CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-200

BIOEQUIVALENCE REVIEW(S)

OCT 10 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-200 APPLICANT: Corepharma LLC

DRUG PRODUCT: Acetaminophen Extended Release Tablet, 650 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The CDER's Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General-Considerations, posted October 27, 2000, states that replicate design bioequivalence studies are recommended for modified release products. Please explain why you used a two-way crossover design for your fasting bioequivalence study instead of a replicate design.

Sincerely yours,

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

Acetaminophen
Extended Release Tablets, 650 mg
ANDA #76-200
Reviewer: Moheb H. Makary
Filename: 76200SD.701

Corepharma LLC
Middlesex, NJ
Submission Dates:
July 2, 2001
August 20, 2001

Review of Bioequivalence studies and Dissolution Data

I. Objective:

The firm has submitted a single dose fasting bioequivalence study and a post-prandial bioequivalence study on its Acetaminophen Extended Release (ER) Tablet, 650 mg.

II. Background:

Acetaminophen is a clinically proven analgesic and antipyretic. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat regulating center. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin and aspirin-containing products.

It is indicated for the temporary relief of minor aches and pains associated with headache, muscular aches, backache, minor arthritis pain, common cold, toothache, menstrual cramps and for the reduction of fever.

The reference listed drug is TYLENOL® Arthritis Pain Extended Relief Caplet, 650 mg, manufactured by McNeil Consumer Healthcare.

III. Fasting In Vivo Bioequivalence Study #003180 for Acetaminophen ER Tablet, 650 mg

Study site: [redacted]

Study design: A randomized, single-dose, two-treatment, two-period, two-sequence crossover study.

Dosing date: February 13, 2001, Period I
February 20, 2001, Period II

Analytical date: From February 26, 2001 to March 16, 2001

Subjects: Twenty-four (24) male subjects and two alternates were enrolled in the study. A total of twenty-five (25) subjects completed the clinical portion of the study. Subject #7 elected to withdraw from the study after completion of period I due to adverse events unrelated to study drug (runny nose, headache, fever and "tired").

Demographic profile of subjects in Study #003180

ANDA #76-200

CRO : [redacted]

Age

Mean:	31.3 years
SD:	6.60
Range:	20-43 years

Groups

< 18	0%
18 - 40	92.3%
41 - 64	7.7%
65 - 75	0%
> 75	0%

Gender

Male	100%
Female	0%

Race

Asian	3.8%
African American	7.7%
Hispanic	0%
Caucasian	88.5%
Other	0%

Washout period: One week

Dose and Treatment: A. Test product:
2 x 650 mg Acetaminophen ER Tablets, manufactured by Corepharma LLC, manufactured date: 12-6-00,

lot #CR0012, lot size [redacted] Tablets, potency 99.3%, content uniformity 99.8%, following an overnight fast.
B. Reference product:
2 x 650 mg TYLENOL® Arthritis Pain Extended Relief Caplets, manufactured by McNeil, lot #CSM121, Exp. 12/2002, potency 100.4%, following an overnight fast.

Blood samples: Blood samples were obtained in heparinized Vacutainers for analysis of acetaminophen at: 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16 and 24 hours post-dose.

Analytical Methodology

Acetaminophen concentrations were determined in human plasma by a validated [redacted] method.

Sensitivity:

Linearity:

Assay specificity:

Recovery:

Precision and accuracy:

Stability:

[redacted]

Precision and

Accuracy:

Sample Reassays: [redacted]

Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for acetaminophen. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure.

IV. In Vivo Results:

Subjects were monitored for adverse events throughout the study as specified in the protocol. No serious adverse events occurred during the study. A summary of adverse events is reported on page 263, Vol.1.1.

The plasma concentrations and pharmacokinetic parameters for acetaminophen are summarized in Table I.

