

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
65115

BIOEQUIVALENCY REVIEW(S)

Cefadroxil Oral Suspension USP,
125 mg/5mL, 250 mg/5mL, 500 mg/5mL
ANDA 65-115
Reviewer: Patrick Nwakama

Ranbaxy Laboratories Limited
US Agent: 600 College Road East
Princeton, New Jersey 08540
Submission Date:
December 17, 2001
March 13, 2002 (Amendment)

Review of Two *in vivo* Bioequivalence Studies, Two Waiver Requests and Dissolution Data

Introduction:

Class: Oral Cephalosporin Antibiotic Agent
Type of Submission: Original ANDA
First Generic: No
Contents of Submission: Fasting, non-fasting bioequivalence studies and dissolution data
RLD: Duricef® for Oral Suspension, 500 mg/5mL (NDA# 50-527; approved
9/12/80; Bristol Myers Squibb)
Recommended dose: 500 – 1000 mg BID

Background:

Cefadroxil is an oral first-generation cephalosporin bactericidal antibiotic with activity primarily against gram-positive organisms. It is indicated for the treatment of urinary tract infections, skin and skin structure infections, pharyngitis, and tonsillitis. Like other beta-lactam antibiotics, it binds to bacterial enzymes and inhibits mucopeptide synthesis in the bacterial cell wall. The ability of cefadroxil to interfere with penicillin-binding proteins (PBPs) – mediated cell wall synthesis ultimately leads to cell lysis.

Cefadroxil is available only in an oral formulation. It is completely and rapidly absorbed following oral administration, with measurable levels present 12 hours following administration. The rate and extent of absorption of cefadroxil are not affected by food. It is widely distributed to tissues and fluids including pleural fluid, synovial fluid, and bone. The distribution of cefadroxil to bile is low, as is the distribution to CSF, even when the meninges are inflamed. It readily crosses the placenta, and fetal serum concentrations may be up to 10% or more of maternal concentrations. Cefadroxil is distributed in low concentrations to breast milk. It is not appreciably metabolized and is excreted primarily unchanged (over 90%) in the urine. The elimination half-life of cefadroxil is about 1–2 hours. Doses should be adjusted in patients with renal disease.

Financial Disclosure: The firm submitted Form FDA 3454 and has no conflict of interest with the investigators.

I. Protocol No.: 012243, Single-Dose, 2-Way Crossover Fasting Study

A. Study Information

STUDY FACILITY INFORMATION

CLINICAL FACILITY:
CLINICAL STUDY DATE: Period I: September 30, 2001; Period II: October 7, 2001
ANALYTICAL FACILITY:
PRINCIPAL INVESTIGATOR:
ANALYTICAL DIRECTOR:
ANALYTICAL STUDY DATES: October 11 – 25, 2001
STORAGE PERIOD: 25 days (Long term stability 65 days)

TREATMENT INFORMATION

TREATMENT ID:	A	B
TEST OR REFERENCE:	T	R
PRODUCT NAME:	Cefadroxil for Oral Suspension	Duricef® for Oral Suspension
MANUFACTURER:	Ranbaxy	Bristol Myers Squibb
MANUFACTURE DATE:	8/2001	N/A
EXPIRATION DATE:	07/2003 (proposed by the firm)	09/2002
STRENGTH:	500 mg / 5mL	500 mg / 5mL
DOSAGE FORM:	Oral Suspension	Oral Suspension
LOT NO.:	1147735	9K15936
ANDA BATCH SIZE:	Kg	
ASSAY:	%	%
CONTENT UNIFORMITY:	N/A	N/A
DOSE ADMINISTERED:	1 x 500 mg (5 mL)	1 x 500 mg (5 mL)
STUDY CONDITION:	Fasting	Fasting
LENGTH OF FASTING:	10 hours	10 hours

RANDOMIZATION

RANDOMIZED: Y
NO. OF SEQUENCES: 2
NO. OF PERIODS: 2
NO. OF TREATMENTS: 2

DESIGN

DESIGN TYPE: Crossover
BALANCED: Y
WASHOUT PERIOD: 7 days

Randomization Scheme:

AB 3,6,7,11,13,14,16,17,19,21,22,23,25
BA 1,2,4,5,8,9,10,12,15,18,20,24,26

DOSING

SINGLE OR MULTIPLE DOSE: Single
VOLUME OF LIQUID INTAKE: 240 mL
ROUTE OF ADMINISTRATION: Oral

Subject Demographics:

AGE (years)	GENDER	ETHNICITY
Mean ± SD: 34.9 ± 7.03	Male: 26 (100%)	Asian: 0 (0%)
Range: 23 – 45	Female: 0 (0%)	Black: 1 (3.8%)
		Hispanic: 0 (0%)
Age Group:		Caucasian: 25 (96.2%)

< 18: 0 (0%)
 18 – 40: 18 (69.2%)
 41 – 64: 8 (30.8%)
 65 – 75: 0 (0%)
 > 75: 0 (0%)

Native American: 0 (0%)

Height (cm)

Mean \pm SD: 175.3 \pm 6.71

Range: 163 - 189

Weight (kg)

Mean \pm SD: 73.18 \pm 8.09

Range: 54.9 – 91.8

SUBJECTS

IRB APPROVAL: Y

INFORMED CONSENT: Y

NO. ENROLLED: 26 healthy male volunteers

NO. COMPLETING: 25

NO. SAMPLES ANALYZED: 864 (excluding samples from Subjects #10 and #25); Statistical and PK analyses were done on data from 24 subjects.

NO. OF DROPOUTS: 1 (Subject #10 did not complete the clinical portion and was replaced with Subject #26 as per protocol)

DIETARY & MEDICATION RESTRICTIONS No alcohol and xanthines allowed 48 hours and 24 hours before and throughout the study period, respectively. No medications (including OTCs) and grapefruit products 7 days prior to initiating study and throughout study. Vitamins may be taken as nutritional supplement at the discretion of the attending physician.

ACTIVITY RESTRICTIONS Housed \geq 10 hours prior to and until at least 24 hours after dosing each period. Subjects were not allowed to engage in strenuous activities during confinement.

Blood Sampling Schedule 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours

SEX(ES) INCLUDED: Males

HEALTHY VOLUNTEERS: Y

NO. OF ADVERSE EVENTS: Only one adverse event (Headache) possibly related to the reference product was reported. It was considered to be mild.

