0.36	1.28 $\pm$ 0.43
k <sub>el</sub> [1/hr]	0.5750 $\pm$ 0.1111	0.5813 $\pm$ 0.1265
t <sub>1/2</sub> [hr]	1.25 $\pm$ 0.24	1.26 $\pm$ 0.34

Table 3a. Summary Statistics for **Amoxicillin** Single-Dose In Vivo Bioequivalence Study #00343 Under Fasting Conditions, **N = 36**

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (ng•hr/mL)	18080.47	17880.96	0.0661	1.01	98.5-103.8
Ln AUCi (ng•hr/mL)	18581.14	18367.16	0.0671	1.01	98.5-103.9
Ln Cmax (ng/mL)	7244.94	7330.37	0.1541	0.99	92.9-105.1

\*geometric mean values for In-transformed data reported

Table 3b. Summary Statistics for **Amoxicillin** Single-Dose In Vivo Bioequivalence Study #00343 Under Fasting Conditions **Excluding Subject 16, N = 35**

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (ng•hr/mL)	18070.85	17896.97	0.0668	1.01	98.3-103.7
Ln AUCi (ng•hr/mL)	18570.73	18378.33	0.0679	1.01	98.3-103.9
Ln Cmax (ng/mL)	7228.91	7416.30	0.1431	0.97	91.9-103.3

\*geometric mean values for In-transformed data reported

Table 4. Fasting Single-Dose In Vivo Bioequivalence Study # 00343 Arithmetic Mean Plasma **Clavulanic Acid** Concentrations [ng/mL] ( $\pm$ S.D.) Vs. Time (N = 36)

Time	Test (treat A)		Ref (treat B)		A/B
	Conc.	S.D.	Conc.	S.D.	
0.0	0.00	-	0.00	-	-
0.33	398.72	303.47	362.35	277.28	1.10
0.67	1089.90	498.32	1013.19	494.26	1.08
1.0	1183.01	417.09	1058.62	402.32	1.12
1.25	1036.60	345.50	939.90	340.83	1.10
1.5	876.59	298.75	786.73	283.03	1.11
1.75	726.03	255.69	643.82	233.79	1.13
2.0	593.06	214.10	516.79	200.71	1.15
2.33	472.26	188.16	420.96	172.44	1.12
2.67	365.77	150.94	325.13	134.19	1.12
3.0	282.54	120.34	246.65	98.33	1.15
3.5	198.43	92.09	169.44	74.64	1.17
4.0	136.22	58.85	115.71	54.84	1.18
5.0	60.00	44.53	44.43	43.45	1.35
6.0	17.34	31.03	16.16	26.61	1.07
7.0	1.55	9.31	0.00	-	-
8.0	0.00	-	0.00	-	-
10.0	0.00	-	0.00	-	-
12.0	0.00	-	0.00	-	-
14.0	0.00	-	0.00	-	-

Table 5. Fasting Single-Dose In Vivo Bioequivalence Study # 00343 Arithmetic Means ( $\pm$ SD) of Pharmacokinetic Parameters for **Clavulanic Acid (N = 36)**

PK Measures	Test (A)	Reference (B)
AUCt [ng•hr/mL]	2318.06 $\pm$ 857.75	2062.28 $\pm$ 800.67
AUCi [ng•hr/mL]	2419.98 $\pm$ 864.45	2159.19 $\pm$ 804.20
Cmax [ng/mL]	1238.04 $\pm$ 430.65	1132.14 $\pm$ 443.66
tmax [hr]	0.96 $\pm$ 0.34	0.95 $\pm$ 0.26
k <sub>el</sub> [1/hr]	0.6983 $\pm$ 0.1147	0.7126 $\pm$ 0.1342
t <sub>1/2</sub> [hr]	1.02 $\pm$ 0.16	1.01 $\pm$ 0.20

Table 6a. Summary Statistics for **Clavulanic Acid** Single-Dose In Vivo Bioequivalence Study #00343 Under Fasting Conditions, N = 36

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (ng•hr/mL)	2156.14	1881.58	0.3228	1.15	100.7-130.4
Ln AUCi (ng•hr/mL)	2263.38	1986.36	0.3039	1.14	100.9-128.6
Ln Cmax (ng/mL)	1157.41	1034.24	0.3003	1.12	99.3-126.2

\*geometric mean values for ln-transformed data reported

Table 6b. Summary Statistics for **Clavulanic Acid** Single-Dose In Vivo Bioequivalence Study #00343 Under Fasting Conditions, **Excluding Subject 16, N = 35**

PK Measures*	Geometric Mean		Root MSE	A/B	90% CI
	Test (A)	Reference (B)			
Ln AUCt (ng•hr/mL)	2157.09	1958.76	0.2732	1.10	98.6-123.0
Ln AUCi (ng•hr/mL)	2263.86	2061.36	0.2589	1.10	98.9-121.9
Ln Cmax (ng/mL)	1164.83	1077.36	0.2613	1.08	97.3-120.2

\*geometric mean values for ln-transformed data reported

Table 7. Comparative Summary of **Amoxicillin** PK Measures for Sub. #16 in comparison to all subjects (N=36) and excluding Sub. #16 (N=35); Study #00343 Under Fasting Conditions

Subjects	PK Measures								
	AUCt [ng•hr/mL]			AUCi [ng•hr/mL]			Cmax [ng/mL]		
	Test (A)	Ref (B)	A/B (%)	Test (A)	Ref (B)	A/B (%)	Test (A)	Ref (B)	A/B (%)
Sub #16 only	18389.8	17446.7	105.4	18875.4	18091.0	104.3	7608.0	5038.5	151.0
N=36 (includes all subjects)	18385.5 $\pm$ 3344.1	18236.4 $\pm$ 3518.0	100.8	18883.7 $\pm$ 3398.6	18725.2 $\pm$ 3585.0	108.5	7459.5 $\pm$ 1810.7	7611.9 $\pm$ 2076.9	98.0
N=35(excludes Sub #16)	18385.3 $\pm$ 3392.9	18258.9 $\pm$ 3566.8	100.6	18883.9 $\pm$ 3448.3	18743.3 $\pm$ 3635.7	100.7	7455.2 $\pm$ 1837.0	7685.4 $\pm$ 2059.1	97.0
Range	11946 - 24380	10238 - 25229	N/A	12347 - 25126	10683 - 25789	N/A	4113 - 10896	4469 - 12291	N/A

Table 8. Comparative Summary of **Clavulanic Acid** Measures for Sub. #16 in comparison to all subjects (N=36) and excluding Sub. #16 (N=35); Study #00343 Under Fasting Conditions

Subjects	PK Measures								
	AUCt [ng•hr/mL]			AUCi [ng•hr/mL]			Cmax [ng/mL]		
	Test (A)	Ref (B)	A/B (%)	Test (A)	Ref (B)	A/B (%)	Test (A)	Ref (B)	A/B (%)
Sub #16 only	2317.0	450.7	514.07	2441.6	533.5	457.7	970.2	239.7	404.8
N=36 (includes all subjects)	2318.1 $\pm$ 857.8	2062.3 $\pm$ 800.7	112.40	2420.0 $\pm$ 864.5	2159.2 $\pm$ 804.2	112.1	1238.0 $\pm$ 430.7	1132.1 $\pm$ 443.7	109.4
N=35(excludes Sub #16)	2318.1 $\pm$ 870.3	2108.3 $\pm$ 762.5	110.0	2419.4 $\pm$ 877.1	2205.6 $\pm$ 765.4	109.7	1245.7 $\pm$ 434.5	1157.6 $\pm$ 422.5	107.6
Range	762 - 4022	450 - 3563	N/A	859 - 4144	533 - 3660	N/A	316 - 2093	240 - 2160	N/A

## Reassays:

A total of 1439 samples were analyzed.

