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APPLICATION NUMBER: 20812

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 23 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-812 **SUBMISSION DATE:** 12/12/96
PRODUCT: Pediatric Advil® (ibuprofen) Drops, 100 mg/2.5 mL
SPONSOR: Whitehall Robins
5 Giralda Farms, Madison, NJ 07940-0871
TYPE OF SUBMISSION: Original Submission **REVIEWER:** Sue-Chih Lee, Ph.D.

I. BACKGROUND:

NDA 20-589 for OTC use of Children's Advil oral suspension 100 mg/5 mL was approved on 6/27/96. The current NDA submission provides for two different formulations (fruit-flavored and grape-flavored, respectively) containing ibuprofen at 100 mg/2.5 mL to be marketed as Pediatric Advil Drops. The product will be indicated only for children aged 2 to 3 years old. The concentrated formulations allow for a smaller volume to be dosed, thus providing more convenient dosing for the target population. The dosing device (syringe) is provided with the 0.5 and 1 fl. oz. sizes of the product to afford accurate dosing.

Included in the current application is a bioequivalence study to compare the proposed product to the approved oral suspension (Protocol # AF-95-04), and the dissolution profiles of the proposed product.

II. FORMULATION and DOSAGE REGIMEN:

The Pediatric Advil Fruit-flavored Drops formulation is identical to the approved Children's Advil Fruit-flavored Suspension formulation except for the higher ibuprofen concentration. The Pediatric Advil Grape-flavored Drops formulation is identical to the Pediatric Advil Fruit-flavored Drops formulation except for the flavors and dyes. (See Table 1 for formulations.)

The proposed dose is 2.5 mL for children aged 2-3 yrs or weighing 24-35 lbs. Physician should be consulted for use in smaller children.

III. BIOEQUIVALENCE STUDY (Protocol # AF-95-04):

A Randomized, Single-Dose, Two-Way Crossover, Bioequivalence Study Comparing Ibuprofen 40 mg/mL Infant Drops and Children's Advil (Ibuprofen) 20 mg/mL Suspension

OBJECTIVES:

To demonstrate the bioequivalency between the proposed product (Pediatric Advil Drops, 100 mg/2.5 mL) and approved product (Children's Advil oral suspension, 100 mg/5 mL).

INVESTIGATOR AND LOCATION:

FORMULATIONS:

Treatment A (Test): Pediatric Advil (Fruit-flavored) Drops, 100 mg/2.5 mL x 5 mL
Treatment B (Reference): Children's Advil (ibuprofen) Suspension, 100 mg/5 mL x 10 mL
Both articles were manufactured in production scale.

STUDY DESIGN:

This is a randomized, single-dose (200 mg), two-way crossover bioequivalence study in normal, healthy adult subjects under fasting condition. The inclusion/exclusion criteria are provided. Twenty-six subjects (age: 27.0±8.0 yrs; wt: 69.6±10.1 kg; Table 2) participated and 24 subjects (12 M+12 F) completed the study. Each subject was randomly assigned a treatment sequence. After an overnight fast of 9 hours, subjects were given the first treatment with 240 mL of water and remained fasted for an additional 4 hours after dosing. Following a 7-day wash-out period, the subjects were then given the second treatment under similar fasted conditions..

Sample collections:

Blood samples were collected at pre-dose, and at 15, 30, 45, 60, 75 and 90 minutes and 2, 2.5, 3, 4, 6, 8, 10, 12 and 16 hours after dosing.

ASSAY:

DATA ANALYSIS:

The pharmacokinetic parameters determined were Cmax, AUC_{0-t}, AUC_{0-inf}, Tmax, T1/2, MRT, K_{el}, V_d and CL. The ANOVA model included the following factors: sequence, gender, subject(sequence*gender), period, treatment and treatment*gender interaction. If the effects of gender and treatment-by-gender interaction were significant ($p \leq 0.15$), additional analyses were performed for weight adjusted CL and Vd. Bioequivalence was evaluated by calculating the 90% confidence interval of the test/reference ratio from 2 one-sided tests. The number of subjects needed for this study was computed based on a power of 80%, significance level of 0.05 (one-sided) and root mean square error of 0.1419 to detect the difference in test/reference ratio as allowed for declaring BE.

Comment: As described above, when the effects of gender and treatment-by-gender interaction were significant ($p \leq 0.15$), additional analyses adjusting for weight were performed. The ANOVA model could have included body weight and weight-by-treatment interaction so that weight would not have been a confounding factor for gender related effects.

RESULTS:

The mean plasma concentration-time profile for each product after a single-dose administration is presented in Figure 1. The arithmetic mean estimates of the pharmacokinetic parameters along with the coefficient of variation are given below:

	AUC_{0-t} (μg.hr/mL)	AUC_{inf} (μg.hr/mL)	Cmax (μg/mL)
Test product	75.89 (21.5%)	76.63 (21.7%)	23.45 (19.2%)
Reference product	70.97 (21.5%)	71.60 (21.6%)	22.49 (16.2%)

The geometric means of AUC and Cmax are given in Table 4 along with their least square means obtained by analysis of ln-transformed paramters. The ratios of least square means (with 90% confidence intervals) for the ln-transformed AUC_{0-t}, AUC_{inf} and Cmax were 107.0% (102.1-112.1%), 107.1% (102.2-112.2%) and 103.8% (96.4-111.7%), respectively. These confidence intervals were all within the allowable range of 80-125%. The power for detecting a difference in test/reference ratio as large as allowed for declaring bioequivalency was determined to be >99.0%. The mean Tmax was 0.85 ± 0.50 hr for the reference product and 1.11 ± 0.93 hr for the test product. The sponsor indicated that the difference in Tmax was not clinically significant and concluded that the two products were bioequivalent. In addition, the sponsor also computed values of MRT, CL, Vd and Kel for the two products. The results indicated no unusal differences in these parameters between the two treatments.

Comments (not to be sent to the firm):

1. The BE study was conducted in adults. Conducting the study in the targeted population would have been more informative but would be difficult considering the product is for children under 3 years of age.