Protocol Deviations:

Two (2) cases of delayed blood sampling (\leq 6 minutes) caused by difficult blood draws were reported. Actual sampling times were used in analysis.

PRE-STUDY ASSAY VALIDATION INFORMATION

ANALYTE: Cefadroxil
 ASSAY METHOD:
 MATRIX: Human Plasma
 INTERNAL STANDARD: Cefaclor
 SENSITIVITY/LOQ: 0.30 mcg/mL
 STANDARD CURVE 0.30 – 49.96 mcg/mL
 QC SAMPLES 0.30, 0.75, 30.0, and 40.0 mcg/mL
 R**2 IS GREATER THAN 0.9968
 SPECIFICITY: Y
 INTER-DAY ACCURACY(%)[STD] 86.7 – 106.0%
 INTER-DAY PRECISION(CV%)[STD] 1.5 – 6.3%
 INTRA-DAY ACCURACY(%)[QCs] 90.4 – 103.2%

INTER-DAY ACCURACY(%)[QCs]	88.8 – 99.8%
INTRA-DAY PRECISION(CV%)[QCs]	0.8 - 3.2%
INTER-DAY PRECISION(CV%)[QCs]	3.7 - 6.9%
ANALYTE RETENT. TIME:	3.81 minutes
INT. STD RETENTION TIME:	8.89 minutes
MEAN % RECOVERY	54.72%
INT. STD RECOVERY (%)	92.80%
STABILITY (QCs):	
Long-term at -80° C	65 days
Short-term (Bench Top) at Room Temp.	6.0 hours
Processed Stability @ 4°C	24.7 hours
Freeze-Thaw Cycles	3 cycles

Comment: The method validation is acceptable.

Within-Study Assay Results:

Assay method, biological matrix, and internal standards were similar to those of pre-study method validation.

ANALYTE:	Cefadroxil
SENSITIVITY	0.30 mcg/mL
STANDARD CURVE RANGE:	0.30 - 30.03 mcg/mL
QC Samples	0.751, 18.035, 24.047 mcg/mL
R**2 IS GREATER THAN:	0.9990
SPECIFICITY:	Y
INTER-DAY ACCURACY (%) [STD]	96.5 – 104.4%
INTER-DAY PRECISION (% CV) [STD]	1.1 – 4.1%
INTER-DAY ACCURACY (%) [QCs]	89.5 – 99.7%
INTER-DAY PRECISION (% CV) [QCs]	2.6 – 2.9%

Sample Reassay Summary

Poor Chromatography 1

Comment: The analytical method is acceptable.

PHARMACOKINETIC / STATISTIC ANALYSES

Mean Plasma Concentrations:	Table 2; Figure 1	
Pharmacokinetic Parameters:	Tables 3 and 4	
90% Confidence Intervals:	LAUC _{0-T}	106.3 – 110.6% (RMSE 0.04)
	LAUC _{0-INF}	105.8 – 109.9% (RMSE 0.04)
	LC _{MAX}	97.5 – 106.8 (RMSE 0.09)

Test/Reference Ratio:	AUC _{0-T}	1.08
	AUC _{0-INF}	1.08
	C _{MAX}	1.02

AUC _{0-T} / AUC _{0-INF} Ratio	Test	0.97
	Reference	0.97

Comments:

1. The maximum (mean) plasma concentrations for cefadroxil was attained at 1 hour for test and reference.
2. No subjects with zero-hour drug level, first scheduled post-dose time point or first measurable drug level as Cmax.
3. There were no PK repeats reported.
4. The reviewer verified the PK data submitted the firm and agrees with the firm's calculations.
5. The 90% confidence intervals were within the acceptable range of 0.80 to 1.25 for ln-transformed AUCT, AUC_t and Cmax. All statistical analyses were verified by the reviewer.
6. The fasting single dose bioequivalence study is acceptable.

II. Protocol No.: 012247, Single-Dose, 2-Way Crossover non-Fasting Study
A. Study Information

STUDY FACILITY INFORMATION

CLINICAL FACILITY:

CLINICAL STUDY DATE: Period I: 9/30/01; Period II: 10/7/01

ANALYTICAL FACILITY:

PRINCIPAL INVESTIGATOR:

ANALYTICAL STUDY DATES: October 10 –22, 2001

STORAGE PERIOD: 22 days

TREATMENT INFORMATION

TREATMENT ID:	A	B
TEST OR REFERENCE:	T	R
PRODUCT NAME:	Cefadroxil Oral Suspension	Duricef® Oral Suspension
MANUFACTURER:	Ranbaxy	Bristol-Myers Squibb Co
STRENGTH:	500 mg /5 mL	500 mg/5 mL
DOSAGE FORM:	Oral Suspension	Oral Suspension
LOT NO.:	1147735	9K15936
DOSE ADMINISTERED:	1 x 500 mg (5 mL)	1 x 500 mg (5 mL)
STUDY CONDITION:	Non-Fasting	Non-Fasting
LENGTH OF FASTING:	N/A	N/A
STD BREAKFAST:	Y	Y
BREAKFAST SPECIFICS:	One buttered English muffin One fried egg One slice of Canadian bacon One slice of American cheese One serving of hash brown potatoes One glass (8 oz) of whole milk One small glass (6 oz) of orange juice	One buttered English muffin One fried egg One slice of Canadian bacon One slice of American cheese One serving of hash brown potatoes One glass (8 oz) of whole milk One small glass (6 oz) of orange juice
STD LUNCH:	Y	Y
STD DINNER:	Y	Y

RANDOMIZATION	DESIGN	
RANDOMIZED:	Y	DESIGN TYPE: Crossover
NO. OF SEQUENCES:	2	REPLICATE- DESIGN: N
NO. OF PERIODS:	2	BALANCED: Y
NO. OF TREATMENTS:	2	WASHOUT PERIOD: 7 days
RANDOMIZATION SCHEME	AB:1,2,5,6,7,8,11,12,13	BA:3,4,9,10,14,15,16,17,18

DOSING

SINGLE OR MULTIPLE DOSE: Single
 VOLUME OF LIQUID INTAKE: 240 mL
 ROUTE OF ADMINISTRATION: Oral

SUBJECTS

IRB APPROVAL: Y
 INFORMED CONSENT: Y
 NO. ENROLLED: 18
 NO. COMPLETING: 18
 NO. PLASMA ANALYZED: 612 (excluding samples from Subject #9)
 NO. OF DROPOUTS: 1 {(Subject # 9 dropped approximately 0.1 mL of his medication during drug administration in period 2, treatment A (test)}

MEDICATION & DIETARY RESTRICTIONS
 No alcohol and xanthines allowed 48 hours and 24 hours before and throughout the study period, respectively. No medications (including OTCs) and grapefruit products 7 days prior to initiating study and throughout study. Vitamins may be taken as nutritional supplement at the discretion of the attending physician.