### For Amoxicillin:

No repeat assay due to any pharmacokinetic anomalies has been reported in this study. A summary of the number of repeat samples due to analytical anomalies is given below:

Reasons for repeat	Number of samples	% of Total Samples
Spoiled sample	36	2.50
Sample not run	2	0.14

### For Clavulanic Acid:

Three samples (0.21%) were reanalyzed due to analytical anomaly – spoiled sample.

There were three repeats (0.21%) due to pharmacokinetic anomalies as follows:

Subject 6, period 1, Test, 14 hr time point ( $T_{max} = 1$  hr)

Subject 7, period 2, Reference, 2 hr time point ( $T_{max} = 1$  hr)

Subject 36, period 3, Reference, 3 hr time point ( $T_{max} = 1$  hr)

The repeat values were reported per SOP 19.2.5 (Vol. 1.11, pp. 4785), and found acceptable by the reviewer.

### **Comments:** On pharmacokinetic data

1. The pharmacokinetic measures ( $AUC_t$ ,  $AUC_i$ ,  $C_{max}$ ,  $t_{max}$  and  $t_{1/2}$ ) and confidence intervals of  $\ln-AUC_t$ ,  $\ln-AUC_i$  and  $\ln-C_{max}$  for amoxicillin and clavulanic acid calculated by the reviewer are in agreement with the values reported by the firm.
2. There were no statistically significant period effects for any of these PK measures.
3. The 90% confidence intervals of  $\ln-AUC_t$ ,  $\ln-AUC_i$ , and  $\ln-C_{max}$  ratios for amoxicillin are within the acceptable limits of 80-125%. However, the 90% confidence intervals of these parameters for clavulanic acid are outside the acceptable limits of 80-125%. The firm notes that the plasma clavulanic acid concentrations for Subject 16 were very low following administration of the reference product relative to those of other subjects. As a result, Subject 16 has a considerably lower clavulanic acid  $AUC_t$ ,  $AUC_i$ , and  $C_{max}$  values for the reference product, compared to the corresponding mean values from 36 subjects (including Subject 16) and 35 subjects (excluding Subject 16, Table 8).

It is noted that the clavulanic acid  $AUC_t$ ,  $AUC_i$ , and  $C_{max}$  values for the test product in Subject 16 are similar to those of the mean values from other subjects including all subjects (N=36) and excluding Subject 16, N=35; Table 7). Consequently, Subject 16 exhibits discordant test/reference ratios for  $AUC_t$ ,  $AUC_i$ , and  $C_{max}$ .

4. Based on the above analysis, the firm identified Subject 16 as a statistical outlier for clavulanic acid  $AUC_t$ ,  $AUC_i$ , and  $C_{max}$ . A second set of data analysis was therefore performed excluding Subject 16 for both analytes. The results of these analyses are presented in Tables 3b and 6b.
5. For 35 subjects (N=35), in which Subject 16 is excluded, the test /reference ratios of geometric means of the PK measures  $AUC_t$ ,  $AUC_i$ , and  $C_{max}$  for amoxicillin and clavulanic acid are within the acceptable limits of 0.80-1.25. The corresponding 90% confidence intervals are also within the acceptable limits of 80-125%.
6. In order to further support the exclusion of Subject 16 from the statistical analysis, the firm conducted a repeat study (Protocol No. 00343R) in four subjects including Subject 16 and three other subjects who participated in the original study. The repeat study was conducted under the same conditions as the original study using the same test and reference products. The details of this study are given below.

**Protocol No. 00343R:** A randomized two-way crossover study to determine the relative bioavailability of two combination oral suspension formulations of Amoxicillin/Clavulanate Potassium, 400 mg/57 mg/5 mL, in normal, healthy, non-smoking, male subjects under fasting conditions.

### Study Information

**Clinical Facility:** \_\_\_\_\_

**Principal Investigator:** \_\_\_\_\_, M.D.

**Clinical Study Dates:** Period I: February 01, 2001, Period II: February 08, 2001

**Analytical Facility:** Novopharm Ltd., 1290 Ellesmere Rd., Toronto, Ontario, Canada

**Analytical Section Head:** Jean Maurice T-Onge

**Analytical Study Dates:** Analysis completed on February 20, 2001, exact dates not specified (Vol. 1.7, pp 2734)

**Storage Period:** 19 days

### Treatment Information

Treatment ID:	A	B
Test or Reference:	T	R
<b>Product Name:</b>	Amoxicillin/Clavulanate Potassium Oral Suspension	Augmentin® Oral Suspension
<b>Manufacturer:</b>	Teva Pharmaceuticals	Smith Kline Beecham
<b>Batch/Lot Number:</b>	10395P1	NA2976
<b>Strength:</b>	400 mg/57 mg/5 mL	400 mg/57 mg/5 mL
<b>Dosage Form:</b>	Oral Suspension	Oral Suspension
<b>Dose Administered:</b>	400 mg/57 mg/5 mL	400 mg/57 mg/5 mL
<b>Study Condition:</b>	Fasting	Fasting
<b>Length of Fasting:</b>	Overnight	Overnight

### RANDOMIZATION

<b>Randomized:</b>	Y	<b>Design Type:</b>	crossover
<b>No. of Sequences:</b>	2	<b>Replicated Treatment</b>	N
<b>No. of Periods:</b>	2	<b>Balanced:</b>	Y
<b>No. of Treatments:</b>	2	<b>Washout Period:</b>	7 days
<b>Number of subjects:</b> Four subjects were enrolled and all four completed the study			

**Randomization Scheme:** AB: 24, 35 BA: 16, 25

**Dosing:**

**Blood Sampling:**

**Dietary Restrictions:**

**Activity Restrictions:**

**Drug Restrictions:**

**Study Results**

Same as those reported in the fasting study  
Protocol 00243

**Adverse Events:** No adverse reports were reported during the repeat study.

**Protocol Deviations:** None other than minor sampling deviations.

**Analytical:** Same method as that used in the fasting study P00343. Within study day assay validations are given below:

<b>Assay Validation – Within Study Analyte: Amoxicillin for Repeat Study #00-343R</b>									
Calibration Curve Standard Conc. (ng/mL)	199.18	398.35	1244.84	2489.69	4979.38	9958.75	14938.10	19917.50	24896.90
Inter day Precision (%CV)	9	10	3	1	2	3	2	1	1
Inter day Accuracy (% Accuracy)	108	93	101	100	99	100	99	99	101
r <sup>2</sup> value of representative calibration curve	0.9991								
Linearity Range (ng/mL)	199.18-24896.90								

<b>Assay Validation – Within Study Analyte: Clavulanic Acid for Study #00-343R</b>									
Calibration Curve Standard Conc. (ng/mL)	50.02	100.04	250.11	500.22	1250.54	2000.86	3001.30	4001.73	5002.16
Inter day Precision (%CV)	2	4	2	4	1	0	2	1	0
Inter day Accuracy (% Accuracy)	102	99	100	98	99	100	100	102	99
r <sup>2</sup> value of representative calibration curve	0.9994								
Linearity Range (ng/mL)	50.02-5002.16								

**Comments on Analytical Methodology:** Analytical method is acceptable

**Pharmacokinetic and Statistical Analysis:**

Mean Plasma Concentrations: Amoxicillin: Table 9, Clavulanic Acid: Table 10

Ratios of Pharmacokinetics Measures: Amoxicillin: Table 11a-b. Clavulanic Acid: Table 12a-b