2. It is noted that the reference product in this study was not the formulation used in the clinical trial but was approved based on a bioequivalence study (NDA 19-833). In that pivotal study, it was demonstrated that Children's Advil oral suspension was bioequivalent to the two Boot's formulations (Brufen syrup and Rufen syrup) used in the clinical trial. The results showed that Children's Advil oral suspension had lower mean AUC and Tmax and a higher Cmax when compared to the two Boot's formulations.

Therefore, a somewhat higher AUC and longer Tmax for the test product in the current BE study is not of much concern. The significance of the higher Cmax for the subject product, however, is more difficult to determine especially when a product for small children is studied in adults.

The problem mentioned here is not unique to this submission. Situations also exist where a generic product was compared to the innovator's product which was not the formulation used in the actual clinical trials.

Gender effect:
The ANOVA analysis indicated there was no significant gender*formulation interaction for log-transformed Cmax and AUC values. Gender was a significant factor for these parameters, but further testing showed gender was not a significant factor when the parameters (CL and Vd) were adjusted for body weight.

Comment: For bioequivalence evaluations, gender*formulation interaction is of more concern than gender effect.

Adverse events:
Three adverse events were considered as probably drug related. Two of these events (nausea and stomach cramps) were experienced by Subject #30 in Period 1 after Treatment A and were resolved 5 hours after dosing. The third adverse event (vomiting) was experienced by the same subject in Period 2 after Treatment B which was resolved 12 minutes after dosing. This subject was then withdrawn from the study. The results of the laboratory tests indicated no clinically significant abnormal findings. Physical examinations revealed unexplained weight loss (17.5 lbs, or 10.5%) from Subject #1 and unexplained weight gain (19 lbs or 12.8%) for Subject #4.

IV. IN VITRO DISSOLUTION STUDIES:

Dissolution method:

Test specification:
Assay:

The dissolution data are provided for both fruit-flavored and grape-flavored formulations, each

in three container sizes (Tables 6 & 7). The results indicated that on average or greater (individual tablet:) was dissolved in 2 minutes. At 10 minutes, most of the tablets tested showed complete dissolution.

Comments:

1. Based on the study results, it appears that the specification should be

2. The dissolution test method for the subject product is similar to that for the approved Children's Advil oral suspension 100 mg/5 mL except for the paddle speed (50 rpm for Pediatric Drops and 25 rpm for Children's Advil oral suspension). We have discussed this matter with the chemist, Dr. Bart Ho. Apparently, the sponsor has changed the paddle speed for the current product to conform to the recently established USP dissolution test method for ibuprofen oral suspension.

V. COMMENTS:

1. The sponsor has demonstrated the bioequivalency of the Pediatric Advil Fruit-flavored Drops formulation (proposed formulation) to the Children's Advil Fruit-flavored Suspension formulation (approved product). The Pediatric Advil Grape-flavored Drops formulation is identical to the Pediatric Advil Fruit-flavored Drops formulation except for the flavors and dyes. Therefore, there is no need to conduct a BE study for the grape-flavored formulation.

2. The dissolution results for the proposed product in both fruit-flavored and grape-flavored formulations indicated that the dissolution specification should be A Q value of at least at 10 minutes appears more appropriate.

VI. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is approvable. Comment #2 should be communicated to the sponsor.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. _____
FT Initialed by Dennis Bashaw, Pharm.D. 4/22/97

CC:
NDA 20-812
HFD-550/Div.File 6/4/97
HFD-550/Holmes DLB 6/5/97

HFD-880 (DPE3 Div. File)
HFD-880 (TL - Bashaw)
HFD-880 (Reviewer - Lee)
Drug File (Barbara Murphy, CDR)
HFD-340 (Viswanathan)

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ON ORIGINAL

Table 1

Comparative Formulations

Component	% W/V (theoretical)		
	Pediatric Drops Grape Flavored Drops WH-0694-0002	Pediatric Fruit Flavored Drops WH-0694-0001	Children's Advil Fruit Flavored Suspension* WH-438-029
Ibuprofen, USP	4.000	4.000	2.000
Sucrose, NF			
Glycerin, USP (96%)			
Sorbitol Solution, USP			
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF			
Polysorbate 80, NF			
Sodium Benzoate, NF			
Citric Acid,USP (Hydrous)			
Xanthan Gum, NF			
Carboxymethylcellulose Sodium, USP			
Artificial Flavor			
Artificial Flavor			
Artificial Flavor			
Edetate Disodium, USP			
FD&C Blue No. 1			
FD&C Red No. 40			
Purified Water, USP (Deionized)			

(*) Approved for Rx use per NDA 19-833 and for OTC use per NDA 20-589.

TABLE 2

SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

	Subject No.	Product Code Period 1 2	Age (yrs)	Height (cm)	Weight (kg)	Frame	Race	Gender
	1	B A	20	176	75.5	Medium	Caucasian	Male
	2	A B	25	173	64.8	Small	Caucasian	Male
	3	A B	20	191	78.8	Small	Caucasian	Male
	4	B A	19	175	66.6	Small	Caucasian	Male
*	5	B A	32	185	83.7	Medium	Caucasian	Male
	6	A B	32	188	73.4	Medium	Caucasian	Male
	7	A B	43	185	75.2	Small	African-American	Male
	8	B A	20	180	81.9	Medium	Caucasian	Male
	9	B A	25	167	69.5	Small	African-American	Male
	10	A B	36	188	82.8	Medium	Caucasian	Male
*	11	B A	25	188	82.4	Medium	Caucasian	Male
	12	A B	22	191	81.5	Medium	Caucasian	Male
	13	A B	22	191	85.5	Medium	African-American	Male
	21	A B	42	160	60.8	Small	Caucasian	Female
	22	B A	40	175	61.7	Medium	Caucasian	Female
	23	A B	20	163	55.4	Small	Other	Female
	24	B A	20	175	74.7	Medium	Caucasian	Female
	25	B A	26	160	61.2	Medium	Caucasian	Female
	26	A B	40	178	70.2	Medium	African-American	Female
	27	A B	18	168	57.6	Medium	African-American	Female
	28	B A	29	165	63.9	Medium	African-American	Female
	29	B A	18	170	51.8	Small	African-American	Female
*	30	A B	32	168	54.0	Small	African-American	Female
	31	B A	28	170	59.0	Small	African-American	Female
	32	A B	18	173	68.4	Medium	African-American	Female
	33	B A	29	163	68.0	Medium	Other	Female
		Mean	27.0	175.6	69.55			
		± SD	8.00	10.12	10.142			
		N	26	26	26			
		CV%	29.7	5.8	14.6			

A = 5 mL of Ibuprofen 40 mg/mL Infant Drops
B = 10 mL of Children's Advil-(r) (Ibuprofen) 20 mg/mL Suspension

* Subject did not complete the crossover.
(r) denotes the registered trademark.
Subject ages are calculated as of Period 1 dosing.