ACTIVITY RESTRICTIONS
 Housed \geq 10 hours prior to and until at least 24 hours after dosing each period. Subjects were not allowed to engage in strenuous activities during confinement.

Blood Sampling Schedule 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours

SEX(ES) INCLUDED: Males

VOLUNTEERS ONLY: Y

NO. OF ADVERSE EVENTS: 0

Subject Demographics:

AGE (years)

Mean \pm SD: 31.6 \pm 6.26
 Range: 21 - 43

Age Group:

< 18: 0 (0%)
 18 - 40: 17 (94.4%)
 41 - 64: 1 (5.6%)
 65 - 75: 0 (0%)
 > 75: 0 (0%)

Height (cm)

Mean \pm SD: 173.9 \pm 7.25
 Range: 159 - 185

Weight (kg)

Mean \pm SD: 70.07 \pm 7.74
 Range: 57.6 - 83.6

GENDER

Male: 18 (100%)
 Female: 0 (0%)

ETHNICITY

Asian: 0 (0%)
 Black: 0 (0%)
 Hispanic: 0 (0%)
 Caucasian: 18 (100.0%)
 Native American: 0 (0%)

Protocol Deviations: None

PRE-STUDY ASSAY VALIDATION INFORMATION

Same as in the fasting study

Within-Study Assay Results:

Assay method, biological matrix, and internal standards were similar to those of pre-study method validation.

ANALYTE:	Cefadroxil
SENSITIVITY	0.30 mcg/mL
STANDARD CURVE RANGE:	0.30 - 30.03 mcg/mL
QC Samples	0.751, 18.035, 24.047 mcg/mL
R**2 IS GREATER THAN:	0.9993
SPECIFICITY:	Y
INTER-DAY ACCURACY (%)[STD]	96.9 - 103.6%
INTER-DAY PRECISION (% CV) [STD]	0.9 - 2.7%
INTER-DAY ACCURACY (%)[QCs]	88.2 - 99.0%
INTER-DAY PRECISION (% CV)[QCs]	1.7 - 2.8%

Sample Reassay Summary

Lost in Processing 18

Comment: The analytical method is acceptable.

PHARMACOKINETIC / STATISTIC ANALYSES

Mean Plasma Concentrations:	Table 5, Figure 2
Pharmacokinetic Parameters:	Tables 6 and 7
LAUC _{0-T} /LAUC _{0-INF} Ratio	Test non-Fasting 0.97
	Reference non-Fasting 0.97

Test-fed/Reference-fed Ratio:	AUC _{0-T}	1.02
(Geometric LS means)	AUC _{0-INF}	1.02
	C _{MAX}	1.00

Comments:

1. No subjects with zero-hour drug level, with first scheduled post-dose time point or first measurable drug level as C_{max}.
2. The reviewer verified the PK data submitted the firm and agrees with the firm's calculations
3. The test/ reference geometric mean ratios were within the acceptable range of (0.80, 1.25). All statistical analyses were verified by the reviewer.
4. There were no pharmacokinetic repeats reported.
5. The non-fasting single dose bioequivalence study is acceptable.

III. Dissolution Testing and Waiver Requests:

There is no official USP dissolution method for Cefadroxil for Oral Suspension. The firm conducted dissolution testing in three media (Tables 6 - 8).

TABLE 1: Formulation - Not to be released under FOI

COMPONENT	Dosage Strength		
	125 mg/5mL	250 mg/5mL	500 mg/5mL
	mg/5mL	mg/5mL	mg/5mL
✓ Cefadroxil USP (monohydrate)* [Cefadroxil			
✓ Sucrose			
✓ Sucrose			
✓ Xanthan Gum,			
✓ Sodium Benzoate,			
✓ Colloidal Silicon Dioxide			
✓ Polysorbate 80			
✓ FD&C Yellow #6 Aluminium Lake			
✓ Flavor Fruit Gum			
✓ Flavor Raspberry			
***Total Weight	2500.0	2500.0	2500.0

*The quantity is based on 98% assay on anhydrous basis and 5.4% water content. The actual quantity required for the batch shall be based on the actual assay and the water content of Cefadroxil USP.

**The quantity of Sucrose shall be adjusted based on the input of Cefadroxil USP (as monohydrate) to maintain constant fill weight.

***To be scaled up to ANDA batch size of Kg and commercial batch size of Kg.

Formulation and Dissolution Comments:

1. The inactive ingredients are within the limits specified in the IIG handbook.
2. The lots used in the dissolution testing are the same as those used in the biostudies.
3. The firm conducted dissolution testing on its product Cefadroxil for Oral suspension, USP, 125/5 mL, 250/5 mL and 500 mg/5mL using
(See Tables 6 – 8).
4. Due to rapid dissolution of cefadroxil from Cefadroxil for Oral suspension, USP, 125/5 mL, 250/5 mL and 500 mg/5mL, f2 analysis is not relevant for this drug product.
5. There is no USP 25 dissolution method for Cefadroxil Oral Suspension. The official compendial dissolution method for Cefadroxil tablets is 900 mL Water, Apparatus II (Paddle) at 50 rpm. (In consultation with Dr. Tran, the DBE dissolution expert, the firm was requested by telephone (3/5/2002) to provide additional dissolution testing data

Deficiency Comment (On Original ANDA Submitted 12/17/2001)

The following comment was communicated to the firm by telephone on 3/5/2002.

*Please provide additional dissolution testing data on 12 dosage units of each strength of the test and reference products for 125 mg / 5 mL, 250 mg / 5 mL strengths with the following parameters:
The dissolution testing of the 500 mg / 5 mL strength should be carried out on the same lot on which bioequivalence studies have been carried out.*

Comments (Study Amendment Submitted 3/13/2002)

1. As per DBE's recommendation, the firm has provided additional dissolution data using (see Table 9).
2. The dissolution testing conducted was selected by the reviewer because it is more discriminatory.