Table 9. Fasting Single-Dose In Vivo Bioequivalence Study # 00343R Arithmetic Mean Plasma Amoxicillin Concentrations [ng/mL] (±S.D.) Vs. Time (N = 4)

Time	Test (treat A)		Ref (treat B)		A/B
	Conc.	S.D.	Conc.	S.D.	
0.0	0.00	-	0.00	-	-
0.33	1522.05	827.08	2017.05	1094.54	0.75
0.67	5256.12	1400.24	6449.75	2011.66	0.81
1.0	7550.67	1765.49	7216.46	2071.99	1.05
1.25	7600.79	1487.73	6647.68	1744.57	1.14
1.5	7009.92	1056.96	5871.50	1566.77	1.19
1.75	6101.23	642.83	5161.91	1258.95	1.18
2.0	5234.18	615.36	4665.83	510.49	1.12
2.33	3879.71	544.64	3854.47	857.04	1.01
2.67	2833.34	386.37	2950.42	667.59	0.96
3.0	2064.22	187.89	2231.71	650.57	0.92
3.5	1306.46	134.02	1514.04	546.14	0.86
4.0	919.03	119.34	1035.50	415.52	0.89
5.0	471.84	181.81	531.68	278.31	0.89
6.0	157.45	101.01	231.32	191.68	0.68
7.0	102.47	118.38	83.93	167.85	1.22

8.0	0.00	-	0.00	-	-
10.0	0.00	-	0.00	-	-
12.0	0.00	-	0.00	-	-
14.0	0.00	-	0.00	-	-

Table 10. Fasting Single-Dose In Vivo Bioequivalence Study # 00343R Arithmetic Mean Plasma Clavulanic Acid Concentrations [ng/mL] ( $\pm$ S.D.) Vs. Time (N = 4)

Time	Test (treat A)		Ref (treat B)		A/B
	Conc.	S.D.	Conc.	S.D.	
0.0	0.00	-	0.00	-	-
0.33	278.56	137.54	485.81	259.12	0.57
0.67	980.92	187.81	1326.81	451.43	0.74
1.0	1030.57	244.84	1250.56	365.25	0.82
1.25	1032.00	213.07	1062.34	294.58	0.97
1.5	851.41	184.17	874.51	267.80	0.97
1.75	713.18	191.92	703.87	209.35	1.01
2.0	584.03	155.34	572.98	186.29	1.02
2.33	431.85	126.15	424.82	127.60	1.02
2.67	317.52	90.04	343.27	125.55	0.92
3.0	253.65	85.60	260.15	89.62	0.98
3.5	182.64	71.61	179.65	66.97	1.02
4.0	127.19	51.31	133.29	49.84	0.95
5.0	42.61	49.21	59.54	45.50	0.72
6.0	0.00	-	12.66	25.31	-
7.0	0.00	-	0.00	0.00	-
8.0	0.00	-	0.00	-	-
10.0	0.00	-	0.00	-	-
12.0	0.00	-	0.00	-	-
14.0	0.00	-	0.00	-	-

Table 11a. Absolute Values of Test and Reference for Amoxicillin PK Measures in 4 Subjects from the Original (Study No. 00343) and Repeat (Study No. 00343R) Studies

Sub #	AUC <sub>t</sub>				AUC <sub>i</sub>				C <sub>max</sub>			
	Test		Ref		Test		Ref		Test		Ref	
	Original	Redose	Original	Redose	Original	Redose	Original	Redose	Original	Redose	Original	Redose
16	18390	13132	17447	15345	18875	13542	18191	15956	7608	5430	5038	4947
24	16572	18719	16992	16742	17271	19081	17517	17133	9383	8267	8317	8082
25	14236	16811	13532	16299	14547	17432	13922	16792	7266	8829	8820	9197
35	15965	16079	15233	16183	16395	16464	15653	16463	7036	8374	7367	7450
Mean (n=35)	18385	N/A	18259	N/A	18834	N/A	18743	N/A	7452	N/A	7685	N/A
	$\pm$ 3393		$\pm$ 3567		$\pm$ 3448		$\pm$ 3636		$\pm$ 1836		$\pm$ 2059	
Mean (n=4)	16290	16185	15801	16142	16772	16630	16296	16586	7824	7725	7386	7419
	$\pm$ 1714	$\pm$ 2320	$\pm$ 1788	$\pm$ 583	$\pm$ 1804	2 $\pm$ 325	$\pm$ 1894	$\pm$ 501	$\pm$ 1066	$\pm$ 1549	$\pm$ 1677	$\pm$ 1799

Table 11b. Comparisons of Test/Reference Ratios for Amoxicillin PK Measures in 4 Subjects Between the Original (Study No. 00343) and Repeat (Study No. 00343R) Studies

Subject Number	Ratio of AUC <sub>t</sub> Means		Ratio of AUC <sub>i</sub> Means		Ratio of C <sub>max</sub> Means	
	New (%)	Old (%)	New (%)	Old (%)	New (%)	Old (%)
16	85.57	105.41	84.87	104.34	109.76	151.00
24	111.81	97.53	111.37	98.60	102.29	113.83
25	103.14	105.20	103.81	104.49	96.00	82.39
35	99.36	104.80	100.01	104.74	112.40	95.51

Table 12a. Comparisons of Test/Reference Ratios for Clavulanic Acid PK Measures in 4 Subjects Between the Original (Study No. 00343) and Repeat (Study No. 00343R) Studies

Sub #	AUC <sub>t</sub>				AUC <sub>i</sub>				C <sub>max</sub>			
	Test		Ref		Test		Ref		Test		Ref	
	Original	Redose	Original	Redose	Original	Redose	Original	Redose	Original	Redose	Original	Redose
16	2317	2123	451	2445	2442	2260	533	2524	970	1040	240	1074
24	2881	1965	2499	2921	2965	2083	2583	2994	1927	1153	1617	1893
25	3519	2675	3010	2765	3603	2792	3106	2874	1679	1310	1763	1488
35	1912	1567	716	1434	1990	1662	786	1548	1235	1056	515	961
Mean (n=35)	2318 ±870	N/A	2108 ±762	N/A	2419 ±877	N/A	2206 ±765	N/A	1246 ±434	N/A	1158 ±422	N/A
Mean (n=4)	2657 ±699	2083 ±459	1668 ±1275	2391 ±668	2750 ±695	2199 ±468	1752 ±1284	2485 ±656	1453 ±431	1140 ±124	1034 ±767	1354 ±425

Table 12b. Comparisons of Test/Reference Ratios for Clavulanic Acid PK Measures in 4 Subjects Between the Original (Study No. 00343) and Repeat (Study No. 00343R) Studies

Subject Number	Ratio of AUC <sub>t</sub> Means		Ratio of AUC <sub>i</sub> Means		Ratio of C <sub>max</sub> Means	
	New (%)	Old (%)	New (%)	Old (%)	New (%)	Old (%)
16	86.83	514.07	89.56	457.66	96.79	404.82
24	67.25	115.28	69.57	114.77	60.90	119.17
25	96.73	116.93	97.13	116.01	88.07	95.24
35	109.30	266.75	107.33	253.15	109.90	239.84

**Reassays:** A total of 160 samples were analyzed.

For Amoxicillin: Nine samples (5.6%) were reanalyzed due to analytical anomaly – spoiled sample. No repeat assay due to any pharmacokinetic anomalies has been reported in this study.