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Table 2
Project Number : 960508
Ibuprofen in Plasma
Pharmacokinetic Parameters
(N = 24)

	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	Cmax (mcg/mL)
Whitehall-Robins (A)			
Mean (Arithmetic)	75.89	76.63	23.4514
CV	21.5	21.7	19.2
n	24	24	24
Children's Advil (B)			
Mean (Arithmetic)	70.97	71.60	22.4871
CV	21.5	21.6	16.2
n	24	24	24
Least-Squares Means			
Whitehall-Robins (A)	75.76	76.50	23.3376
Children's Advil (B)	70.77	71.40	22.3440
Ratio of Least-Squares Means (A/B)%	107.1	107.1	104.4
90% Confidence Intervals (A/B)%			
lower limit:	102.6%	102.6%	97.2%
upper limit:	111.5%	111.6%	111.7%
p-Value (ANOVA)			
A vs B	0.0131	0.0127	0.3046

See Statistics Report for details on calculation of parameters.
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Table 4
Project Number : 960508
Ibuprofen in Plasma
Pharmacokinetic Parameters
(N = 24)

	~~ln~~ AUC 0-t* (mcg·h/mL)	~~ln~~ AUCinf* (mcg·h/mL)	~~ln~~ Cmax* (mcg/mL)	MRT (h)	CL (mL/h)	Vd (mL)	tmax (h)	kel (1/h)	Half-life (h)
Whitehall-Robins (A)									
Mean (geometric)	74.313	75.017	23.01270	3.280	2722.5	9196.3	1.110	0.3016	2.335
CV	21.1	21.2	20.4	15.6	21.2	29.9	84.0	12.7	13.0
n	24	24	24	24	24	24	24	24	24
Children's Advil (B)									
Mean (geometric)	69.544	70.155	22.20369	3.103	2906.1	9297.8	0.848	0.3121	2.255
CV	20.5	20.5	16.4	13.4	19.7	14.2	59.0	13.0	12.3
n	24	24	24	24	24	24	24	24	24
Least-Squares Mean									
Whitehall-Robins (A)	74.260	74.965	22.88987	3.285	2722.1	9194.3			
Children's Advil (B)	69.400	70.013	22.06198	3.117	2910.7	9342.3			
Ratio of Least-Squares Means (A/B)%	107.0	107.1	103.8						
90% Confidence Intervals (A/B)%									
lower limit:	102.1%	102.2%	96.4%						
upper limit:	112.1%	112.2%	111.7%						
p-Value (ANOVA)									
A vs B	0.0208	0.0204	0.3973						

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Statistics Report for details on calculation of parameters.

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Table 5
Project Number : 960508
Ibuprofen in Plasma
Pharmacokinetic Parameters
(N = 24)

	CL (mL/h)		Vd (mL)	
	Males	Females	Males	Females
UNADJUSTED:				
Whitehall-Robins (A)				
Mean	2938.2	2506.7	10326.7	8065.9
CV	22.3	16.4	32.8	15.3
n	12	12	12	12
Children's Advil (B)				
Mean	3206.6	2605.6	10102.7	8492.9
CV	17.5	15.9	9.9	13.2
n	12	12	12	12
p-value for gender difference +	0.0193		0.0068	
ADJUSTED BY BODY WEIGHT:	CL (mL/h.kg)		Vd (mL/kg)	
	Males	Females	Males	Females
Whitehall-Robins (A)				
Mean	38.41	40.03	134.15	128.75
CV	21.1	14.9	29.0	12.2
n	12	12	12	12
Children's Advil (B)				
Mean	41.98	41.53	132.08	135.75
CV	17.4	12.7	7.8	11.2
n	12	12	12	12
p-value for gender difference +	0.7977		0.9848	

See Statistics Report for details on calculation of parameters.
+ Obtained from the Least-Squares Mean Difference between Genders

Figure 1

Project No. 960508

Mean Plasma Ibuprofen Concentrations

(Linear Plot)

(SD not shown)