IV. Recommendations

- I. The *in vivo* bioequivalence study conducted under fasting conditions by Ranbaxy on its Cefadroxil for Oral Suspension, 500 mg/ 5mL, Batch # 1147735, comparing it to the reference product, Duricef® for Oral Suspension, 500 mg/ 5 mL, Lot # 9K15936, manufactured by Bristol-Myers Squibb is acceptable to the Division of Bioequivalence. The study demonstrates that Ranbaxy's Cefadroxil for Oral Suspension, 500 mg/ 5mL, is bioequivalent to the reference product, Duricef ® for Oral Suspension, 500 mg/ 5 mL, manufactured by Bristol-Myers Squibb.
- II. The *in vivo* bioequivalence study conducted under non-fasting conditions by Ranbaxy on its Cefadroxil for Oral Suspension, 500 mg/ 5mL, Batch # 1147735, comparing it to the reference product, Duricef® for Oral Suspension, 500 mg/ 5 mL, Lot # 9K15936, manufactured by Bristol-Myers Squibb is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Ranbaxy's Cefadroxil for Oral Suspension, 500 mg/ 5mL, is similar to the reference product, Duricef ® for Oral Suspension, 500 mg/ 5 mL, manufactured by Bristol-Myers Squibb.
- III. The *in vitro* dissolution testing data submitted by the firm on its Cefadroxil for Oral Suspension, 500 mg / 5 mL, 250 mg/ 5 mL and 125 mg/ 5 mL has been found acceptable. The formulations for the 250 mg/ 5 mL and 125 mg/ 5 mL are proportionally similar to the 500 mg / 5 mL which underwent bioequivalence testing. The waivers of the *in vivo* bioequivalence study requirements for 250 mg/ 5 mL and 125 mg/ 5 mL are granted. The 250 mg/ 5 mL and 125 mg/ 5 mL are therefore deemed bioequivalent to Duricef® for Oral Suspension, 250 mg/ 5 mL and 125 mg/ 5 mL, respectively, manufactured by Bristol Myers Squibb.
- IV. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted

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

TST ✓ *5/22/2002*

Patrick Nwakama, Pharm.D.
Review Branch III
Division of Bioequivalence

RD INITIALED M. MAKARY ^{miam}
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Concur: */S/* Date *5/22/2002*
fx Dale P. Conner, Pharm.D,
Director,
Division of Bioequivalence

Table 2. Mean Plasma Concentrations (mcg/mL) of CEFADROXIL, n = 24

Treatment A = Cefadroxil 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, fasting
 Treatment B = Duricef®, 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, fasting

Time(hour)	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
0.00	0.00	0.00	0.0	0.00	**
0.25	2.25	68.1	2.40	54.2	0.94
0.50	7.95	44.6	8.06	36.3	0.99
0.75	11.44	33.1	11.30	23.7	1.01
1.00	12.91	23.2	12.81	18.7	1.01
1.25	12.87	20.5	12.56	17.2	1.02
1.50	12.39	17.8	12.04	15.4	1.03
1.75	11.50	16.6	10.95	17.7	1.05
2.00	10.54	15.5	9.79	18.9	1.08
2.25	9.69	16.3	8.77	19.5	1.10
2.50	8.67	17.7	7.76	20.7	1.12
3.00	6.81	20.3	5.90	22.0	1.15
4.00	4.13	24.5	3.67	23.6	1.12
5.00	2.43	28.3	2.20	28.9	1.10
6.00	1.73	29.1	1.53	28.2	1.13
8.00	0.81	31.8	0.74	33.5	1.09
10.0	0.36	55.2	0.30	79.6	1.20
12.0	0.12	168.1	0.07	230.2	1.71

Table 3. Mean Plasma Concentrations (mcg/mL) of CEFADROXIL, Pharmacokinetic Parameters

Treatment A = Cefadroxil 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, fasting

Treatment B = Duricef®, 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, fasting

Mean Plasma PK Parameters

Parameter	Test Mean (A)	Test (%CV) (A)	Ref Mean (B)	Ref (%CV) (B)	T/R Ratio (A)/(B)
AUCT	42.60	15.68	39.42	17.86	1.08
AUCI	43.71	15.36	40.66	17.61	1.07
C _{MAX}	13.59	18.69	13.28	16.64	1.02
T _{MAX}	1.30	34.87	1.13	26.78	1.15
THALF	1.91	14.61	1.94	19.13	0.98
KEL	0.37	15.30	0.37	17.14	1.00

UNIT: AUC = mcg.hr/mL C_{MAX} = mcg/mL T_{MAX} = hr

Summary Statistics for CEFADROXIL

Treatment A = Cefadroxil 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, fasting

Treatment B = Duricef®, 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, fasting

A vs B GEOMETRIC MEANS

Parameter	A	B	Ratio	Lower 90% CI	Upper 90% CI
AUCI	43.25	40.10	1.08	105.8	109.9
AUCT	42.14	38.86	1.08	106.3	110.6
C _{MAX}	13.36	13.09	1.02	97.5	106.8

Table 4. Mean Plasma Concentrations (mcg/mL) of CEFADROXIL, n = 17

Treatment A = Cefadroxil 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, non-fasting
 Treatment B = Duricef®, 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, non-fasting

Time(hour)	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B) **
0.00	0.00	0.00	0.0	0.00	
0.25	1.37	77.0	1.55	74.3	0.88
0.50	5.36	42.9	5.29	49.5	1.01
0.75	8.59	33.0	8.19	41.0	1.05
1.00	10.19	28.4	9.84	36.1	1.04
1.25	10.47	30.3	10.64	28.9	0.98
1.50	10.99	21.3	10.65	23.5	1.03
1.75	10.60	18.6	10.18	18.3	1.04
2.00	10.15	15.2	9.78	14.9	1.04
2.25	9.47	13.7	9.23	12.9	1.03
2.50	8.90	13.7	8.60	11.8	1.03
3.00	7.57	14.6	7.47	16.0	1.01
4.00	5.17	19.9	5.11	22.0	1.01
5.00	3.19	22.0	3.13	21.7	1.02
6.00	1.95	23.8	1.92	19.9	1.02
8.00	0.87	24.5	0.84	20.5	1.04
10.0	0.33	71.0	0.36	51.7	0.92
12.0	0.06	223.1	0.04	282.4	1.50

Table 5. Mean Plasma Concentrations (mcg/mL) of CEFADROXIL, Pharmacokinetic Parameters

Treatment A = Cefadroxil 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, non-fasting
 Treatment B = Duricef®, 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, non-fasting