Table I
Mean Acetaminophen Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 2x650 mg Acetaminophen ER Tablets Under Fasting Conditions
(N=24)

Time hr	CorePharma Test Product Lot #CR0012 ug/mL (CV%)	McNeil Reference Product Lot #CSM121 ug/mL (CV%)	T/R
0	0.00 (.)	0.00 (.)	.
0.25	3.56 (105)	5.24 (107)	0.68
0.5	9.72 (49.3)	8.72 (44.8)	1.11
0.75	10.32 (30.3)	9.65 (31.6)	1.07
1	10.38 (27.0)	9.81 (24.8)	1.07
1.25	10.13 (27.2)	9.85 (22.6)	1.03
1.5	10.04 (23.3)	9.83 (18.8)	1.02
1.75	9.89 (20.0)	9.66 (20.4)	1.02
2	9.79 (17.3)	9.42 (18.9)	1.04

2.5	9.19 (17.5)	8.95 (18.6)	1.03
3	8.50 (16.8)	8.33 (18.5)	1.02
4	6.91 (18.2)	6.87 (20.4)	1.01
6	4.05 (22.5)	4.35 (24.3)	0.93
8	2.49 (27.7)	2.58 (29.1)	0.97
10	1.52 (35.6)	1.53 (31.7)	1.00
12	0.99 (36.1)	0.96 (33.4)	1.03
14	0.68 (34.7)	0.67 (33.8)	1.01
16	0.51 (35.4)	0.50 (33.5)	1.02
24	0.22 (38.3)	0.23 (38.6)	0.95

Pharmacokinetic Parameters

	Test	Reference	T/R (Geometric Mean)	RMSE
AUC(0-t) (ug.hr/mL)	63.75(21)	63.81(20)	1.00	0.089
AUCinf (ug.hr/mL)	65.97(21)	66.21(20)	0.99	0.098
Cmax (ug/mL)	12.05(22)	11.49(32)	1.06	0.133
Tmax (hr)	1.075	1.167		
Kel(1/hr)	0.11	0.11		
t1/2 (hr)	6.54	6.79		

	90% CI
LnAUC(0-t)	95.3-104.2%
LnAUCinf	95.1-103.9%
LnCmax	99.0-113.0%

1. The mean acetaminophen plasma levels peaked at 1 and 1.25 hours for the test and the reference products, respectively, following their administration under fasting conditions.

2. For Corepharma test product, the mean AUC(0-t), AUCinf and Cmax values were 0.1%, 0.4% and 4.9% lower and higher, respectively, than those for the reference product values under fasting conditions. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

V. Study #011329 for Single-Dose, 2-way Crossover Study of Aacetaminophen ER Tablets, 650 mg, Under Nonfasting Conditions

Study site: [redacted]

Study design: Open-label, randomized, 2-way crossover study under nonfasting conditions.

Study date: Period I 5/30/2001
Period II 6/4/2001

Analytical date: From June 7, 2001 to June 14, 2001

Subjects: A total of 18 healthy male volunteers enrolled in and completed the clinical phase of the study.

Demographic profile of subjects in Study #011329

ANDA #76-200

CRO : [redacted]

Age

Mean:	30.2 years
SD:	7.24
Range:	19-44 years

Groups	
< 18	0.0%
18 - 40	88.9%
41 - 64	11.1%
65 - 75	0.0%
> 75	0.0%
Gender	
Male	100%
Female	0.0%

Race	
Asian	0.0%
African American	0.0%
Hispanic	0.0%
Caucasian	100.0%
Other	0.0%

Washout period: Five days

Dose and Treatment:

A. 2 x 650 mg Aacetaminophen ER Tablets manufactured by Corepharma LLC, lot #CR0012, following a standard breakfast.
B. 2 x 650 mg TYLENOL® Arthritis Pain Extended Relief Caplets, manufactured by McNeil, lot #CSM121, following a standard breakfast.

Food and fluid intake:

Subjects on regimens A and B were required to fast overnight until 30 minutes prior to their scheduled dosing times, when they were administered breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6ounces of orange juice). Water was restricted from one hour before until one hour after dosing except for water (240 mL) administered with the dose.

Analytical Methodology

Same as the fasting study

Precision and Accuracy:

[ ]

[ ]

VI. In Vivo Results:

Subjects were monitored for adverse events throughout the study as specified in the protocol. No serious adverse events occurred during the study. A summary of adverse events is reported on page 1232, Vol.1.2.

The plasma concentrations and pharmacokinetic parameters for acetaminophen are summarized in Table II.

Table II

Mean Acetaminophen Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 2x650 mg Acetaminophen ER Tablets Under Nonfasting Conditions

(N=18)

Time hr	CorePharma Test Product Lot #CR0012 ug/mL (CV%)	McNeil Reference Product Lot #CSM121 ug/mL (CV%)	T/R
0	0.00 (.)	0.00 (.)	.
0.25	0.91 (196)	0.62 (186)	0.15
0.5	4.34 (75.0)	2.95 (93.6)	1.47
0.75	6.76 (36.5)	4.70 (63.6)	1.43
1	7.93 (24.9)	6.27 (42.9)	1.26
1.5	8.35 (19.5)	7.50 (27.6)	1.11
2	8.42 (19.4)	8.17 (25.7)	1.03
2.5	8.51 (19.6)	8.10 (23.3)	1.05
3	8.61 (22.0)	8.25 (25.2)	1.04
3.5	7.77 (23.0)	7.68 (25.7)	1.01
4	6.96 (25.1)	7.33 (28.7)	0.95
5	5.32 (30.3)	5.45 (26.1)	0.98
6	3.64 (31.0)	3.83 (31.4)	0.95
8	1.78 (31.6)	1.89 (29.5)	0.94
10	1.01 (32.2)	1.06 (30.6)	0.95
12	0.67 (36.2)	0.73 (28.9)	0.92
14	0.50 (34.0)	0.54 (31.3)	0.93
16	0.39 (39.8)	0.40 (35.4)	0.98
24	0.19 (54.7)	0.18 (53.3)	1.06

Pharmacokinetic Parameters

	Test	Reference	T/R (Geometric Mean)	RMSE
AUC(0-t) (ug.hr/mL)	53.31(19)	52.03(19)	1.03	0.032
AUCinf (ug.hr/mL)	56.17(19)	54.23(19)	1.04	0.034
Cmax (ug/mL)	9.92(16)	9.38(20)	1.07	0.133
Tmax (hr)	2.18	2.74		
Kel(1/hr)	0.11	0.12		
t1/2 (hr)	8.20	6.85		

1. The acetaminophen plasma levels peaked at 3 hours for both the test and reference products under nonfasting conditions.

2. For Corepharma's acetaminophen, the mean AUC(0-t), AUCinf and Cmax values were 2.46%, 3.58% and 5.76% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the geometric means are within the acceptable 0.8-1.25 range for AUC(0-t), AUCinf and Cmax. The reviewer's calculations are similar to those submitted by the firm.

VII. Formulation:

The formulation of Acetaminophen ER tablets, 650 mg, is shown below:

Ingredient	mg/Tablet
Acetaminophen	325.0
Hydroxypropyl Methylcellulose	
Microcrystalline Cellulose	
Pregelatinized Strach	
Sodium Lauryl Sulfate	
Magnesium Stearate	
Acetaminophen	
Total Weight	770.0 mg

VIII. Dissolution Testing:

Method:	USP 24 apparatus II (paddle) at 50 rpm
Medium:	900 mL of phosphate buffer pH 5.8
Number of Tablets:	12
Test products:	Corepharma's Acetaminophen ER Tablets 650 mg, lot #CR0012
Reference Products:	McNeil's Tylenol^{R} Arthritis Extended Relief Caplets, 650 mg, lot #CSM121
Specifications:	NLT (Q) in 1 hour NLT (Q) in 4 hours

On August 7, 2001, the firm was asked to submit additional dissolution testing results using at least three dissolution media, e.g., water, pH 1.2, 4.5 and 6.8. On August 20, 2001, the firm submitted the dissolution testing results.

Dissolution testing results are shown in Table III.

Table III

I. Conditions for Dissolution Testing:						
USP 24 Basket: Paddle:X RPM: 50 No. Units Tested: 12 Medium: 900 mL of phosphate buffer pH 5.8						
II. Results of In Vitro Dissolution Testing:						
Sampling Times	Test Product Lot #CR0012 Strength(mg) 650			Reference Product Lot #CSM121 Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
15 min	54.4	[redacted]	3.4	52.9	[redacted]	3.1
30 min	60.4	[redacted]	2.2	59.3	[redacted]	3.4
45 min	65.1	[redacted]	2.2	64.5	[redacted]	3.2
1 hr	69.9	[redacted]	2.5	69.4	[redacted]	3.7
2 hr	84.2	[redacted]	2.3	83.4	[redacted]	3.4
3 hr	93.2	[redacted]	1.8	91.7	[redacted]	2.2
4 hr	97.3	[redacted]	0.9	95.9	[redacted]	1.3

I. Conditions for Dissolution Testing:						
USP 24 Basket: Paddle:X RPM: 50 No. Units Tested: 12 Medium: 900 mL of water						
II. Results of In Vitro Dissolution Testing:						
Sampling Times	Test Product Lot #CR0012 Strength(mg) 650			Reference Product Lot #DLM083 Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
15 min	56.2	[redacted]	3.9	55.2	[redacted]	3.1
30 min	64.5	[redacted]	4.3	61.8	[redacted]	3.3

45 min	70.9			5.6	67.8		3.7
1 hr	76.2			7.0	73.3		4.2
2 hr	90.6			5.2	89.2		3.5
3 hr	97.2			2.9	96.8		1.8
4 hr	99.2			1.3	99.2		0.8

I. Conditions for Dissolution Testing:

USP 24 Basket: Paddle:X RPM: 50
No. Units Tested: 12
Medium: 900 mL of Simulated Gastric Fluid without enzyme pH 1.2

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot #CR0012 Strength(mg) 650			Reference Product Lot #DLM083 Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
15 min	53.4		2.7	53.6		2.6
30 min	59.6		2.0	59.4		2.4
45 min	65.0		2.3	64.1		2.5
1 hr	69.3		2.9	68.2		2.7
2 hr	84.1		4.1	79.2		2.4
3 hr	91.6		2.8	89.5		1.8
4 hr	96.4		1.1	93.7		1.3

I. Conditions for Dissolution Testing:

USP 24 Basket: Paddle:X RPM: 50
No. Units Tested: 12
Medium: 900 mL of Acetate Buffer pH 4.5

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot #CR0012 Strength(mg) 650			Reference Product Lot #DLM083 Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
15 min	57.6		2.7	56.2		2.9
30 min	66.9		2.6	63.4		3.2
45 min	70.7		2.1	69.2		2.6

1 hr	76.7	[redacted]	2.1	74.1	[redacted]	2.3
2 hr	93.8	[redacted]	2.1	94.0	[redacted]	1.3
3 hr	99.7	[redacted]	0.8	98.3	[redacted]	1.0
4 hr	99.8	[redacted]	0.9	98.7	[redacted]	0.8

I. Conditions for Dissolution Testing:

USP 24 Basket: Paddle:X RPM: 50
No. Units Tested: 12
Medium: 900 mL of Phosphate Buffer pH 6.8

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot #CR0012 Strength(mg) 650			Reference Product Lot #DLM083 Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
15 min	53.5	[redacted]	3.3	54.9	[redacted]	2.7
30 min	59.9	[redacted]	2.7	60.5	[redacted]	3.3
45 min	65.5	[redacted]	2.8	65.5	[redacted]	3.9
1 hr	71.1	[redacted]	2.6	70.7	[redacted]	5.0
2 hr	83.8	[redacted]	1.6	85.0	[redacted]	5.2
3 hr	91.4	[redacted]	1.2	91.6	[redacted]	2.4
4 hr	96.3	[redacted]	1.4	95.5	[redacted]	2.0

IX. Comments:

1. The firm's *in vivo* bioequivalence studies conducted on its Acetaminophen Extended Release Tablet, 650 mg, under fasting and nonfasting conditions are acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions. The ratios of the geometric means are within the acceptable range of 0.80-1.25 for AUC(0-t), AUCinf and Cmax under nonfasting conditions.

2. The dissolution testing conducted by the firm on its Acetaminophen Extended Release Tablet, 650 mg, Lot # CR0012, is acceptable. The dissolution testing method using [redacted] appears to be

adequately discriminating for routine dissolution testing for Acetaminophen Extended Release Tablet, 650 mg.

3. All inactive ingredients were reviewed and found to be present in the formulation at or below the levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products.

X. Deficiency Comment:

The CDER's Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General-Considerations, posted October 27, 2000, states that replicate design bioequivalence studies are recommended for modified release products. The firm should explain why they used a two-way crossover design for its fasting bioequivalence study on Acetaminophen Extended Release Tablet, 650 mg, instead of a replicate design.

XI. Recommendations:

1. The bioequivalence studies under fasting and nonfasting conditions conducted by Corepharma LLC, on its Acetaminophen Extended Release Tablet, 650 mg, lot # CR0012, comparing it to Tylenol[R] Arthritis Pain Extended Relief Caplet, 650 mg, manufactured by McNeil Consumer Healthcare, have been found incomplete for the reason given in the deficiency comment.

2. The dissolution testing conducted by Corepharma LLC, on its Acetaminophen Extended Release Tablet, 650 mg, lot # CR0012, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of Simulated Gastric Fluid without enzyme pH 1.2 using USP 24 apparatus II (paddle) at 50 rpm. The test product should meet the following tentative specifications:

Time (min)	Mean (% of claim)
15	[redacted]
60	[redacted]
180	NLT [redacted]

The firm should be informed of the deficiency comment and recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 9/4/01

RD INITIALLED BDAVIT BNW 8/31/01
FT INITIALLED BDAVIT Barbara M Davit

Date 9/4/01

Concur: Dale P. Conner

Date: 9/26/01

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 8-20-01, 9-4-01, 76200SD.701
cc: ANDA #76-2000, original, HFD-658 (Makary), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-200 APPLICANT: Corepharma LLC

DRUG PRODUCT: Acetaminophen Extended Release Tablet, 650 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The CDER's Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General-Considerations, posted October 27, 2000, states that replicate design bioequivalence studies are recommended for modified release products. Please explain why you used a two-way crossover design for your fasting bioequivalence study instead of a replicate design.

Sincerely yours,

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

CC: ANDA #76-200
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

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Printed in final on 9/4/01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM
HFD-658/ Bio team Leader B. Davit 9/4/01
HFD-650/ D. Conner 9/26/01

BIOEQUIVALENCY - DEFICIENCIES submission date: July-2-01

1. FASTING STUDY (STF) Strength: 650 mg
Clinical Sit:
Analytical Site:
Outcome: IC

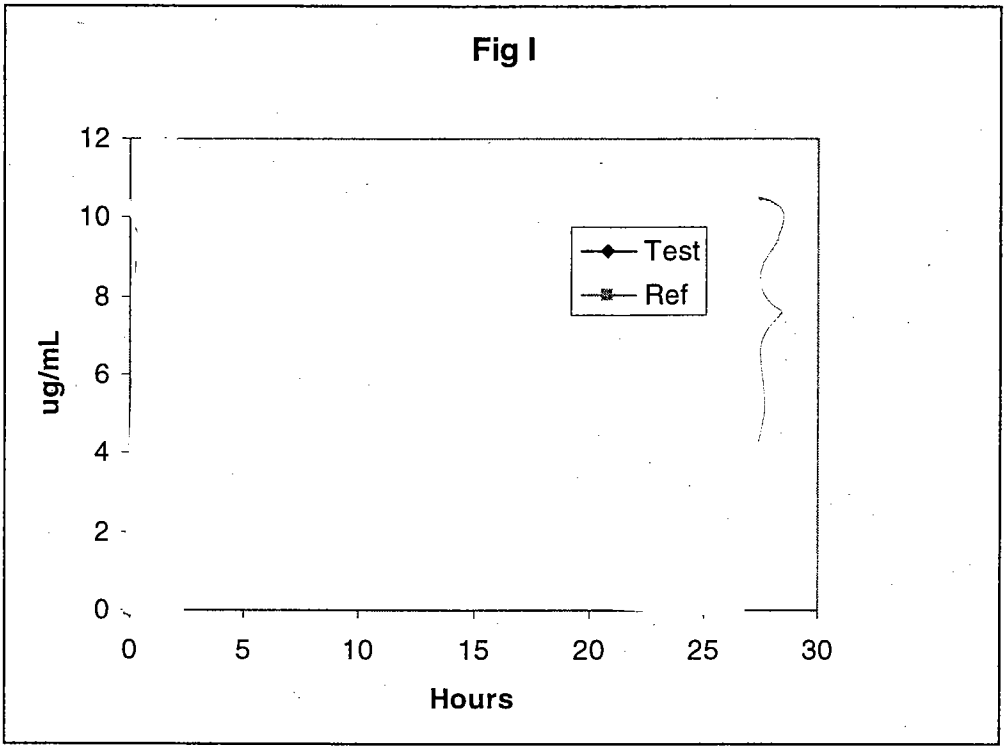
2. FOOD STUDY (STP) Strength: 650 mg
Clinical Sit:
Analytical Site: Outcome: IC

3. STUDY AMENDMENT (STA) Strengths: 650
Date: August 20, 2001 Outcome: IC

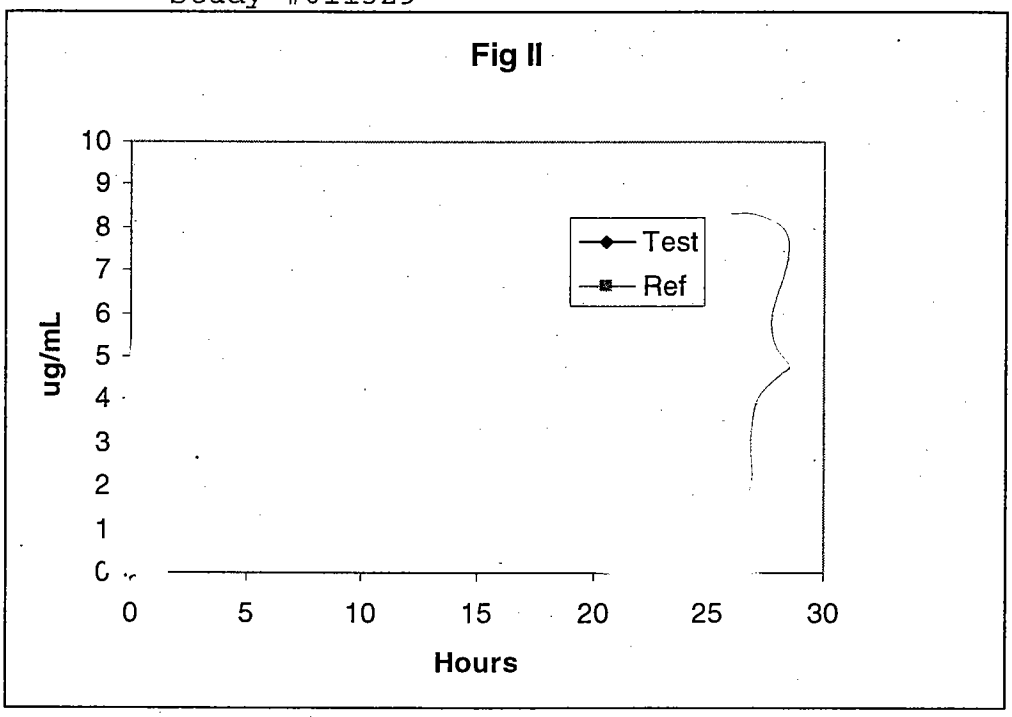
Outcome Decisions: IC - Incomplete

APPEARS THIS WAY
ON ORIGINAL

Study #003180



Study #011329



Acetaminophen
Extended Release Tablets, 650 mg
ANDA #76-200
Reviewer: Moheb H. Makary
W 76200STA.O01

Corepharma LLC
Middlesex, NJ
Submission Date:
October 18, 2001

Review of an Amendment

I. Objective:

The firm has replied to the reviewer's comment made in the review of the July 2, 2001 submission (bioequivalence studies on Acetaminophen Extended Release Tablets, 650 mg).

II. Comment:

The firm was asked to explain why it used a two-way crossover design for its fasting bioequivalence study on Acetaminophen Extended Release Tablet, 650 mg, instead of a replicate design. The CDER's Guidance for Industry *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations*, posted October 27, 2000, states that replicate design bioequivalence studies are recommended for modified release products.

Firm's Response

The firm indicated that its interpretation of the FDA guidance dated October 27, 2000, was that a fully replicated design for modified release products was a recommendation but not an absolute requirement.

In addition, Corepharma stated that the observed variability was very low in preliminary pilot studies conducted on the 650 mg Acetaminophen Extended Release Tablet. From the variability, it was determined that 24 subjects would provide sufficient statistical power to conclude bioequivalence in a two-way crossover design. The firm stated that its understanding was to enroll a minimum of 24 subjects in the pivotal bioequivalence study. Therefore, it was judged unethical to expose the same number of subjects to four periods of treatment. The firm did not realize that a minimum of 12 subjects could be used in a replicate-design study until after the January 2001 posting of the Guidance for Industry *Statistical Approaches to Establishing Bioequivalence*.

In support of its argument that Acetaminophen is not a variable substance, Corepharma noted that Acetaminophen is classified as Class I (highly soluble, highly permeable) under the Biopharmaceutics Classification System.

Comments

1. The Division of Bioequivalence concludes that it is acceptable to conduct a two-way crossover study for this product based on the observation that intra-subject variability in acetaminophen pharmacokinetics is low. From data in Corepharma's fasting bioequivalence study #003180, intrasubject variability is estimated as 8.9%, 9.8%, and 13.3% for AUC(0-t), AUCinf, and Cmax, respectively. The probability of a subject*formulation interaction occurring with this product is low. It is likely that little if any additional information about this acetaminophen extended-release tablet formulation would be gained from a replicate study design.

2. The Division of Bioequivalence disagrees with the argument that a replicate study design is unethical. With a replicate study design, the firm could reduce the number of subjects dosed by using as few as 12 subjects instead of 24. Moreover, the safety profile from a single 650-mg dose of acetaminophen is good. There is very little safety risk associated with 4 single doses of acetaminophen with each taken following a washout period.

3. The firm's argument that it did not understand that 12 subjects could be enrolled is not acceptable. The pivotal fasting bioequivalence study was initiated in February, 2001. The CDER Guidance for Industry *Statistical Approaches to Establishing Bioequivalence*, which recommends 12 as a minimum number of study subjects, was posted in January, 2001.

4. The observation that Acetaminophen is a Class I drug substance applies only to immediate-release Acetaminophen oral formulations.

5. The firm's conclusion that a replicate study design need not be used for acetaminophen extended release tablet products because the Agency recommends but does

not absolutely require this study design is not a correct interpretation of the CDER Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations*. The decision to conduct a two-way rather than replicated crossover design for a modified-release drug product should be supported by sound scientific justification.

III. Recommendations:

1. The bioequivalence studies under fasting and nonfasting conditions conducted by Corepharma LLC, on its Acetaminophen Extended Release Tablet, 650 mg, lot #CR0012, comparing it to Tylenol^{R} Arthritis Pain Extended Relief Caplet, 650 mg, manufactured by McNeil Consumer Healthcare, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Corepharma's Acetaminophen Extended Release Tablet, 650 mg, is bioequivalent to McNeil's Tylenol^{R} Arthritis Pain Extended Relief Caplet, 650 mg.

2. The dissolution testing conducted by Corepharma LLC, on its Acetaminophen Extended Release Tablet, 650 mg, lot #CR0012, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of Simulated Gastric Fluid without enzyme pH 1.2 using USP 24 apparatus II (paddle) at 50 rpm. The test product should meet the following tentative specifications:

Time (min)	Mean (% of claim)
15	[redacted]
60	[redacted]
180	[redacted]

The firm should be informed of the above comments and recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 10/26/01

BDM 10/25/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara Davit Date 10/26/01

Concur: Dale P. Conner Date: 11/19/01

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 10-24-01, 10-26-01, 76200STA.001
cc: ANDA #76-2000, original, HFD-658 (Makary), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

3. The observation that Acetaminophen is a Class I drug substance applies only to immediate-release Acetaminophen oral formulations.

4. You state that a replicate study design need not be used for acetaminophen extended release tablet products because the Agency recommends but does not absolutely require this study design. This is not a correct interpretation of the CDER Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations*. The decision to conduct a two-way rather than replicated crossover design for a modified-release drug product should be supported by sound scientific justification.

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 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

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

CC: ANDA #76-200
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

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Printed in final on 10/26/01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM
HFD-658/ Bio team Leader B. Davit BMD 10/26/01
HFD-650/ D. Conner 11/19/01

BIOEQUIVALENCY - ACCEPTABLE submission date: 10-18-01

1. **STA (Study Amendment)** Strengths: 650 mg
Outcome: AC

Outcome Decisions: **AC** – Acceptable

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF BIOEQUIVALENCE

ANDA # 76-200 SPONSOR : Corepharma LLC

DRUG AND DOSAGE FORM : Acetaminophen Extended Release Tablets

STRENGTH(S) : 650 mg

TYPES OF STUDIES : Two bioequivalence studies

CLINICAL STUDY SITE(S) : _____
ANALYTICAL SITE(S) : _____

STUDY SUMMARY : The studies are acceptable

DISSOLUTION : Dissolution testing is acceptable .

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

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 10/24/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 10/26/01

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

INITIAL : DPC **DATE :** 11/19/01