For Clavulanic Acid: Two samples (1.25%) were reanalyzed due to analytical anomaly – spoiled sample. No repeat assay due to any pharmacokinetic anomalies has been reported in this study.

**Comments:** On pharmacokinetic data from Repeat Study (00343R):

1. The ratios of the  $\ln\text{-AUC}_t$ ,  $\ln\text{-AUC}_i$  and  $\ln\text{-C}_{max}$  between the test and reference products for amoxicillin and clavulanic acid calculated by the reviewer were in agreement with the values reported by the firm.
2. The comparative results indicate that  $\text{AUC}_t$ ,  $\text{AUC}_i$  and  $\text{C}_{max}$  for all four subjects in the repeat study are similar to those in the original study for amoxicillin.
3. In Subject 16, the ratios of test/reference  $\text{AUC}_t$  for clavulanic acid changed from 514.07% in the original study to 86.83% in the repeat study. Similarly, the clavulanic acid  $\text{AUC}_i$  and  $\text{C}_{max}$  ratios changed from 457.66% (original study) to 89.56% (repeat study), and from 404.82% (original study) to 96.79% (repeat study), respectively. Whereas, the results for the other three subjects in the repeat study were comparable to those in the original study.
4. The comparative clavulanic acid data between the repeat and original studies, support the firm's argument that the observations in the original study for subject 16 were aberrant.

**Protocol No. 00385:** A randomized three-way crossover, study to determine the relative bioavailability of two combination oral suspension formulations of Amoxicillin/Clavulanate Potassium, 400 mg/57 mg/5 mL, in normal, healthy, non-smoking, male subjects under non-fasting conditions.

**Study Information**

**Clinical Facility:** \_\_\_\_\_  
**Principal Investigator:** \_\_\_\_\_, M.D.  
**Clinical Study Dates:** Period I: September 18, 2000, Period II: September 25, 2000  
 Period III: October 02, 2000  
**Analytical Facility:** Novopharm Ltd., 1290 Ellesmere Rd., Toronto, Ontario, Canada  
**Analytical Section Head:** Jean Maurice T-Onge  
**Analytical Study Dates:** 11/13/00 to 12/27/00  
**Storage Period:** 100 days

**Treatment Information**

Treatment ID:	A	B	C
Test or Reference	T	T	R
Product Name:	Amoxicillin/Clavulanate Potassium Oral Suspension	Amoxicillin/Clavulanate Potassium Oral Suspension	Augmentin Oral Suspension
Manufacturer:	Teva Pharmaceuticals	Teva Pharmaceuticals	Smith Kline Beecham
Batch Number:	10395P1	10395P1	NA 2976
Dose Administered:	400 mg/57 mg/5 mL	400 mg/57 mg/5 mL	400 mg/57 mg/5 mL
Study Condition:	fasting	non fasting	non fasting
Length of Fasting:	overnight	overnight	overnight
Standardized Breakfast*:	N	Y	Y

\*Breakfast included a standard high-fat, high-caloric diet consisting of one buttered English muffin, one fried egg, one slice of Canadian bacon, one slice of processed cheese, one serving of hash brown potatoes 4oz., 240 mL of whole milk, and 180 mL of orange juice.

RANDOMIZATION		DESIGN	
Randomized:	Y	Design Type:	Crossover
No. of Sequences:	6	Replicated Treatment	N
No. of Periods:	3	Balanced:	N
No. of Treatments:	3	Washout Period:	7 days

**Randomization Scheme:** ABC: 4,12,17,19  
 ACB: 3,7,18  
 BAC: 6,9,16,20  
 BCA: 1,11,13,21  
 CAB: 5,8,15  
 CBA: 2,10,14

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	21*
Route of Administration:	Oral	No. of Subjects Completing:	17
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	17
Number of Doses:	N/A	No. of Dropouts:	Four*
Loading Dose:	N/A	Sex(es) Included:	Male
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	13

\*Eighteen subjects plus three alternates were enrolled. Subject #12 and #18 withdrew from the study prior to period II due to personal reasons. Subject #19 was withdrawn from the study prior to period III dosing due to a positive drugs of abuse screen. Subject #2 withdrew from the study prior to Period III due to influenza.

**Blood Sampling:**  
**Dietary Restrictions:**  
**Activity Restrictions:**  
**Drug Restrictions:**

} same as those reported in the fasting study

## Study Results

### 1) Clinical

**Adverse Events:** During the study, 13 adverse events were reported by 6 of the 21 subjects. The adverse events are summarized in the table below:

Adverse Events	Sub. No./ Study drug	Severity	Action Taken	Relationship to study drugs
Influenza	2, Test fed	Mild	None	Unrelated
Dizziness	12, Test fast	Mild	None	Unlikely
Tenderness left arm	15, Test fed	Mild	None	Unrelated
Stomach Upset	18, Test fasted	Mild	None	Unrelated
Decreased RBC count	3, Post Clinical Lab	Mild	None	Unrelated
Decreased Hemoglobin	3, Post Clinical Lab	Mild	None	Unrelated
Decreased Hematocrit	3, Post Clinical Lab	Mild	None	Unrelated
Decreased Platelet Count	3, Post Clinical Lab	Mild	None	Unrelated
Elevated Creatinine	3, Post Clinical Lab	Mild	None	Unrelated
Elevated AST	3, Post Clinical Lab	Mild	None	Unrelated
Elevated ALT	3, Post Clinical Lab	Mild	None	Unrelated
Elevated Urea	8, Post Clinical Lab	Mild	None	Unrelated
Elevated Creatinine	8, Post Clinical Lab	Mild	None	Unrelated

**Protocol Deviations:** None other than minor sampling deviations.

2) **Analytical:** Same method as that used in the fasting study. Within study day assay validations are given below:

III Assay Validation – Within Study Analyte: Amoxicillin for Repeat Study #00-385									
Calibration Curve Standard Conc. (ng/mL)	199.18	398.35	1244.84	2489.69	4979.38	9958.75	14938.10	19917.50	24896.90
Inter day Precision (%CV)	6	5	2	10	2	3	4	3	1
Inter day Accuracy (% Accuracy)	102	101	99	96	100	100	100	100	100
r <sup>2</sup> value of representative calibration curve	0.9996								
Linearity Range (ng/mL)	199.18-24896.90								

IV B Assay Validation – Within Study Analyte: Clavulanic Acid for Study #00-385									
Calibration Curve Standard Conc. (ng/mL)	50.02	100.04	250.11	500.22	1250.54	2000.86	3001.30	4001.73	5002.16
Inter day Precision (%CV)	4	3	3	4	2	4	3	2	1
Inter day Accuracy (% Accuracy)	103	99	98	100	101	101	100	99	100
r <sup>2</sup> value of representative calibration curve	0.9994								
Linearity Range (ng/mL)	50.02-5002.16								

**Comments on Analytical Methodology:** Analytical method is acceptable

### 3) Pharmacokinetic and Statistical Analysis:

Mean Plasma Concentrations: Amoxicillin: Table 13

Clavulanic Acid: Table 16

Pharmacokinetics Measures: Amoxicillin: Tables 14 and 15

Clavulanic Acid: Tables 17 and 18

Table 13. Fasting/Non-fasting Single-Dose In Vivo Bioequivalence Study # 00385 Arithmetic Mean Plasma Amoxicillin Concentrations [ng/mL] ( $\pm$ S.D.) Vs. Time (N = 17)

Time (hr)	Test (Fast) A		Test (Fed) B		Ref (Fed) C		B/A	B/C
	Mean	SD	Mean	SD	Mean	SD		
0.0	0.0	-	0.0	-	0.0	-	-	-
0.33	1947.26	1188.66	600.34	514.85	467.35	382.74	0.31	1.28
0.67	5702.53	2282.46	1833.42	1144.83	1914.19	957.13	0.32	0.96
1.0	7150.34	2268.02	2956.97	1492.74	3063.67	1594.86	0.41	0.97
1.25	6897.49	2074.03	3887.72	1329.17	3979.09	1760.99	0.56	0.98
1.5	6093.21	1583.91	4734.63	1150.24	4513.53	1613.35	0.78	1.05
1.75	5137.83	1029.55	5287.67	1176.39	4835.74	1260.05	1.03	1.09
2.0	4252.07	715.57	5345.44	1215.16	4916.64	928.40	1.26	1.09
2.33	3636.79	688.60	5058.91	1033.48	4648.10	824.72	1.39	1.09
2.67	2932.83	528.82	4501.65	927.04	4179.02	746.96	1.53	1.08
3.0	2368.26	498.84	3839.78	858.18	3693.60	702.00	1.62	1.04
3.5	1922.25	400.29	3149.66	803.73	3237.41	710.16	1.64	0.97
4.0	1577.67	349.27	2586.50	583.00	2657.10	619.05	1.64	0.97
5.0	816.06	198.53	1383.64	308.91	1396.83	336.26	1.70	0.99
6.0	442.35	153.60	784.56	198.92	798.47	213.62	1.77	0.98
7.0	243.98	130.20	444.40	134.62	450.13	138.22	1.82	0.99
8.0	83.12	117.38	202.59	150.86	219.09	141.80	2.44	0.92
10.0	0.00	-	0.00	-	0.00	-		
12.0	0.000	-	0.00	-	0.00	-		
14.0	0.00	-	0.00	-	0.00	-		

Table 14. Fasting/Non-fasting Single-Dose In Vivo Bioequivalence Study # 00385 Arithmetic Means ( $\pm$ SD) of Pharmacokinetic Parameters for Amoxicillin, N = 17

PK Measures	Test (Fast): A	Test (Fed): B	Ref (Fed): C
AUC <sub>t</sub> (ng·hr/mL)	18516.83 $\pm$ 3564.51	18142.22 $\pm$ 2594.20	17625.06 $\pm$ 2658.85
AUC <sub>i</sub> (ng·hr/mL)	18977.55 $\pm$ 3578.77	18666.90 $\pm$ 2632.73	18137.58 $\pm$ 2655.18
C <sub>max</sub> (ng/mL)	7440.25 $\pm$ 2050.97	5634.33 $\pm$ 1126.14	5287.50 $\pm$ 1179.00
t <sub>max</sub> (hr)	1.18 $\pm$ 0.24	2.12 $\pm$ 0.54	2.10 $\pm$ 0.47
t <sub>1/2</sub> (hr)	1.25 $\pm$ 0.30	1.22 $\pm$ 0.18	1.21 $\pm$ 0.14
Kel	0.585 $\pm$ 0.140	0.581 $\pm$ 0.081	0.578 $\pm$ 0.064

Table 15. Summary Statistics for Amoxicillin Single-Dose In Vivo Bioequivalence Study # 00385 Under Fasting/Non-fasting Conditions (N=17)

PK Measures*	Geometric Mean			Root Mean Square	Ratio	
	Test (Fast) A	Test (Fed) B	Ref (Fed)		B/A	B/C
Ln AUC <sub>t</sub> (ng·hr/mL)	18450.58	18227.80	17675.51	0.63545	0.98	1.03
Ln AUC <sub>i</sub> (ng·hr/mL)	18919.22	18768.97	18199.73	0.06199	0.99	1.03
Ln C <sub>max</sub> (ng/mL)	7294.17	5617.90	5230.71	0.10866	0.77	1.07

\*geometric mean values for ln-transformed data reported

Table 16. Fasting/Non-fasting Single-Dose In Vivo Bioequivalence Study # 00385 Arithmetic Mean Plasma Clavulanic Acid Concentrations [ng/mL] ( $\pm$ S.D.) Vs. Time (N = 17)

Time (hr)	Test (Fast) A		Test (Fed) B		Ref (Fed) C		B/A	B/C
	Mean	SD	Mean	SD	Mean	SD		
0.0	0.0	-	0.0	-	0.0	-	-	-
0.33	398.05	261.96	63.71	61.48	52.41	63.45	0.16	1.22
0.67	1180.37	517.42	250.61	170.99	298.67	154.73	0.21	0.84

1.0	1289.75	504.97	435.78	235.11	499.95	248.75	0.34	0.87
1.25	1146.88	419.83	550.45	230.65	615.73	280.84	0.48	0.89
1.5	880.77	303.98	605.38	231.11	617.54	252.89	0.69	0.98
1.75	691.53	233.53	604.56	253.60	549.04	238.85	0.87	1.10
2.0	525.91	165.41	540.64	287.26	471.53	226.61	1.03	1.15
2.33	410.37	130.33	435.28	232.48	373.28	204.80	1.06	1.17
2.67	318.00	102.12	370.59	269.65	303.27	185.30	1.17	1.22
3.0	250.92	80.55	264.74	167.02	231.08	155.10	1.06	1.15
3.5	196.58	64.56	165.72	68.70	185.40	123.17	0.84	0.89
4.0	152.44	49.69	157.88	105.53	136.83	87.30	1.04	1.15
5.0	75.35	37.03	58.77	66.31	50.22	54.90	0.78	1.17
6.0	12.75	29.95	13.01	37.01	10.39	29.66	1.02	1.25
7.0	3.37	13.89	7.32	21.01	3.43	14.14	2.17	2.13
8.0	0.00	-	0.00	-	0.00	0.00	-	-
10.0	0.00	-	0.00	-	0.00	0.00	-	-
12.0	0.00	-	0.00	-	0.00	0.00	-	-
14.0	0.00	-	0.00	-	0.00	0.00	-	-

Table 17. Fasting/Non-fasting Single-Dose In Vivo Bioequivalence Study # 00385 Arithmetic Means ( $\pm$ SD) of Pharmacokinetic Parameters for Clavulanic Acid, N = 17

PK Measures	Test (Fast): A	Test (Fed): B	Ref (Fed): C
AUC <sub>t</sub> (ng•hr/mL)	2586.00 $\pm$ 957.79	1588.48 $\pm$ 765.06	1517.12 $\pm$ 782.66
AUC <sub>i</sub> (ng•hr/mL)	2694.88 $\pm$ 961.05	1685.64 $\pm$ 772.02	1609.91 $\pm$ 785.71
C <sub>max</sub> (ng/mL)	1328.49 $\pm$ 498.63	677.39 $\pm$ 261.53	655.09 $\pm$ 258.67
t <sub>max</sub> (hr)	1.06 $\pm$ 0.37	1.65 $\pm$ 0.48	1.53 $\pm$ 0.31
t <sub>1/2</sub> (hr)	1.04 $\pm$ 0.11	0.89 $\pm$ 0.14	0.91 $\pm$ 0.10
Kel	0.675 $\pm$ 0.073	0.796 $\pm$ 0.124	0.766 $\pm$ 0.087

Table 18. Summary Statistics for Clavulanic Acid Single-Dose In Vivo Bioequivalence Study # 00385 Under Fasting/Non-fasting Conditions (N=17)

PK Measures*	Geometric Mean			Root Mean Square	Ratio	
	Test (Fast) A	Test (Fed) B	Ref (Fed) C		B/A	B/C
Ln AUC <sub>t</sub> (ng•hr/mL)	2370.33	1415.24	1352.14	0.34255	0.60	1.05
Ln AUC <sub>i</sub> (ng•hr/mL)	2491.48	1518.72	1452.87	0.32276	0.61	1.05
Ln C <sub>max</sub> (ng/mL)	1209.14	622.73	606.24	0.33780	0.52	1.03

\*geometric mean values for In-transformed data reported

## Reassays:

### For Amoxicillin:

A total of 10 out of 1140 (0.88%) samples were repeated due to analytical reasons – spoiled samples or samples not run. There were two repeats due to pharmacokinetic anomalies. Both of these repeats were for subject #20: Treatment B (Test fed) 2.67 hr draw point and Treatment C (Reference fed) 2.67 hr draw point. Test fed and Reference fed T<sub>max</sub> value for this subject is 1.33 hr. The repeat values were reported per SOP 19.2.5 (Vol. 1.11, pp. 4785), and found acceptable by the reviewer.

For Clavulanic Acid:

One out of 1140 (0.09%) samples was repeated due to analytical reason – spoiled sample. No repeat assays due to pharmacokinetic anomaly were reported.

**Comments:** On pharmacokinetic/statistical data:

1. The pharmacokinetic measures ( $AUC_t$ ,  $AUC_i$ , and  $C_{max}$ ) and ratios of their geometric means for amoxicillin and clavulanic acid were recalculated by the reviewer. The reported values are in agreement with those obtained by the reviewer. There were no statistically significant period effects for any of these measures.
2. Ratios of  $\ln-AUC_t$ ,  $\ln-AUC_i$ , and  $\ln-C_{max}$  of amoxicillin and clavulanic acid between test non-fasting and reference non-fasting are within the acceptable limits of 0.80-1.25.
3. For the test product, the mean Amoxicillin  $C_{max}$  value was decreased by about 23%, under non-fasting conditions.
4. For the test product, the mean clavulanic acid  $AUC_t$  and  $AUC_i$  values were decreased by about 40%, and the mean  $C_{max}$  value was decreased by 48% under non-fasting conditions.
5. For the test product the mean amoxicillin  $t_{max}$  value was about 80% (2.12 hr vs. 1.18 hr) higher under non-fasting conditions compared to that under fasting conditions.

**Formulation** (Not to be released under FOI)

Comparative Components and Composition Table

Ingredients	Amoxicillin and Clavulanic Acid for Oral Suspension 200 mg/28.5mg/5 mL		Amoxicillin Clavulanic Acid for Oral Suspension 400 mg/57mg/ 5 mL	
	mg	%*	mg	%*
Amoxicillin Trihydrate, USP**				
Clavulanate Potassium/Silicon Dioxide (1:1)***				
Colloidal Silicon Dioxide, NF				
Mannitol, USP				
Sodium Saccharin, USP				
Citrus Acid, USP				
Sodium citrate, USP				
Xanthan Gum, NF				
Aspartame, NF				
Natural Orange Flavor				
Artificial Raspberry Powder				
Total weight	600		1000	

\*The percentage is calculated on w/w basis of powder constituents only.

\*\*1.148 mg of Amoxicillin Trihydrate = 1 mg of Amoxicillin Anhydrous.

\*\*\*1.914 mg of Clavulanate Potassium/Silicon Dioxide (1:1) = 1 mg of Clavulanic Acid/Silicon Dioxide (1:1).

(Note: Based on the molecular formula of clavulanate potassium, the reviewer calculated 1.191 mg of clavulanate potassium = 1 mg of clavulanic acid)

**Comments on Formulation:** (Not to be released under FOI)

1. The formulation for the 200 mg/28.5 mg/5 mL strength is similar to that of the 400 mg/57 mg/5 mL strength, except for the amount of \_\_\_\_\_ which is \_\_\_\_\_% more, compared to that in the 400 mg/57 mg/5 mL formulation (\_\_\_\_\_ % vs. \_\_\_\_\_ %). This increase in % w/w of \_\_\_\_\_ is compensatory to the higher % w/w of active ingredients in the 400 mg/57 mg/5 mL formulation.
2. All inactive ingredients utilized in the formulation are within the listed levels in the Inactive Ingredient Guide (1996) for oral dosage form.
3. The firm has used a \_\_\_\_\_% and \_\_\_\_\_% overage of amoxicillin trihydrate and clavulanate potassium/silicon dioxide (1:1), respectively in its formulation — based on 1.148 mg of amoxicillin trihydrate = 1 mg of amoxicillin anhydrous and 1.191 mg of clavulanate potassium = 1 mg of clavulanic acid. It is noted that per USP specifications, Amoxicillin and Clavulanate Potassium for Oral Suspension contains the equivalent of not less than 90.0% and not more than 120.0% of the labeled amount of amoxicillin and the equivalent of not less than 90.0% and not more than 125.0% of the labeled amount of clavulanic acid. *The Division of Chemistry should be made aware of this.*

**Dissolution**

Currently, the USP does not have a dissolution method for this product. The firm has used the following method:

Medium: Water, 900 ml  
 Apparatus: USP Apparatus 2, 75 rpm  
 Temperature: 37 °C  
 Time Points: 5, 10, 15, and 20 minutes  
 Specifications (firms' proposed): Not less than \_\_\_\_\_% (Q) of the labeled amount of amoxicillin and \_\_\_\_\_% (Q) of the labeled amount of clavulanic acid dissolved in 15 minutes.

The dissolution results are summarized in the Table below:

Amoxicillin Dissolution for Test and Reference Products

Test Products: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP Dose strengths: 200 mg/ 28.5 mg/ 5 mL and 400 mg/57 mg /5 mL Reference Products: Augmentin® for Oral Suspension USP, 200 mg/ 28.5 mg/ 5 mL and 400 mg/57 mg /5 mL Assay methodology: HPLC						
Results of dissolution testing (% dissolved in minutes)						
Sampling time (min)	Test product 200 mg/28.5mg/5 mL Lot # 10394P1			Reference Product 200 mg/28.5mg/5 mL Lot # MT 2852		
	Mean	Range	%CV	Mean	Range	%CV
5	103.0	_____	0.8	102.0	_____	1.5
10	106.3	_____	0.6	106.8	_____	0.8
15	106.2	_____	1.1	107.1	_____	1.4
20	106.5	_____	0.6	107.3	_____	0.7

Sampling time (min)	Test product 400 mg/57mg/ 5 mL Lot # 10395P1			Reference Product 400 mg/57mg/ 5 mL Lot # NA 2976		
	Mean	Range	%CV	Mean	Range	%CV
5	100.5	—————	3.5	98.7	—————	2.0
10	103.3	—————	3.4	103.3	—————	2.3
15	104.3	—————	3.1	104.3	—————	2.1
20	104.0	—————	2.9	104.6	—————	1.9

**Clavulanic Acid Dissolution for Test and Reference Products**

Test Products: Amoxicillin, and Clavulanate Potassium for Oral Suspension, USP Dose strengths: 200 mg/ 28.5 mg/ 5 mL and 400 mg/57 mg /5 mL Reference Products: Augmentin® for Oral Suspension USP, 200 mg/ 28.5 mg/ 5 mL and 400 mg/57 mg /5 mL Assay methodology: HPLC						
Results of dissolution testing (% dissolved in minutes)						
Sampling time (min)	Test product 200 mg/28.5mg/5 mL, Lot #10394P1			Reference Product 200 mg/28.5mg/5 mL, Lot # MT 2852		
	Mean	Range	%CV	Mean	Range	%CV
5	108.8	—————	1.2	102.1	—————	2.1
10	111.5	—————	0.4	104.6	—————	1.4
15	111.1	—————	1.1	104.1	—————	1.4
20	111.2	—————	0.4	104.0	—————	1.4
Sampling time (min)	Test product 400 mg/57mg/ 5 mL, Lot # 10395P1			Reference Product 400 mg/57mg/ 5 mL, Lot # NA 2976		
	Mean	Range	%CV	Mean	Range	%CV
5	104.1	—————	2.5	104.4	—————	1.7
10	105.5	—————	2.6	106.2	—————	1.3
15	105.9	—————	2.4	106.0	—————	1.3
20	105.5	—————	2.2	105.8	—————	1.3

**Comments on Dissolution Testing:**

- The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence studies.
- In a control document correspondence to \_\_\_\_\_ (Bio control #C00049.200), the DBE recommended the following dissolution method (based on NDA 50-725 review dated May 2, 1996):

Medium: Water, 900 ml  
 Apparatus: USP Apparatus 2, 75 rpm  
 Temperature: 37 °C  
 Time Points: 5, 10, 20, 30, and 40 minutes

The specifications in the above method are as follows (NOT TO BE RELEASED UNDER FOI):

Not less than —% (Q) of the labeled amount of amoxicillin and —% (Q) of the labeled amount of clavulanic acid dissolved in 30 minutes.

3. The firm's dissolution method is similar to that of the Agency's method, except for the sampling time points of 5, 10, 15 and 20 minutes compared to 5, 10, 20, 30, and 40 minutes in the Agency's method.
4. It is noted that more than 95% of each of the active components of the drug product — amoxicillin and clavulanic acid — is dissolved in 5 minutes. Additionally, the test product exhibits mean dissolution of about 106% and 112% for the amoxicillin and clavulanic acid, respectively.
5. Firm's dissolution is acceptable.

#### **Overall Comments on Formulation and Dissolution:**

It is noted that more than 95% of each of the active components of the drug product — amoxicillin and clavulanic acid — is dissolved in 5 minutes. Additionally, the test product exhibits mean dissolution of about 106% and 112% for the amoxicillin and clavulanic acid, respectively.

The firm has used a —% and —% overage of amoxicillin trihydrate and clavulanate potassium/silicon dioxide (1:1), respectively in its formulation — based on 1.148 mg of amoxicillin trihydrate = 1 mg of amoxicillin anhydrous and 1.191 mg of clavulanate potassium = 1 mg of clavulanic acid. It is noted that the potencies of the test amoxicillin and clavulanate potassium are 104.9% and 107.1%, respectively, and those for the reference product are 107.3% and 106.7%, respectively. Additionally, per USP specifications, Amoxicillin and Clavulanate Potassium for Oral Suspension contains the equivalent of not less than 90.0% and not more than 120.0% of the labeled amount of amoxicillin and the equivalent of not less than 90.0% and not more than 125.0% of the labeled amount of clavulanic acid. ***The Division of Chemistry should be made aware of this.***

#### **Recommendations**

1. The single-dose fasting and non-fasting bioequivalence studies conducted by Teva Pharmaceuticals on its Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/ 57 mg/5 mL, Lot # 10395P1, comparing it to Augmentin® Suspension 400 mg/ 57 mg/5 mL, Lot # NA 2976 have been found acceptable. The studies demonstrate that Teva's Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/ 57 mg/5 mL is bioequivalent to Augmentin® Suspension 400 mg/ 57 mg/5 mL manufactured by Smith Kline and Beecham.
2. The dissolution testing conducted by the firm on its Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/ 57 mg/5 mL, Lot # 10395P1 is acceptable.
3. The dissolution testing conducted by the firm on its Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200 mg/ 28.5 mg/5 mL, Lot # 10394P1 is acceptable. The firm has conducted acceptable in vivo bioequivalence studies

comparing its 400 mg/ 57 mg/5 mL of the test product with 400 mg/ 57 mg/5 mL of the reference product Augmentin® manufactured by Smith Kline and Beecham. The formulations for the 200 mg/ 28.5 mg/5 mL strength are similar to the 400 mg/ 57 mg/5 mL of the test product, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for 200 mg/ 28.5 mg/5 mL of the test product is granted. The 200 mg/28.5 mg/5L Amoxicillin and Clavulanate Potassium for Oral Suspension is, therefore, deemed bioequivalent to the 200 mg/ 28.5 mg/5mL Augmentin® manufactured by Smith Kline and Beecham.

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37 °C using USP apparatus 2 (paddle) at 75 rpm. The test products should meet the following interim specifications:

Not less than — % (Q) of the labeled amount of amoxicillin and — % (Q) of the labeled amount of clavulanic acid dissolved in 30 minutes.

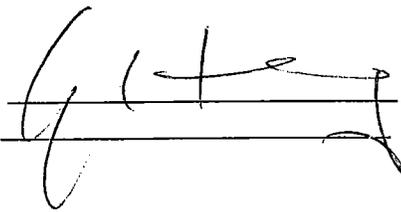
5. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing, and the application is approvable.

The firm should be informed of the above recommendations.

  
Chandra S. Chaurasia  
Review Branch I  
Division of Bioequivalence

Date: 7/27/2001

RD INITIALED YHUANG  
FT INITIALED YHUANG



Date: 7/27/2001

  
Concur: \_\_\_\_\_  
Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence

Date: 7/31/2001

ANDA:65-089

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/ 57 mg/5 mL and 200 mg/ 28.5 mg/5 mL

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CC: DIVISION FILE, HFD-652/Bio Secretary-Bio Drug File, HFD-650/C.Chaurasia

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:65-089

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium for Oral  
Suspension USP, 400 mg/ 57 mg/5 mL and 200 mg/  
28.5 mg/5 mL

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

We acknowledge that the following dissolution testing method has been incorporated into your manufacturing controls and stability program:

The dissolution testing should be conducted in 900 mL of water at 37 °C using USP apparatus II (paddle) at 75 rpm. The test products should meet the following interim specifications:

Not less than — % (Q) of the labeled amount of amoxicillin and  
— % (Q) of the labeled amount of clavulanic acid dissolved in  
30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

CC: ANDA 65-089

ANDA DUPLICATE  
DIVISION FILE  
HFD-652/Bio Secretary-Bio Drug File  
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)

HFD-652/CS Chaurasia

HFD-652/YC Huang

HFD-617/K Scardina

HFD-650/Dale Conner

*7/27/2001*  
*7/13/2001*

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Printed in Final on 07/27/2001

BIOEQUIVALENCY – **Acceptable**

Submission Dates: 04/12/2001

- |    |   |  |
|----|---|--|
| 1. | <b>FASTING STUDY (STF)</b> <i>oic</i><br>_____<br>(Clinical)<br>Novopharm Ltd., Toronto, Ontario, Canada (Analytical) | Strength: 400 mg/ 57 mg/5 mL<br>Outcome: <b>AC</b>   |
| 2. | <b>FASTING STUDY Repeat (STF)</b><br>_____<br>(Clinical)<br>Novopharm Ltd., Toronto, Ontario, Canada (Analytical)     | Strength: 400 mg/ 57 mg/5 mL<br>Outcome: <b>AC</b>   |
| 3. | <b>FOOD STUDY (STP)</b> <i>oic</i><br>_____<br>(Clinical)<br>Novopharm Ltd., Toronto, Ontario, Canada (Analytical)    | Strength: 400 mg/ 57 mg/5 mL<br>Outcome: <b>AC</b>   |
| 4. | <b>DISSOLUTION WAIVER (DIW)</b> <i>oic</i>  | Strength: 200 mg/ 28.5 mg/5 mL<br>Outcome: <b>AC</b> |

Outcome Decisions:

**AC** - Acceptable

WinBio Comments:

- Fasting and non-fasting studies on Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/ 57 mg/5 mL are acceptable.
- Dissolution testing on Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/ 5100 mg/5 mL and 200mg/ 28.5 mg/5 mL is acceptable.
- Biowaiver request on Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 200mg/ 28.5 mg/5 mL is granted.

**OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE**

ANDA #: 65-089

SPONSOR: Teva Pharmaceuticals, USA

DRUG AND DOSAGE FORM: Amoxicillin and Clavulanate Potassium for Oral Suspension, USP

STRENGTH(S): 400 mg/ 57 mg/ 5 mL and 200 mg/ 28.5 mg/5 mL

TYPES OF STUDIES: Fasting and non-fasting Bioequivalence Studies on 400 mg/ 57 mg/5 mL strength.

CLINICAL STUDY SITE (S): \_\_\_\_\_

ANALYTICAL SITE (S): Novopharm Ltd., 1290 Ellesmere Rd., Toronto Ontario, Canada

STUDY SUMMARY : Bioequivalence studies are acceptable.

DISSOLUTION: Dissolution testing on 400 mg/ 57 mg/5 mL and 200 mg/ 28.5 mg/5 mL strengths is acceptable. Biowaiver on amoxicillin and clavulanate potassium for oral suspension USP, 200 mg/ 28.5 mg/5 mL is granted.

**DSI INSPECTION STATUS**

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D.

BRANCH : I

INITIAL : CS Chaurasia

DATE : 7/27/2001

TEAM LEADER : YIH-CHAIN HUANG, Ph. D.

BRANCH : I

INITIAL : YCH

DATE : 7/27/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : D P Conner

DATE : 7/27/2001

Rep 7/31/2001

**Amoxicillin and Clavulanate Potassium  
For Oral Suspension USP,  
200 mg/28.5 mg/5 mL and 400 mg/57 mg/5 mL  
ANDA 65-089**

**Teva Pharmaceuticals, USA  
North Wales, PA 19454  
Submission Date: 04/12/2001**

**Reviewer: Chandra S. Chaurasia**  
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**A Dissolution Addendum To The Review of Two Bioequivalence Studies and  
Dissolution Data**

**HISTORY**

1. The ANDA 65-089 containing a fasting study, a food study, dissolution data and waiver request was submitted for review on 4/12/01. The application was reviewed by this reviewer and determined acceptable by DBE on 07/31/01. The dissolution method was found acceptable. The firm's dissolution method was similar to that of the Agency's method, except for the sampling time points of 5, 10, 15 and 20 minutes compared to 5, 10, 20, 30, and 40 minutes in the Agency's method. More than 95% of each of the active components of the drug product — amoxicillin and clavulanic acid — was dissolved in 5 minutes.
2. The Division recommended the firm to incorporate the following dissolution testing into its manufacturing controls and stability programs:

Medium: Water, 900 mL  
 Apparatus: USP Apparatus 2, 75 rpm  
 Temperature: 37 °C  
 Time Points: 5, 10, 15, and 20 minutes

**Specifications:** Not less than — % (Q) of the labeled amount of amoxicillin and — % (Q) of the labeled amount of clavulanic acid dissolved in 30 minutes.

**ADDENDUM**

Currently, the DBE recommends the following interim specifications for this drug product:

**Specifications:** Not less than — % (Q) of the labeled amount of amoxicillin and — % (Q) of the labeled amount of clavulanic acid are dissolved in 20 minutes  
**(NOT TO BE RELEASED UNDER FOI).**

The firm is therefore, requested to incorporate the following dissolution testing into its manufacturing controls and stability programs:

Medium: Water, 900 mL, 37 °C  
 Apparatus: USP Apparatus 2, 75 rpm  
 Time Points: 5, 10, 15, and 20 minutes

**Specifications:** Not less than — % (Q) of the labeled amount of amoxicillin and — % (Q) of the labeled amount of clavulanic acid are dissolved in 20 minutes

**Revised Recommendation on Dissolution Testing:**

The dissolution testing conducted by the firm on its Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/ 57 mg/5 mL, Lot # 10395P1 and 200 mg/ 28.5 mg/5 mL, Lot # 10394P1 is acceptable.

The dissolution method should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of water at 37 °C using USP apparatus 2 (paddle) at 75 rpm. The test products should meet the following interim specifications:

Not less than — % (Q) of the labeled amount of amoxicillin and — % (Q) of the labeled amount of clavulanic acid dissolved in 20 minutes.

The firm should be informed of the above recommendations.

*Chandra S. Chaurasia*

Chandra S. Chaurasia, Ph. D.  
Review Branch I  
Division of Bioequivalence

Date: 4/10/2002

RD INITIALED YHUANG  
FT INITIALED YHUANG

*[Signature]*  
Date: 4/10/2002

Concur: *Dale P. Conner*  
Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence

Date: 4/17/02

ANDA:65-089

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium for Oral Suspension USP, 400 mg/ 57 mg/5 mL and 200 mg/ 28.5 mg/5 mL

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CC: DIVISION FILE, HFD-652/Bio Secretary-Bio Drug File, HFD-650/C.Chaurasia

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:65-089

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Amoxicillin and Clavulanate Potassium for Oral  
Suspension USP, 400 mg/ 57 mg/5 mL and 200 mg/  
28.5 mg/5 mL

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet, and has no further questions at this time.

The Division of Bioequivalence recommends that the following **revised dissolution specification** should be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37 °C using USP apparatus II (paddle) at 75 rpm. The test products should meet the following interim specifications:

**Not less than —% (Q) of the labeled amount of amoxicillin and —% (Q) of the labeled amount of clavulanic acid dissolved in 20 minutes.**

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

CC: ANDA 65-089

ANDA DUPLICATE  
DIVISION FILE  
HFD-652/Bio Secretary-Bio Drug File  
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates).  
HFD-652/CS Chaurasia *CS 4/9/2002*  
HFD-652/YC Huang *YH 4/10/2002*  
HFD-617/K Scardina  
HFD-650/Dale Conner *DC 4/17/02*

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Printed in Revised Final on 04/09/2002

BIOEQUIVALENCY – **Acceptable**

Submission Dates: 04/12/2001

Other (US Document) *OK*

Strengths: All

Outcome Decisions:

**AC** - Acceptable

WinBio Comments: US Document

**OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE**

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ANDA #: 65-089

SPONSOR: TEVA Pharmaceuticals

DRUG AND DOSAGE FORM: **Amoxicillin/Clavulanate Potassium for Oral Suspension, USP**

STRENGTH(S): **200mg/28.5mg/5mL and 400mg/57mg/5mL**

TYPES OF STUDIES: N/A

CLINICAL STUDY SITE(S): N/A

ANALYTICAL SITE(S): N/A

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DISSOLUTION: This is an addendum to the original review to change the dissolution specifications

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**DSI INSPECTION STATUS**

Inspection needed: NO	Inspection status: N/A	Inspection results: N/A
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

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PRIMARY REVIEWER: Chandra S. Chaurasia, Ph.D. BRANCH: I

INITIAL: CC DATE: 5/1/2002

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TEAM LEADER: Yih-Chain Huang, Ph.D. BRANCH: I

INITIAL: YCH DATE: 5/1/2002

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DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: DP DATE: 5/2/02