Mean Plasma PK Parameters

Parameter	Test Mean (A)	Test (%CV) (A)	Ref Mean (B)	Ref (%CV) (B)	T/R Ratio (A)/(B)
AUCT	41.66	14.27	40.83	12.80	1.02
AUCI	42.81	13.62	41.92	12.50	1.02
C _{MAX}	11.57	17.72	11.54	17.24	1.00
T _{MAX}	1.51	23.69	1.57	38.39	0.96
T _{HALF}	1.71	11.77	1.73	12.29	0.99
K _{EL}	0.41	11.94	0.41	11.28	1.00

UNIT: AUC = mcg.hr/mL C_{MAX} = mcg/mL T_{MAX} = hr

Summary Statistics for CEFADROXIL

Treatment A = Cefadroxil 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, non-fasting
 Treatment B = Duricef®, 500 mg/5 mL Oral Suspension, Dose Administered = 1 x 500 mg, non-fasting

A vs B GEOMETRIC MEANS

Parameter	A	B	Ratio
AUCI	42.52	41.68	1.02
AUCT	41.26	40.45	1.02
C _{MAX}	11.36	11.35	1.00

Figure 1: Mean Plasma Cefadroxil Levels [Fasting Study]

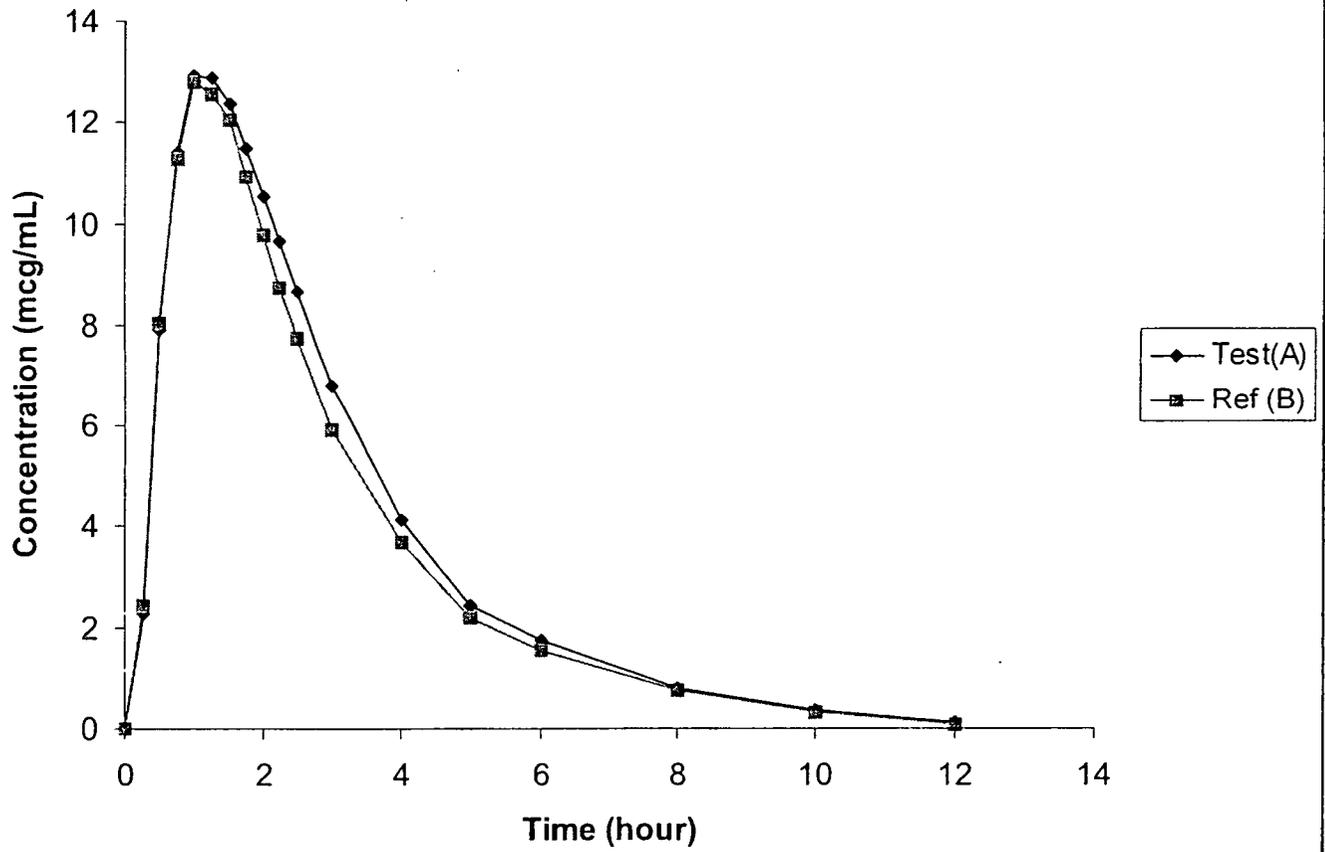


Figure 2: Mean Plasma Cefadroxil Levels
[Non-fasting Study]