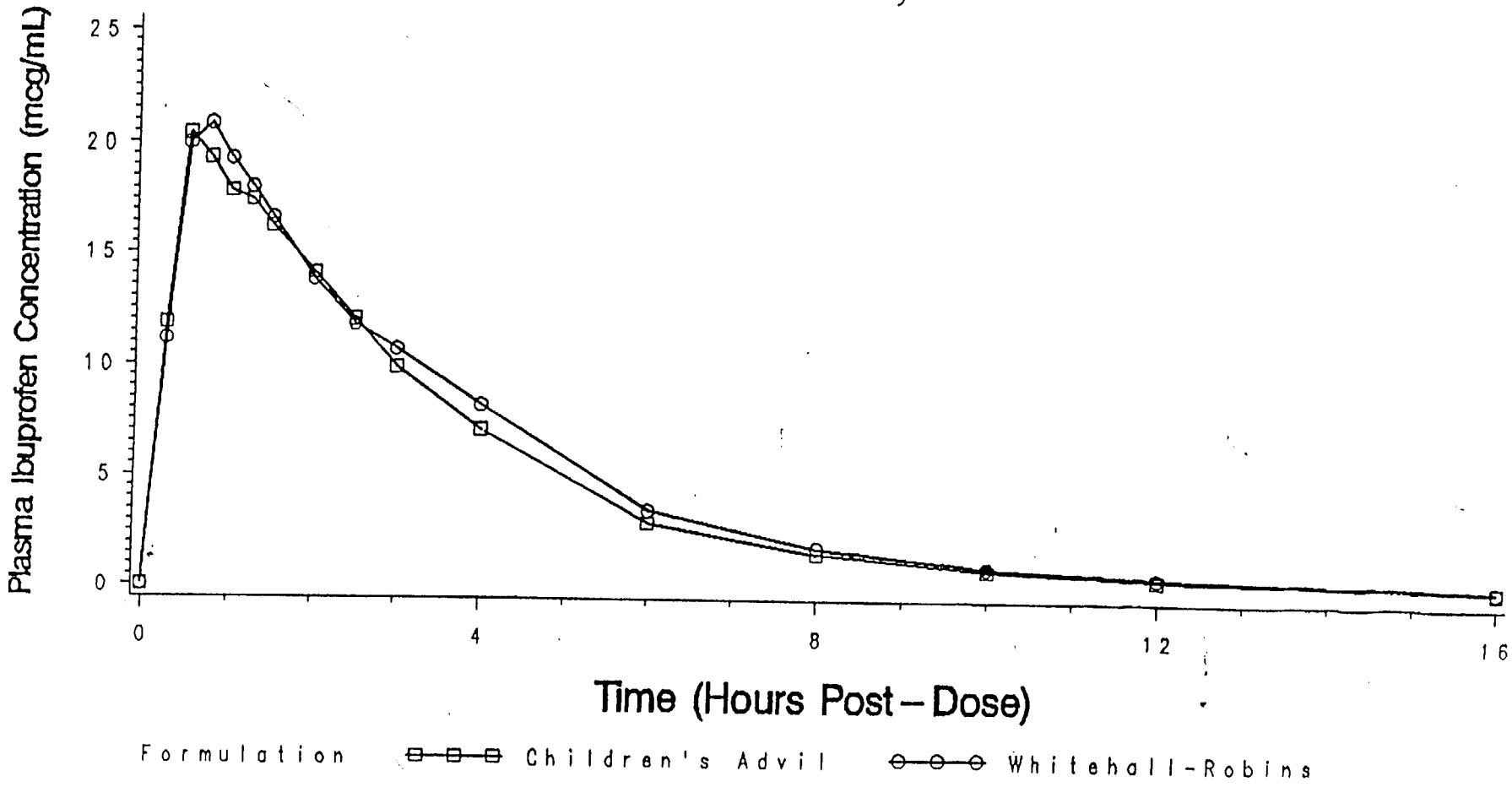


Table 6-a

Pediatric Advil Drops, Fruit

Formula: WH-0694-0001A
Lot #: R-95-5
Package: 213-01 (0.88 oz glass)
Fill: 0.25 oz
Condition: Initial
Period: Initial

	Time (min)	% Ibuprofen Dissolved									
	0	2	4	6	8	10	12	14	16	18	20
R1	0										
R2	0										
R3	0										
R4	0										
R5	0										
R6	0										
Avg	0	98	100	101	102	102	102	102	102	102	102
SD											

Dissolution Profile

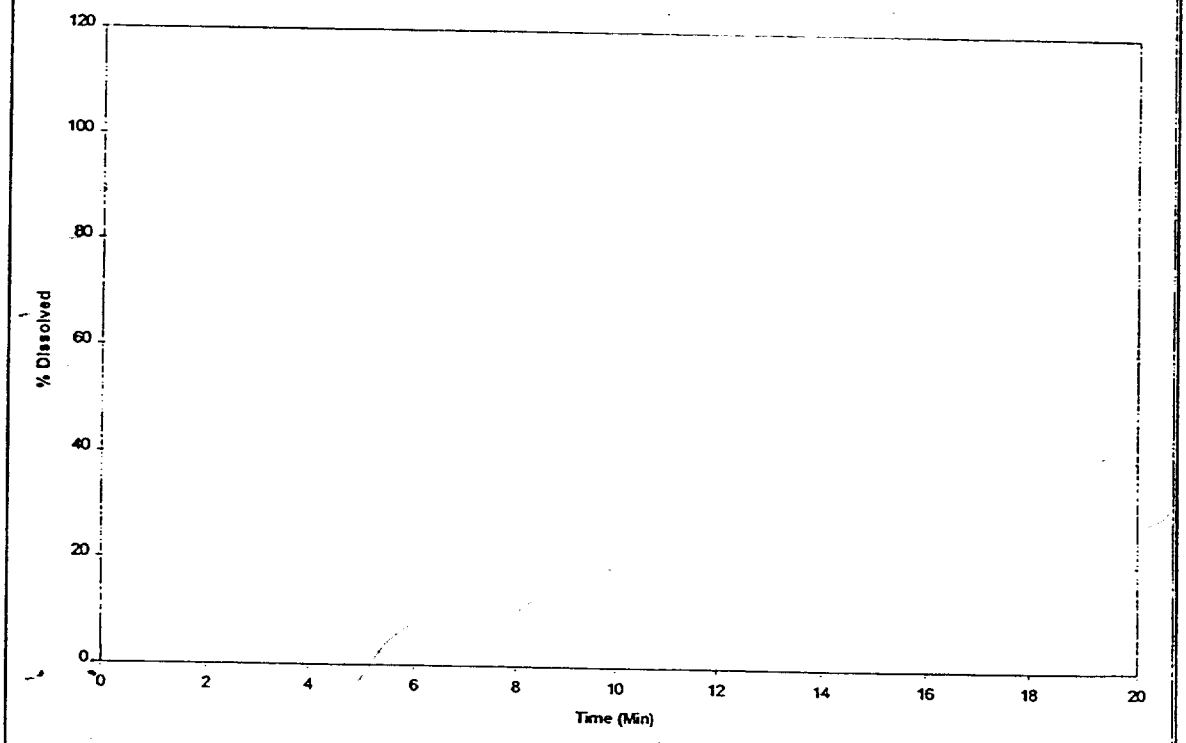


Table 6-b

Pediatric Advil Drops, Fruit

Formula: WH-0694-0001B
Lot #: R-95-6
Package: 562-01 (1 oz HDPE, Natural)
Condition: Initial
Period: Initial

	Time (min)						% Ibuprofen Dissolved				
Vessel #	0	2	4	6	8	10	12	14	16	18	20
R1	0										
R2	0										
R3	0										
R4	0										
R5	0										
R6	0										
Avg	0	94	96	97	98	98	98	98	98	98	98

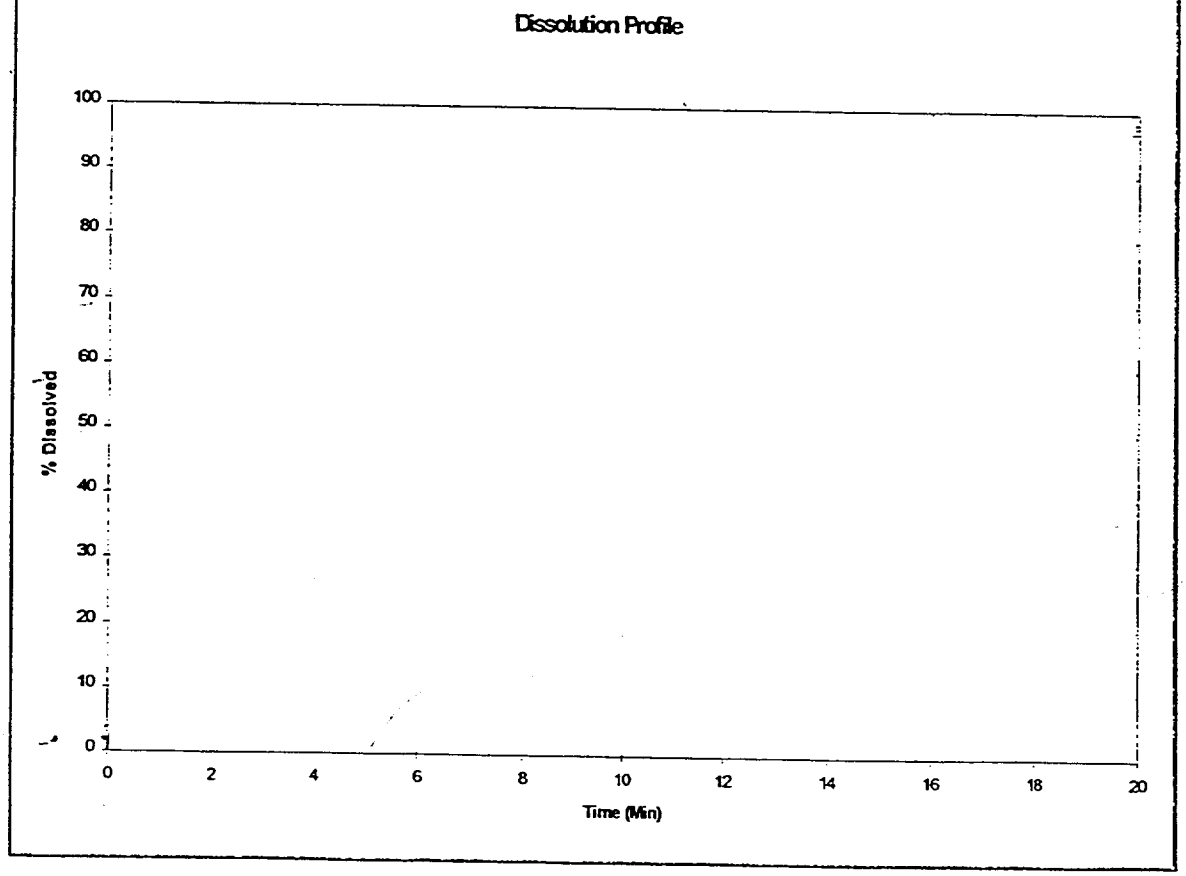


Table 6-C

Pediatric Advil Drops, Fruit

Formula: WH-0694-0001C
Lot #: R-95-8
Package: 405-01 (1 oz PP, Natural)
Condition: Initial
Period: Initial

	Time (min)						% Ibuprofen Dissolved				
	0	2	4	6	8	10	12	14	16	18	20
R1											
R2											
R3											
R4											
R5											
R6											
Avg	0	96	98	99	100	100	100	100	100	100	100
SD											

Dissolution Profile

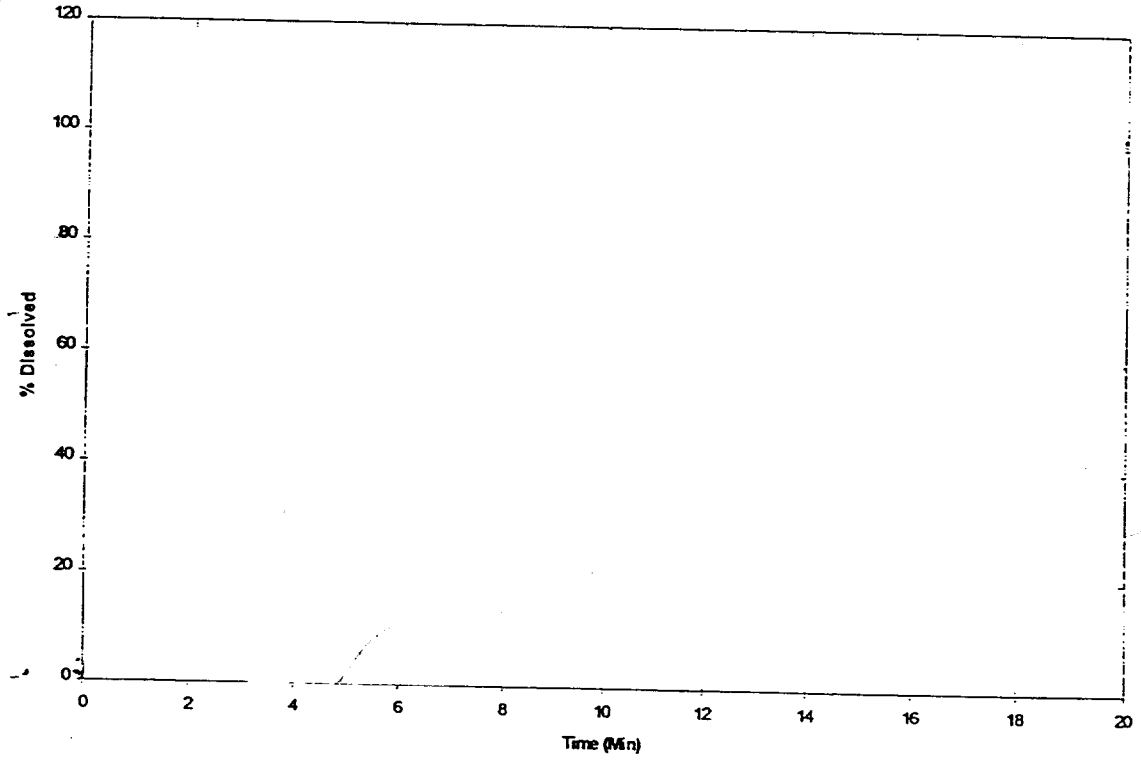


Table 7-a

Pediatric Advil Drops, Grape

Formula: WH-0694-0002A
Lot #: R-96-1
Package: 213-01 (0.88 oz glass)
Fill: 0.5 oz
Condition: Initial
Period: Initial

	Time (min)					% Ibuprofen Dissolved					
Vessel #	0	2	4	6	8	10	12	14	16	18	20
R1											
R2											
R3											
R4											
R5											
R6											
Avg	0	90	94	97	98	99	99	99	100	100	100
SD											

Dissolution Profile

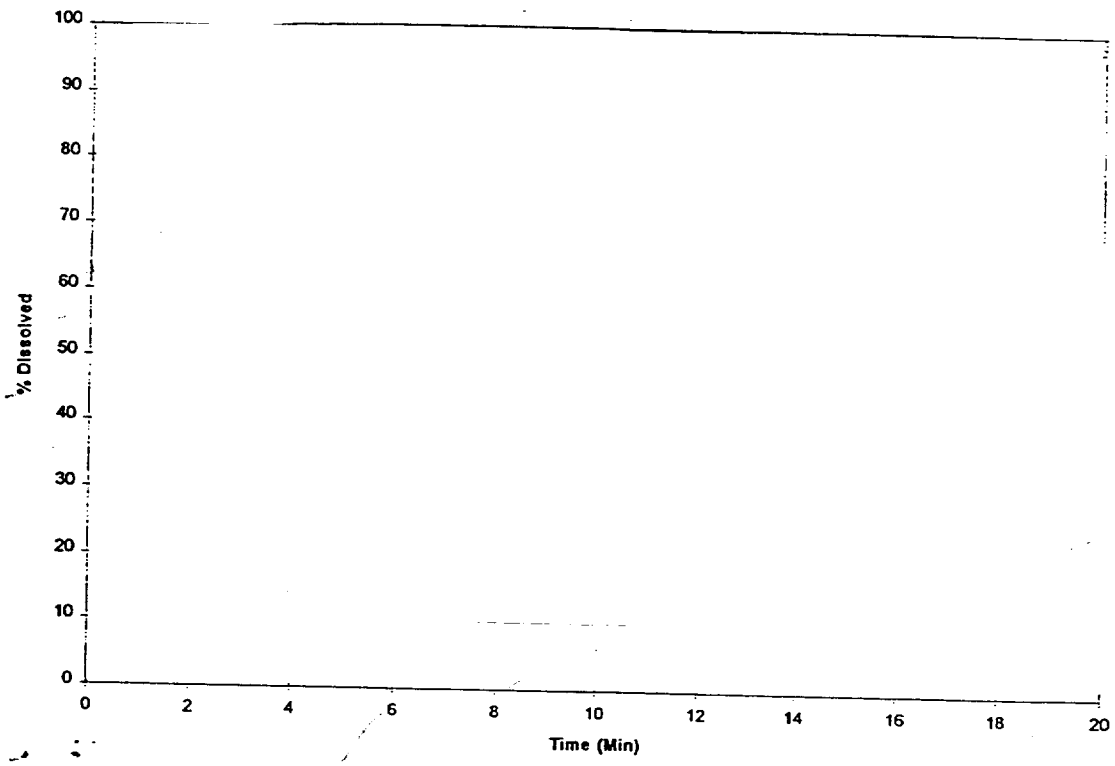


Table 7-b

Pediatric Advil Drops, Grape

Formula: WH-0694-0002B
Lot # R-96-2
Package: 566-01 (1 oz HDPE, Opaque)
Condition: Initial
Period: Initial

	Time (min)	% Ibuprofen Dissolved									
Vessel #	0	2	4	6	8	10	12	14	16	18	20
R1	0										
R2	0										
R3	0										
R4	0										
R5	0										
R6	0										
Avg	0	98	97	99	99	100	100	100	100	100	100

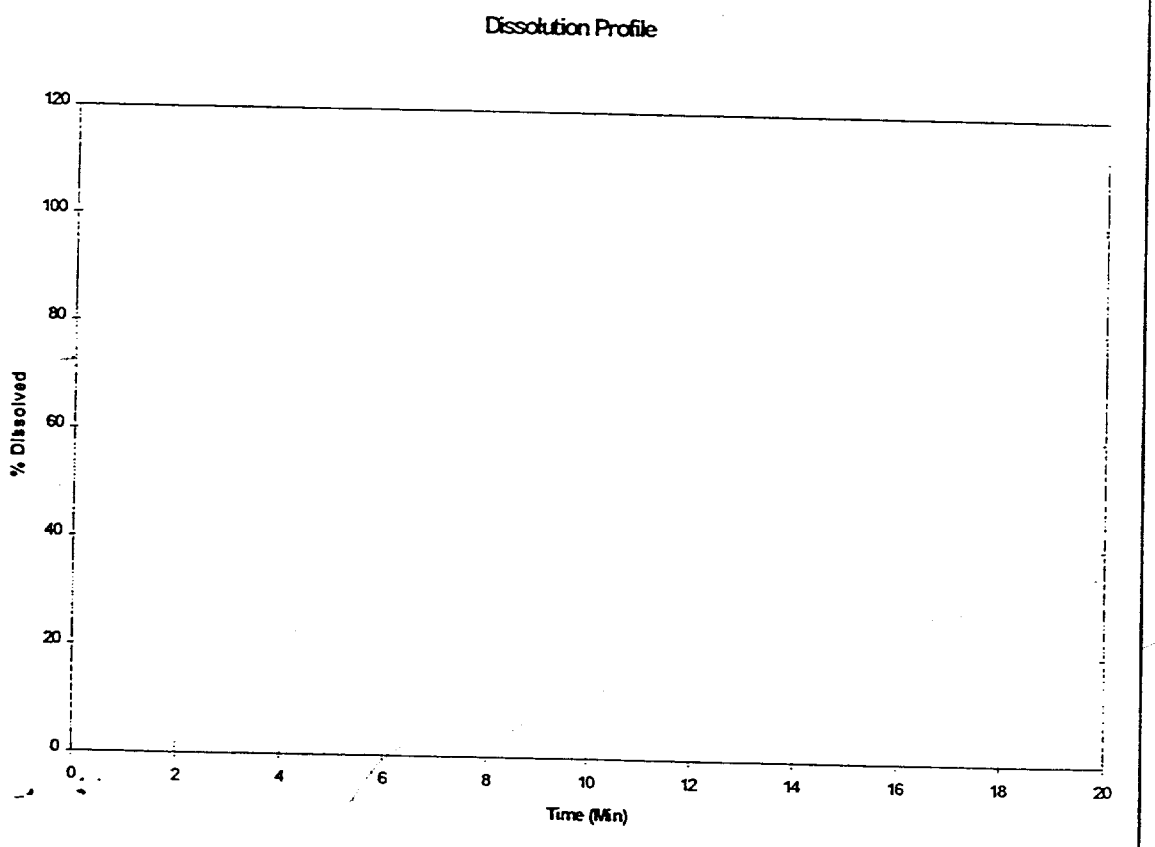


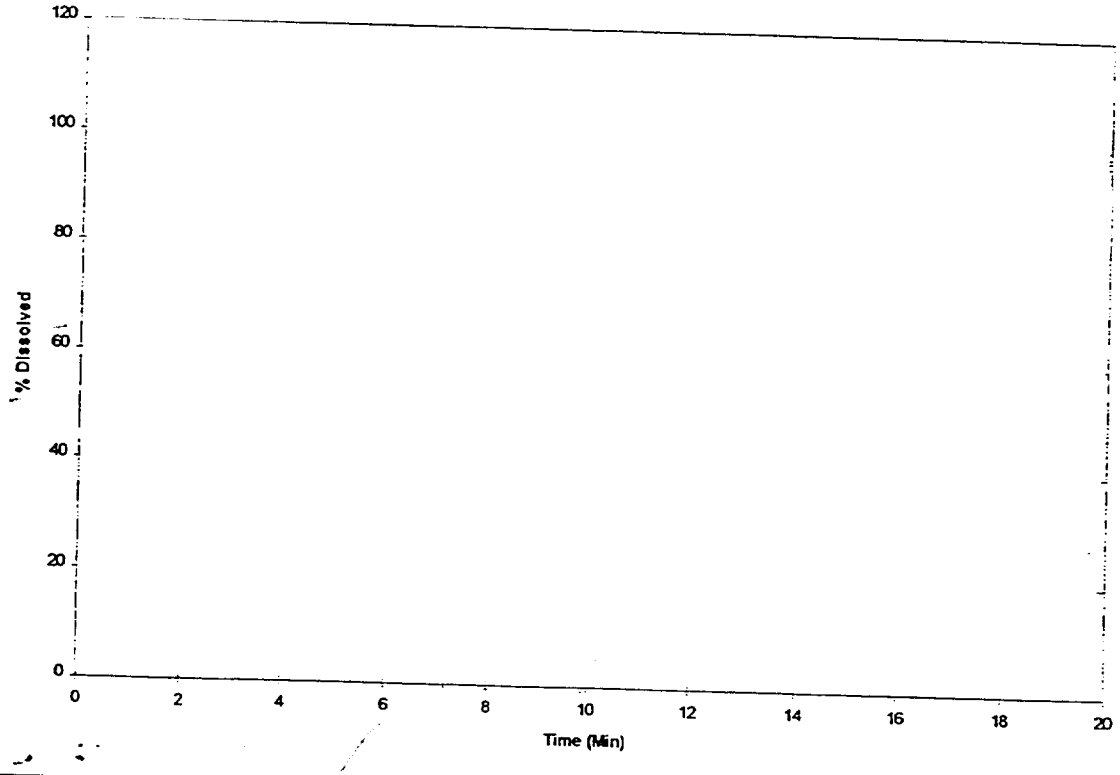
Table 7-C

Pediatric Advil Drops, Grape

Formula: WH-0694-0002C
Lot #: R-96-3
Package: 407-01 (1 oz PP, Opaque)
Condition: Initial
Period: Initial

	Time (min)										
Vessel #	0	2	4	6	8	10	12	14	16	18	20
	% Ibuprofen Dissolved										
R1	0										
R2	0										
R3	0										
R4	0										
R5	0										
R6	0										
Avg	0	94	95	97	98	98	98	98	98	98	98

Dissolution Profile



APPENDIX 1:

INDIVIDUAL PK DATA

Table
Project Number : 960508
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Whitehall-Robins (A)

Subject ID	Period	0	0.25	0.5	0.75	1	1.25	1.5	2
1	2	BLQ							
2	1	BLQ							
3	1	BLQ							
4	2	BLQ							
5	2	BLQ							
6	1	BLQ							
7	1	BLQ							
8	2	BLQ							
9	2	BLQ							
10	1	BLQ							
11	2	BLQ							
13	1	BLQ							
21	1	BLQ							
22	2	BLQ							
23	1	BLQ							
24	2	BLQ							
25	2	BLQ							
26	1	BLQ							
27	1	BLQ							
28	2	BLQ							
29	2	BLQ							
31	2	BLQ							
32	1	BLQ							
33	2	BLQ							
Arithmetic Mean		0.0000	11.1483	19.9799	20.8276	19.2835	18.0349	16.6580	13.7649
± SD		0.00000	7.80508	6.69300	5.42164	4.49987	4.54876	4.46558	4.04415
CV%		0.0	70.0	33.5	26.0	23.3	25.2	26.8	29.4
n		24	24	24	24	24	24	24	24

T -Time adjusted based on late blood draw

BLQ -Below Limit of Quantitation

BLQ -Value set to zero for pharmacokinetics and statistics

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Table D1
Project Number : 960508
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Whitehall-Robins (A)

Subject ID	Period	2.5	3	4	6	8	10	12	16
1	2								
2	1								
3	1								
4	2								
5	2								
6	1								
7	1								
8	2								
9	2								
10	1								
11	2								
13	1								
21	1								
22	2								
23	1								
24	2								
25	2								
26	1								
27	1								
28	2								
29	2								
31	2								
32	1								
33	2								
Arithmetic Mean		11.8065	10.7092	8.1693	3.4759	1.8174	0.9318	0.5216	0.1852
± SD		3.44745	3.59253	3.24330	1.44694	0.78655	0.42817	0.24591	0.12102
CV%		29.2	33.5	39.7	41.6	43.3	46.0	47.1	65.3
n		24	24	24	24	24	24	24	23

N -No Sample
BLQ -Below Limit of Quantitation

T -Time adjusted based on late blood draw

BLQ -Value set to zero for pharmacokinetics and statistics

PhAST CTAB 2.3-000

Table D2
Project Number : 960508
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Children's Advil (B)

Subject ID	Period	0	0.25	0.5	0.75	1	1.25	1.5	2
1	1	BLQ							
2	2	BLQ							
3	2	BLQ							
4	1	BLQ							
5	1	BLQ							
6	2	BLQ							
7	2	BLQ							
8	1	BLQ							
9	1	BLQ							
10	2	BLQ							
11	1	BLQ							
13	2	BLQ							
21	2	BLQ							
22	1	BLQ							
23	2	BLQ							
24	1	BLQ							
25	1	BLQ							
26	2	BLQ							
27	2	BLQ							
28	1	BLQ							
29	1	BLQ							
31	1	BLQ							
32	2	BLQ							
33	1	BLQ							
Arithmetic Mean		0.0000	11.8428	20.4140	19.3228	17.8613	17.4765	16.2711	14.0759
± SD		0.00000	5.57617	5.33888	3.48456	2.59370	3.99204	3.75477	3.62842
CV%		0.0	47.1	26.2	18.0	14.5	22.8	23.1	25.8
n		24	24	24	24	24	24	24	24

T -Time adjusted based on late blood draw

BLQ -Below Limit of Quantitation

BLQ -Value set to zero for pharmacokinetics and statistics

PhAST CTAB 2.3-000

Table D2
Project Number : 960508
Ibuprofen in Plasma
Concentrations (mcg/mL) at Each Sampling Time (h)
Formulation: Children's Advil (B)

Subject ID	Period	2.5	3	4	6	8	10	12	16
1	1								
2	2								
3	2								
4	1								
5	1								
6	2								
7	2								
8	1								
9	1								
10	2								
11	1								
13	2								
21	2								
22	1								
23	2								
24	1								
25	1								
26	2								
27	2								
28	1								
29	1								
31	1								
32	2								
33	1								
Arithmetic Mean		12.0051	9.8810	7.0566	2.9206	1.5402	0.7967	0.4413	0.1448
± SD		3.37621	2.96113	2.27361	1.09406	0.68298	0.41920	0.25321	0.11468
CV%		28.1	30.0	32.2	37.5	44.3	52.6	57.4	79.2
n		24	24	24	24	24	24	24	24

T -Time adjusted based on late blood draw

BLQ -Below Limit of Quantitation

BLQ -Value set to zero for pharmacokinetics and statistics

PhAST CTAB 2.3-000

21-08-1996

Table D3
Project Number : 960508
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Whitehall-Robins (A)

16:04

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	MRT (h)
1	2						
2	1						
3	1						
4	2						
5	2						
6	1						
7	1						
8	2						
9	2						
10	1						
11	2						
13	1						
21	1						
22	2						
23	1						
24	2						
25	2						
26	1						
27	1						
28	2						
29	2						
31	2						
32	1						
33	2						
Arithmetic Mean		75.89	76.63	99.06	23.4514	1.110	3.280
± SD		16.302	16.619	0.397	4.50851	0.9330	0.5121
CV%		21.5	21.7	0.4	19.2	84.0	15.6
n		24	24	24	24	24	24

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26-08-1996

Table D3
Project Number : 960508
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Whitehall-Robins (A)

Subject ID	Period	CL (mL/h)	Vd (mL)	Half-life (h)	kel (1/h)	kel Start (h)	kel Stop (h)
1	2						
2	1						
3	1						
4	2						
5	2						
6	1						
7	1						
8	2						
9	2						
10	1						
11	2						
13	1						
21	1						
22	2						
23	1						
24	2						
25	2						
26	1						
27	1						
28	2						
29	2						
31	2						
32	1						
33	2						
Arithmetic Mean		2722.5	9196.3	2.335	0.3016		
± SD		578.04	2749.34	0.3040	0.03830		
CV%		21.2	29.9	13.0	12.7		
n		24	24	24	24		

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Table D4
Project Number : 960508
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Children's Advil (B)

Subject ID	Period	AUC 0-t (mcg·h/mL)	AUCinf (mcg·h/mL)	AUC/AUCinf (%)	Cmax (mcg/mL)	tmax (h)	MRT (h)
1	1						
2	2						
3	2						
4	1						
5	1						
6	2						
7	2						
8	1						
9	1						
10	2						
11	1						
13	2						
21	2						
22	1						
23	2						
24	1						
25	1						
26	2						
27	2						
28	1						
29	1						
31	1						
32	2						
33	1						
Arithmetic Mean		70.97	71.60	99.13	22.4871	0.848	3.103
± SD		15.255	15.490	0.346	3.64453	0.5005	0.4163
CV%		21.5	21.6	0.3	16.2	59.0	13.4
n		24	24	24	24	24	24

PhAST PTAB 2.3-000

Table D4
Project Number : 960508
Ibuprofen in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Children's Advil (B)

Subject ID	Period	CL (mL/h)	Vd (mL)	Half-life (h)	kel (1/h)	kel Start (h)	kel Stop (h)
1	1						
2	2						
3	2						
4	1						
5	1						
6	2						
7	2						
8	1						
9	1						
10	2						
11	1						
13	2						
21	2						
22	1						
23	2						
24	1						
25	1						
26	2						
27	2						
28	1						
29	1						
31	1						
32	2						
33	1						
Arithmetic Mean		2906.1	9297.8	2.255	0.3121		
± SD		572.36	1323.15	0.2763	0.04070		
CV%		19.7	14.2	12.3	13.0		
n		24	24	24	24		

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