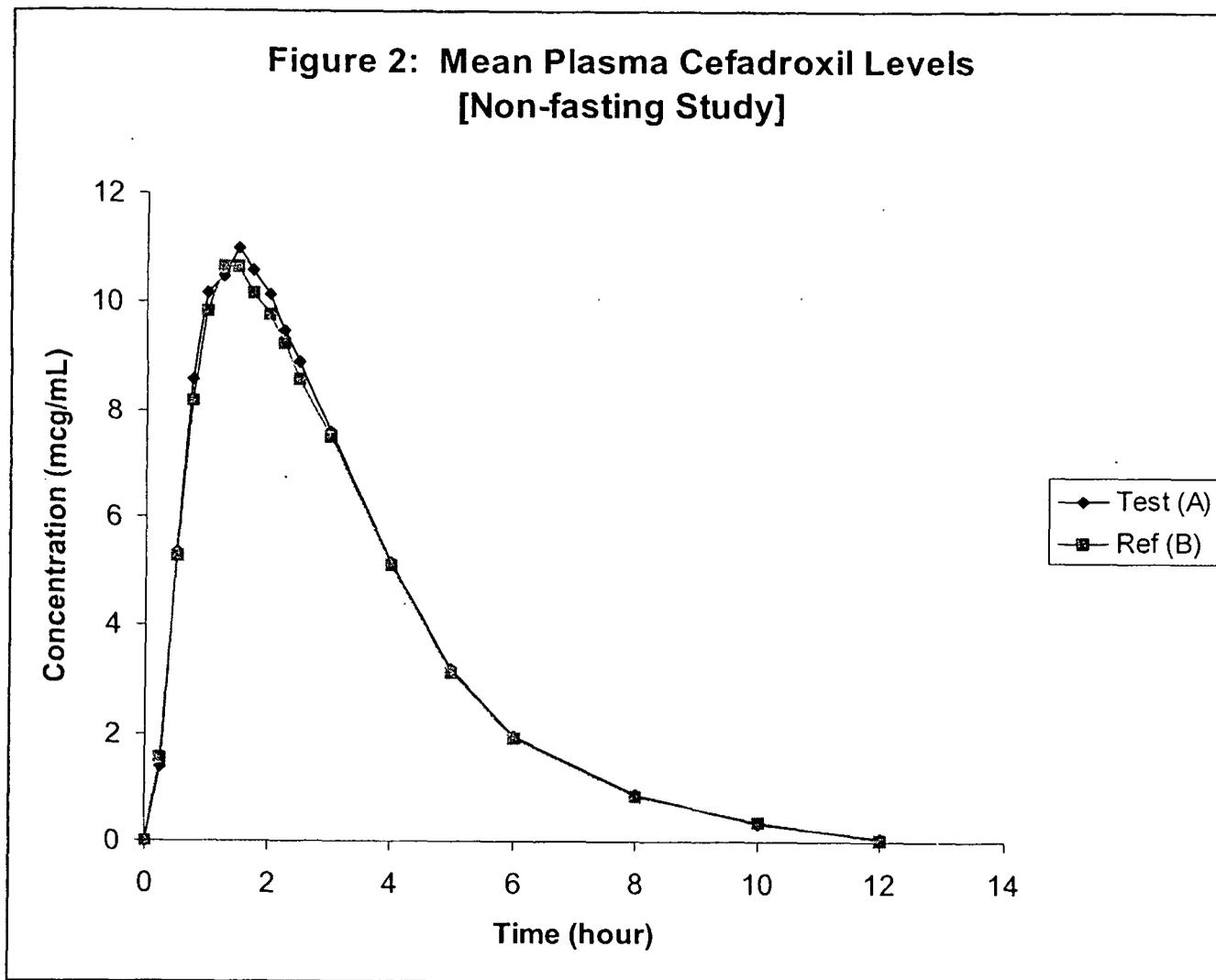


TABLE 6: In Vitro Dissolution Testing

Drug Name: Cefadroxil for Oral Suspension USP
 Method: non-USP Method
 USP 24 Apparatus: II (Paddle)
 Volume: 900mL
 No. Unit Tested: 12

Strength: **125 mg/5 mL**
 Medium: Water, 0.1N HCl, pH 6.5 Buffer
 RPM: 50
 Tolerance: N/A
 Assay Method: nm

Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1151468 Strength: 125 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9E03627 Strength: 125 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
Water						
5	83		2.77	98		1.43
10	86		4.07	99		1.21
20	88		3.97	100		1.40
30	92		3.80	101		1.61
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1151468 Strength: 125 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9E03627 Strength: 125 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
0.1 N HCl						
5	100		1.30	94		1.81
10	101		1.88	96		1.35
20	102		2.35	97		1.13
30	102		2.94	98		1.43
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1151468 Strength: 125 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9E03627 Strength: 125 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
pH 6.5 Phosphate Buffer						
5	82		4.15	95		1.37
10	85		4.70	96		1.37
20	89		3.48	97		1.75
30	92		2.83	97		1.44
F2	N/A					

TABLE 7: In Vitro Dissolution Testing

Drug Name: Cefadroxil for Oral Suspension USP
 Method: non-USP Method
 USP 24 Apparatus: II (Paddle)
 Volume: 900mL
 No. Unit Tested: 12

Strength: **250 mg/5 mL**
 Medium: Water, 0.1N HCl, pH 6.5 Buffer
 RPM: 50
 Tolerance: N/A
 Assay Method: nm

Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147713 Strength: 250 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9J12012 Strength: 250 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
Water						
5	77		3.64	93		1.29
10	81		2.72	95		1.05
20	86		3.25	96		0.94
30	90		3.00	97		1.03
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147713 Strength: 250 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9J12012 Strength: 250 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
0.1 N HCl						
5	88		2.95	86		6.28
10	91		2.42	89		5.95
20	93		2.58	92		5.54
30	94		2.02	92		5.11
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147713 Strength: 250 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9J12012 Strength: 250 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
pH 6.5 Phosphate Buffer						
5	75		2.93	91		1.21
10	79		3.54	93		1.29
20	84		4.52	94		1.06
30	87		4.60	96		1.77
F2	N/A					

TABLE 8: In Vitro Dissolution Testing

Drug Name: Cefadroxil for Oral Suspension USP
 Method: non-USP Method
 USP 24 Apparatus: II (Paddle)
 Volume: 900mL
 No. Unit Tested: 12

Strength: **500 mg/ 5mL**
 Medium: Water, 0.1N HCl, pH 6.5 Buffer
 RPM: 50
 Tolerance: N/A
 Assay Method: nm

Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147735 Strength: 500 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9K15936 Strength: 500 mg/ 5 mL		
	Water					
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	84		4.52	93		1.93
10	87		4.48	95		1.47
20	89		4.94	97		1.55
30	95		7.74	98		1.33
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147735 Strength: 500 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9K15936 Strength: 500 mg/ 5 mL		
	0.1 N HCl					
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	92		1.96	95		0.95
10	94		1.81	96		0.83
20	95		1.89	97		0.93
30	96		2.50	98		0.82
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147735 Strength: 500 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9K15936 Strength: 500 mg/ 5 mL		
	pH 6.5 Phosphate Buffer					
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	76		2.89	94		1.81
10	78		2.69	95		1.68
20	82		2.80	97		1.75
30	86		2.44	98		1.02
F2	N/A					

TABLE 9: In Vitro Dissolution Testing [Submitted In Amendment - 3/13/2002]

Drug Name: Cefadroxil for Oral Suspension USP Strength: 125 mg/5 mL, 250 mg/mL and 500 mg/5 mL
 Method: non-USP Method Medium: **Water**
 USP 24 Apparatus: II (Paddle) RPM: **25 rpm**
 Volume: 900mL Tolerance: N/A
 No. Unit Tested: 12 Assay Method: nm

Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1151468 Strength: 125 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9J12023 Strength: 125 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	56		4.28	83		6.75
10	67		4.78	90		6.67
20	78		3.08	101		2.77
30	86		2.67	104		0.96
F2	31.9					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147713 Strength: 250 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: ID45185 Strength: 250 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	54		9.25	81		3.33
10	66		5.30	88		2.27
20	78		3.59	93		1.50
30	85		2.12	97		1.55
F2	35.0					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147735 Strength: 500 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9K15936 Strength: 500 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	47		4.26	82		1.95
10	58		4.31	87		2.07
20	70		4.71	92		1.63
30	80		4.12	95		1.37
F2	28.9					

	Test
F2 =	500 mg vs 125 mg 54.4
F2 =	500 mg vs 250 mg 57.2

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-115

APPLICANT: Ranbaxy Laboratory Limited

DRUG PRODUCT: Cefadroxil for Oral Suspension, 500 mg/5 mL,
250 mg/5 mL, and 125 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 following dissolution testing should be incorporated into your stability and quality control programs:

The dissolution testing should be conducted
The test product should meet the following interim specifications:

Not less than % (Q) of the labeled amount of the drug in dosage form is dissolved in 30 minutes

Please note that the bioequivalence 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 reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

Sincerely yours,

f ^{/S/}
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 65-115
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama *PN* 5/22/2002

Printed in final on //

Endorsements: (Final with Dates)
HFD-658/ P.Nwakama *PN*
HFD-658/ M.Makary *MM* 5/22/02
HFD-652/ N. Tran *N* 5/22
HFD-650/ S.Mazzella
HFD-650/ D. Conner *DC* 5/22/2002

BIOEQUIVALENCY - ACCEPTABLE Submission Date: December 17,2001

- | | | |
|----|--|--|
| 1. | FASTING STUDY (STF)
Clinical: :
Analytical: | Strengths: 500 mg/5 mL
Outcome: AC |
| 2. | FOOD STUDY (STP)
Clinical:
Analytical: | Strength: 500 mg/5 mL
Outcome: AC |
| 3. | Dissolution Waiver (DIW) | Strength: 250 mg/5 mL
Outcome: AC |
| 4. | Dissolution Waiver (DIW) | Strength: 125 mg/5mL
Outcome: AC |
| 5. | Study Amendment (STA)
(3/13/2002) | Strength: All
Outcome: AC |

Outcome Decisions: AC - Acceptable

Cefadroxil for Oral Suspension USP
125 mg/5mL, 250 mg/5mL and 500 mg/5 mL
ANDA #: 65115
Reviewer: Patrick Nwakama

Ranbaxy Laboratories Limited
600 College Road East
Princeton, NJ 08540
Submission Date:
June 14, 2002

Review Of A Study Amendment

Historical Background

- 12/17/2001- Ranbaxy Laboratories submitted original ANDA (65-115) on Cefadroxil for Oral Suspension, USP, 125 mg/5mL, 250 mg/5mL and 500 mg/5 mL with dissolution method (Paddle and 50 rpm) in various media (water, 0.1N HCl and pH 6.5 Phosphate Buffer). Both the test and reference drug products demonstrated rapid dissolution in the media at 50 rpm paddle speed.
- 3/5/2002- In consultation with Dr. Nhan Tran, the firm was requested through teleconference to provide additional dissolution data using
- 3/13/2002- The firm submitted dissolution data requested by the DBE. The dissolution testing conducted in
- 5/22/2002- The firm was informed that the ANDA has been found acceptable and was requested to incorporate into its stability and quality control programs the following dissolution method and specifications:
- 900 mL Water, Apparatus II (Paddle) at 25 rpm with specification of NLT % (Q) in 30 minutes.*

In this submission, the firm proposes to

TABLE 1: In Vitro Dissolution Testing

Drug Name: Cefadroxil for Oral Suspension USP
 Method: non-USP Method
 USP 24 Apparatus: II (Paddle)
 Volume: 900mL
 No. Unit Tested: 12

Strength: 125 mg/5 mL
 Medium: Water, 0.1N HCl, pH 6.5 Buffer
 RPM: 50
 Tolerance: N/A
 Assay Method: nm

Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1151468 Strength: 125 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9E03627 Strength: 125 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
Water						
5	83		2.77	98		1.43
10	86		4.07	99		1.21
20	88		3.97	100		1.40
30	92		3.80	101		1.61
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1151468 Strength: 125 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9E03627 Strength: 125 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
0.1 N HCl						
5	100		1.30	94		1.81
10	101		1.88	96		1.35
20	102		2.35	97		1.13
30	102		2.94	98		1.43
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1151468 Strength: 125 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9E03627 Strength: 125 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
pH 6.5 Phosphate Buffer						
5	82		4.15	95		1.37
10	85		4.70	96		1.37
20	89		3.48	97		1.75
30	92		2.83	97		1.44
F2	N/A					

TABLE 2: In Vitro Dissolution Testing

Drug Name: Cefadroxil for Oral Suspension USP
 Method: non-USP Method
 USP 24 Apparatus: II (Paddle)
 Volume: 900mL
 No. Unit Tested: 12

Strength: 250 mg/5 mL
 Medium: Water, 0.1N HCl, pH 6.5 Buffer
 RPM: 50
 Tolerance: N/A
 Assay Method: nm

Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147713 Strength: 250 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9J12012 Strength: 250 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
Water						
5	77		3.64	93		1.29
10	81		2.72	95		1.05
20	86		3.25	96		0.94
30	90		3.00	97		1.03
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147713 Strength: 250 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9J12012 Strength: 250 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
0.1 N HCl						
5	88		2.95	86		6.28
10	91		2.42	89		5.95
20	93		2.58	92		5.54
30	94		2.02	92		5.11
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147713 Strength: 250 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9J12012 Strength: 250 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
pH 6.5 Phosphate Buffer						
5	75		2.93	91		1.21
10	79		3.54	93		1.29
20	84		4.52	94		1.06
30	87		4.60	96		1.77
F2	N/A					

TABLE 3: In Vitro Dissolution Testing

Drug Name: Cefadroxil for Oral Suspension USP
 Method: non-USP Method
 USP 24 Apparatus: II (Paddle)
 Volume: 900mL
 No. Unit Tested: 12

Strength: 500 mg/ 5mL
 Medium: Water, 0.1N HCl, pH 6.5 Buffer
 RPM: 50
 Tolerance: N/A
 Assay Method: nm

Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147735 Strength: 500 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9K15936 Strength: 500 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	84		4.52	93		1.93
10	87		4.48	95		1.47
20	89		4.94	97		1.55
30	95		7.74	98		1.33
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147735 Strength: 500 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9K15936 Strength: 500 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	92		1.96	95		0.95
10	94		1.81	96		0.83
20	95		1.89	97		0.93
30	96		2.50	98		0.82
F2	N/A					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147735 Strength: 500 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9K15936 Strength: 500 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	76		2.89	94		1.81
10	78		2.69	95		1.68
20	82		2.80	97		1.75
30	86		2.44	98		1.02
F2	N/A					

TABLE 4: In Vitro Dissolution Testing [Submitted In Amendment - 3/13/2002]

Drug Name: Cefadroxil for Oral Suspension USP Strength: 125 mg/5 mL, 250 mg/mL and 500 mg/5 mL

Method: non-USP Method
 USP 24 Apparatus: II (Paddle)
 Volume: 900mL
 No. Unit Tested: 12

Medium: **Water**
 RPM: **25 rpm**
 Tolerance: N/A
 Assay Method: nm

Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1151468 Strength: 125 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9J12023 Strength: 125 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	56		4.28	83	-	6.75
10	67		4.78	90	-	6.67
20	78		3.08	101	-	2.77
30	86		2.67	104	-	0.96
F2	31.9					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147713 Strength: 250 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: ID45185 Strength: 250 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	54		9.25	81		3.33
10	66		5.30	88		2.27
20	78		3.59	93		1.50
30	85		2.12	97		1.55
F2	35.0					
Sampling Times (MINUTES)	Test Product: Cefadroxil for Oral Suspension Lot Number: 1147735 Strength: 500 mg/ 5 mL			Test Product: Duricef® for Oral Suspension Lot Number: 9K15936 Strength: 500 mg/ 5 mL		
	%Mean	Range	%RSD	%Mean	Range	%RSD
5	47		4.26	82		1.95
10	58		4.31	87		2.07
20	70		4.71	92		1.63
30	80		4.12	95		1.37
F2	28.9					
	Test					
F2 =	500 mg vs 125 mg 54.4					
F2 =	500 mg vs 250 mg 57.2					

NOV 21 2002

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-115

APPLICANT: RANBAXY LABORATORIES

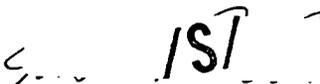
DRUG PRODUCT: CEFADROXIL FOR ORAL SUSPENSION, USP,
125 mg/5mL, 250 mg/5mL and 500 mg/5 mL

The Division of Bioequivalence has completed its review of your submission(s). The following deficiencies have been noted:

1. Although you stated in your letter of June 14, 2002, that the rpm paddle speed was not the suitable dissolution method for your product because the rate of agitation was not sufficient to prevent heap formation, your submitted data show dissolution at paddle speed rpm to be more discriminatory and reproducible than at rpm.
2. Therefore, the Agency's recommendation regarding dissolution testing remains unchanged. The dissolution should be conducted in 900 mL Water, at 37°C using USP Apparatus 2 (paddle) at **25 rpm** with the following specifications:

Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Sincerely yours,


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

CC: ANDA 65-115
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Patrick Nwakama

Per 11/12/2002

Printed in final on 11/12/2002

Endorsements: (Final with Dates)

HFD-655/ P. Nwakama *Per*
HFD-655/ GJP Singh *CLPS 11-12-02*
HFD-655/ N. Tran
HFD-650/ D. Conner *ATZ 11/19/02*

BIOEQUIVALENCY - UNACCEPTABLE submission date: June 14, 2002

1. **STUDY AMENDMENT (STA)** Strengths: 125 mg/5mL, 250 mg/5mL,
500 mg/5 mL
Outcome: UN

Outcome Decisions: UN - Unacceptable

WinBio Comments:

Cefadroxil for Oral Suspension USP
125 mg/5mL, 250 mg/5mL and 500 mg/5 mL
ANDA #: 65115
Reviewer: Patrick Nwakama

Ranbaxy Laboratories Limited
600 College Road East
Princeton, NJ 08540
Submission Date:
December 6, 2002

Addendum to the Review

Historical Background:

- 12/17/2001- Ranbaxy Laboratories submitted original ANDA (65-115) on Cefadroxil for Oral Suspension, USP, 125 mg/5mL, 250 mg/5mL and 500 mg/5 mL with dissolution method (Paddle and 50 rpm) in various media (water, 0.1N HCl and pH 6.5 Phosphate Buffer). Both the test and reference drug products demonstrated rapid dissolution in the media at 50 rpm paddle speed.
- 3/5/2002- In consultation with Dr. Nhan Tran, the firm was requested through teleconference to provide additional dissolution data using
- 3/13/2002- The firm submitted dissolution data requested by the DBE. The dissolution testing conducted in
- 5/22/2002- The firm was informed that the ANDA has been found acceptable and was requested to incorporate into its stability and quality control programs the following dissolution method and specifications:
- 900 mL Water, Apparatus II (Paddle) at 25 rpm with specification of NLT % (Q) in 30 minutes.*
- 6/14/2002- The firm proposed adopting
- 11/21/2002- The firm was informed by the Agency that comparison of the dissolution profiles from

Therefore, the firm's proposal was not acceptable.

Current Submission:

The firm has accepted the following Agency's recommendation:

The dissolution should be conducted in 900 mL Water, at 37°C using USP Apparatus II (paddle) at 25 rpm with the following specifications:

Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Recommendations:

- I. The firm has accepted the Agency's recommendation for dissolution testing. No further action is necessary.
- II. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is approvable.

[Handwritten signature] 12/20/2002

Patrick Nwakama, Pharm.D.
Review Branch III
Division of Bioequivalence

RD INITIALED GJP SINGH
FT INITIALED GJP SINGH

[Handwritten initials] DATE 12-20-02

Concur: *[Handwritten signature]*
Dale P. Conner, Pharm.D,
Director, Division of Bioequivalence

Date 12/29/02

CC: ANDA 65-115
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P. Nwakama

Printed in final on 12/19/2002

Endorsements: (Final with Dates)
HFD-658/ P. Nwakama *PK 12/20/2002*
HFD-658/ GJP Singh *COPS 12-20-02*
HFD-650/ D. Conner *AK 12/29/02*

BIOEQUIVALENCY - ACCEPTABLE submission date: December 6, 2002

1. OTHER (OTH)

Strengths: 125 mg/5mL, 250 mg/5mL,
500 mg/5 mL

Outcome: **AC**

Outcome Decisions: AC - Acceptable

WinBio Comments: