CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-472

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number:	**21-472**
Submission Date(s):	**12/14/01 and 09/10/02**
Generic Name:	**Ibuprofen**
Formulation; Strength(s):	**Liquigel Capsule, Ibuprofen (200mg)**
Indication:	**—**
Sponsor:	**Banner Pharmacaps Inc., High Point, North Carolina**
Relevant IND(s):	**62,553**
Submission Type; Code:	**505 (b)(2) NDA;3S**
Reviewer:	**Abimbola Adebowale Ph.D.**
Team Leader:	**Dennis Bashaw Pharm.D.**
OCPB Division:	**DPEIII**
OND division:	**HFD-550**

1 Executive Summary

In this application, the sponsor is seeking approval for ibuprofen (200mg) free-acid soft gelatin liquid filled capsules. This drug product is intended to be marketed over-the-counter (OTC) as an analgesic and antipyretic. The applicant states that their ibuprofen free-acid soft gelatin capsule is a modification of the currently marketed ibuprofen drug products. The ibuprofen capsules that are currently marketed employ either a — containing the ibuprofen free-acid or an ibuprofen potassium salt active ingredient.

Banner Pharmacaps inc. (BPI) consulted the office of generic drugs (OGD) on January 5th 2000 regarding the appropriate reference listed drug (RLD) for ibuprofen soft gelatin capsules, 200mg. A response, sent by OGD (dated April 5th, 2000) included the following statements:

1. Pharmaceutical Formulations, Inc. (PFI) ibuprofen capsules, 200mg, ANDA #. 74-782 contains ibuprofen as the free acid and has recently been designated as the RLD for capsule formulations containing ibuprofen as the free acid for the 200 mg strength.
2. Whitehall-Robins' Provel® (Ibuprofen Potassium Capsule) 200 mg, NDA #20-402, has been designated as the RLD for capsule formulations of ibuprofen potassium containing the equivalent of 200mg ibuprofen.

The applicant was unable to file an ANDA for their ibuprofen capsules using PFI's capsule (RLD), because this uses a solid core and a hard gelatin capsule rather than the soft gelatin and liquid core proposed by the applicant. Because solid capsules and soft gelatin, liquid filled formulations typically exhibit different bioavailability characteristics, the applicant believed that it would be inappropriate to demonstrate traditional bioequivalence between its product and the PFI product. Thus, an ANDA based on what would appear to be the only appropriate RLD was not feasible.

The applicant stated that they were also precluded from filing an ANDA based on the Provel® (now known as Advil®) liqui-gels® product because it contains a different active ingredient namely ibuprofen potassium. While the applicant believes that the two products should exhibit similar bioavailability since they are both soft gelatin capsules, section 505(j) of the Act prohibits the approval of an ANDA for a drug product that contains an active ingredient that is different from the listed drug.

Therefore based on the aforementioned, the applicant decided to submit this application as a 505(b) (2). This application is supported by two bioequivalence studies (ROO-133 and ROO-134). Study ROO-133 evaluated the bioequivalence of BPI's ibuprofen 200 mg capsule with that of Advil® Liqui-gels® 200 mg in healthy adults under fasting conditions. Study ROO-134 was an evaluation of the bioequivalence of both products in the fed state. The data from a comparative dissolution profile study (#PD01-287) was also included. The applicant is relying on the FDA's finding of safety and efficacy for approved Nuprin® [ibuprofen 200 mg (NDA 19-012)] tablets and Advil® [ibuprofen 200mg (NDA 20-402)] Liqui-gel® capsules to support the clinical portion of this application.

The data from study ROO-133 demonstrated that the estimated 90% confidence intervals for log transformed Cmax and AUC for ibuprofen capsules, 200 mg versus Advil liquigels 200mg in the fasting state were within the acceptable limits (80-125%). A longer mean Tmax (1.43 (0.88) hrs) was observed with the ibuprofen capsules when compared with the Advil® liquigels (0.78 (0.32) hrs). An evaluation of the exposure-response performance of other reference listed drug (RLD) products containing ibuprofen free-acid demonstrated that the distribution of the time to achieve effective plasma concentrations (range 0.33-4 hours) was consistent with that of the applicants' ibuprofen capsules, 200 mg. This indicates that effective plasma levels are obtained with the applicants' ibuprofen capsules and the attainment of Tmax is not necessary for clinical efficacy. Also the Tmax obtained for the ibuprofen capsules was consistent with that of the RLD's evaluated. Based on the aforementioned, the observed difference in Tmax is highly unlikely to be clinically relevant.

The data from study ROO-134 demonstrated that the estimated 90% confidence intervals for log transformed AUC for ibuprofen capsules, 200 mg versus Advil® liquigels® 200mg in the fed state were also within the acceptable limits (80-125%). However, the estimated 90% confidence intervals for log transformed Cmax for ibuprofen capsules, 200 mg versus Advil® liquigels® 200 mg in the fed state were outside the acceptable limits (80-125%). The mean Cmax of ibuprofen capsules 200 mg was ~ 12 % higher than that of the Advil liquigels in the fed state and the 90% CI at the upper level was 127.96 %. This higher mean Cmax is unlikely to be clinically significant from a safety perspective, since it is still ~30% lower than the mean Cmax obtained in the fasting state.

The applicant also conducted a comparative dissolution study between the test (ibuprofen capsules, 200 mg) and, the reference (Advil liquigels, 200 mg) products. The results of this study could not be fully evaluated because the applicant proposed [redacted] This was conveyed to the applicant by fax on September 6th, 2002. The applicant sent a response to the Agency on September 10th, 2002 that stated the following:

The choice of dissolution conditions was based on the following:

1. These are the conditions used in the USP when the development of the project occurred (USP 23-1995)

APPEARS THIS WAY
ON ORIGINAL

2. It was our understanding that these were the same conditions submitted by Sandoz for Provel NDA # 20-402
3. It was also our understanding that these were the same conditions submitted by Whitehall-Robins in the Advil NDA # 18-989.

The condition used in the USP that was referred to by the applicant was for Ibuprofen tablets, which is a different dosage form from their proposed liquigel capsule. Also the current USP 25-2002 for ibuprofen tablets specifies a different speed of 50 RPM. With regards to the NDA's the applicant has referred to, this cannot be discussed with them because it represents information on both test methods and specifications that are trade secret in nature. Therefore based on the aforementioned we sent a fax back to the applicant on October 2nd, 2002 requesting that they conduct dissolution studies at the lower speeds of 50, 75 and 100 RPM and, that the data should be submitted by December 1st, 2002. The applicant responded on October 3rd, 2002 via facsimile with an agreement to conduct the studies by the stated date.

1.1 Recommendation

The data demonstrating in-vivo bioequivalence of the proposed ibuprofen capsules to an approved reference product under fasting conditions is acceptable. Although a difference in T max was observed under fasting conditions this is highly unlikely to be clinically relevant based on previous exposure-response data.

The food effect study demonstrated an effect on the rate but not the extent of absorption. A comparison with the data obtained under fasting conditions indicated that this food effect is unlikely to be clinically relevant.

The dissolution method and specifications proposed by the applicant was found to be unacceptable due to insufficient data to support their choice of [redacted]. The applicant has since agreed to conduct dissolution studies at lower agitation speeds and submit this data to the Agency by December 1st, 2002. Until the Agency reviews this data and the dissolution method and specifications found acceptable, the currently described dissolution test is considered an interim method.

Abimbola Adebowale, Ph.D.
Pharmacokinetics Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Dennis Bashaw, Pharm.D.
Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

APPEARS THIS WAY
ON ORIGINAL

2 Table of Contents

3 Summary of CPB Findings

Introduction and Background: Ibuprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) that also possesses analgesic, and antipyretic activity. Numerous manufacturers have marketed ibuprofen (200 mg) in the USA as an OTC analgesic and antipyretic since 1984 for adults and, since 1995 for children. In the past, the relatively poor solubility of ibuprofen has precluded a soft gelatin, liquid filled capsule containing ibuprofen in the free-acid form. Ibuprofen 200mg capsule is a soft gelatin capsule of ibuprofen free acid solubilized in a mixture of PEG — Povidone and Vitamin E TPGS (tocopheryl polyethylene glycol succinate). The proposed indication is for use in temporarily relieving the minor aches and pains due to the common cold, headache, tooth ache, muscular aches, backache, minor pain — arthritis, menstrual cramps, — . It is intended for adults and children 12 years and older.

In the pharmacokinetic studies, analysis for ibuprofen was by ——— ——— with ——— —. The method validation results indicated that it was reproducible and accurate and, therefore acceptable for the intended use.

Clinical Pharmacology: This NDA is supported by two bioavailability studies (ROO-133 and ROO-134). Study ROO-133 was a randomized, single dose, two-way crossover bioequivalence study conducted in the fasting state. The treatments evaluated were Ibuprofen capsules, 200 mg (Banner Pharmacaps Inc.) and Advil® liquigel (ibuprofen 200 mg). The results of this study demonstrated that the two products were bioequivalent.

Biopharmaceutics: Study ROO-134 was a randomized, single dose, two-way crossover bioequivalence study conducted in the fed state. The treatments evaluated were Ibuprofen capsules, 200 mg (Banner Pharmacaps Inc.) and Advil® liquigel (ibuprofen 200 mg). The results

of this study demonstrated that the two products had a similar extent of absorption but not rate under fed conditions. Ibuprofen capsules had a higher Cmax than the Advil liquigels in the fed state, however this is unlikely to be clinically significant in terms of safety since the levels are much lower than that obtained in the fasted state which is the intended clinical usage conditions.

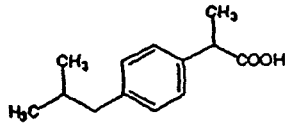
For the dissolution method proposed by the applicant the agitation speed value was —— RPM. This speed appears too high to allow for discriminating power and, to detect products with poor in vivo performance. Therefore, the applicant would need to provide adequate information to justify the choice of this speed. Also a preliminary review of the dissolution results suggest that a tighter specification of NLT —— (Q) instead of the proposed —— (Q) in 30 minutes, would be appropriate for ensuring lot-to-lot uniformity of the drug product. This was based on the fact that —— of ibuprofen was dissolved in 30 minutes.

The applicant also conducted a comparative dissolution study between the two products. Since the proposed dissolution method was not acceptable a preliminary review of this data was conducted. The data indicated that the mean % dissolved after 15 minutes was lower (mean = 86 %; range = —— for the ibuprofen capsules than for the Advil liquigels (mean = 97 %; range = —— However, both products had similar amounts dissolved —— from the 30-60 minutes sampling times. Since the mean percent dissolved for both products exceeded 85% at the first sampling time point of 15 minutes, analysis of the similarity (f2) factor by the applicant was not useful.

4 Review

4.1 General Attributes

Physical-chemical properties of ibuprofen:

Drug Name	Ibuprofen
Chemical Name	(±)-2-(p-isobutylphenyl) propionic acid
Structure	
Molecular formula	$C_{13}H_{18}O_2$
Molecular weight	206.29
pKa	5.4 (weak acid)
pH	Between 3.6 and 4.6
Description	White or almost white powder or crystals with a characteristic odor.
Solubility	Low solubility in water, Soluble in alcohol, acetone and chloroform. Soluble in an aqueous solution of alkali hydroxides and carbonates.

Formulation: Ibuprofen 200 mg capsule is a soft gelatin capsule of ibuprofen free-acid solubilized in a mixture of PEG [redacted] povidone and vitamin E TPGS (tocopheryl polyethylene glycol succinate) NF. A copy of the unit dose composition of the final product is inserted below:

Capsule Fill	
Ibuprofen [redacted] USP	200
Polyethylene Glycol [redacted], NF	
[redacted], USP (Povidone, USP)	
Vitamin E TPGS, NF	
Theoretical Total Fill Amount	
Capsule Shell	
Gelatin, NF	
[redacted] (sorbitol, sorbitan, mannitol)	
Purified Water, USP	
FD&C Blue #1	
FD&C Yellow #5	
Theoretical Total Shell Amount	
Theoretical Capsule Weight	

Dosage and Route of Administration:

One softgel capsule every 4-6 hours while symptoms persist. If symptoms do not respond to 1 softgel capsule, 2 softgel capsules may be used. Do not use more than 6 softgel capsules in 24-hours unless directed by a doctor.

Proposed mechanism of drug action(s):

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The exact mechanism of action of NSAIDs is not known, but anti-inflammatory effects are believed to be secondary to inhibition of synthesis and/or release of prostaglandins. Ibuprofen probably has a peripheral rather than central action as an analgesic. Antipyretic activity may be due to its action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation.

Therapeutic Indications:

The proposed indications are for the temporary relief of minor aches and pains due to: headache, backache, muscular aches, the common cold, minor pain of arthritis, menstrual cramps and toothache.

4.2 General Clinical Pharmacology

Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

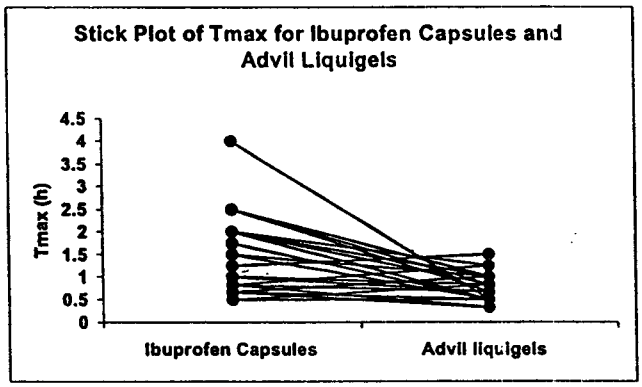
Yes, the active moiety, ibuprofen was appropriately identified and measured (refer to the Analytical Section in 4.6).

Are the pharmacokinetic parameters of Ibuprofen 200mg softgel capsule comparable to that of the Advil® Liqui-Gels® capsule 200mg?

The data reproduced in the table below show that the PK parameters are comparable for both products except Tmax in the fasting state and Cmax in the fed state.

	Mean (SD) Pharmacokinetic values					
	C_{max} (ng/mL)	$AUC_{(0-\infty)}$ ng*hr/mL)	$AUC_{(0-12)}$ ng*hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	MRT (hr)
Fasted State (Study ROO133) (N=24)						
Ibuprofen Capsules (test)	23044.43 (5333.15)	72929.54 (18143.73)	71152.54 (17380.03)	1.43 (0.88)	2.05 (0.27)	3.40 (0.62)
Advil Liquigels (ref.)	25552.49 (6845.93)	72360.63 (17186.51)	70770.67 (16525.79)	0.78 (0.32)	2.09 (0.32)	3.03 (0.33)
Fed State (Study ROO133) (N=17)						
Ibuprofen Capsules (test)	16917.89 (6642.24)	56950.35 (14357.63)	54796.24 (13563.40)	2.32 (1.26)	2.20 (0.37)	4.00 (0.91)
Advil Liquigels (ref.)	14398.67 (2743.35)	57371.88 (13356.27)	55320.82 (12450.28)	2.13 (0.88)	2.16 (0.33)	4.01 (0.65)

The Tmax for the test product although within 1.5 hours is about 2 fold higher than that of the reference product. Inserted below is the stick plot of the individual Tmax values



showing that one subject (#21, 30 year old male Caucasian weighing 94.2 kg) had an extreme Tmax value of 4 hours for the test product. The mean values with this subject included were 1.43 (0.88) h and 0.78 (0.32) h for ibuprofen capsules (test) and Advil liquigels (reference) respectively. The median values with this subject included were also very different (1.13 and 0.75 h respectively for Test and Reference). Recalculation of the Tmax excluding the data from subject # 21 resulted in mean values of 1.32 (0.70) h and 0.79 (0.32) h for test and reference products respectively, suggesting that there were probably other factors contributing to the differences in Tmax. The median values were however closer, 1.00 and 0.83 h for test and reference products respectively.

This difference in Tmax was further evaluated for its clinical relevance using previous exposure-response data by assessing the time to achieve minimum effective plasma concentrations (6-8 mcg/mL) of other reference listed products containing ibuprofen free-acid and comparing this with that of the test product. Inserted below are representative graphs showing the distribution of the individual data and the cumulative % for the ibuprofen capsules, Advil liquigels (their reference) and another reference listed product.

What is the inter- and intra-subject variability of PK parameters in volunteers, and what are the major causes of variability?

The intra-subject and inter-subject variability expressed as the CV % variability for the healthy adult subjects following the administration of Advil Cold and Sinus Liqui-gels are reproduced in the table below:

Table: Inter-subject and Intra-subject Variability of Ibuprofen from the two drug products

Type of Variability/PK Parameters	Coefficient of Variation (CV%)			
Intra-subject	**Study # ROO-133 (fasted)**		**Study # ROO-134 (fed)**	
AUC inf	6.35		12.15	
AUC t	6.38		12.09	
Cmax	16.52		16.09	
Inter-subject	**Test**	**Reference**	**Test**	**Reference**
AUC inf	24.88	23.75	25.21	23.28
AUC t	24.43	23.35	24.75	22.51
Cmax	23.14	26.79	39.26	19.05
Tmax	61.19	41.15	54.23	41.27
T1/2	13.20	15.16	16.66	15.44

The data in the table above indicate that Tmax had a higher inter-subject variability for the test product compared to the reference product in the fasted and fed states. Also the Cmax had a higher inter-subject variability for the test product compared to the reference product in the fed state. This higher variability could have contributed to the differences in Tmax and Cmax obtained between the two products.

4.3 General biopharmaceutics

Are the Ibuprofen 200 mg capsules made by BPI bioequivalent to the approved reference product (Advil Liquigels)?

Yes the two formulations are bioequivalent. This is shown in the table inserted below obtained from the bioequivalence study (# ROO-133) conducted under fasting conditions:

The data in the table above demonstrate that the confidence intervals for the log trans

The following tables summarize the results of the analyses performed on the pharmacokinetic parameters.

VS.

bioe

Ibuprofen	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
Test Product Geometric Mean	22611.47	69441.33	71099.22
Reference Product Geometric Mean	24724.70	68917.63	70391.27
% Ratio	91.45	100.76	101.01
90% Confidence Interval	(84.24, 99.29)	(97.61, 104.01)	(97.87, 104.25)

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The following tables summarize the results of the analyses performed on the pharmacokinetic parameters.

Ibuprofen	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
Test Product Geometric Mean	15756.56	53174.94	55190.30
Reference Product Geometric Mean	14044.85	54218.89	56159.56
% Ratio	112.19	98.07	98.27
90% Confidence Interval	(98.36, 127.96)	(92.81, 103.64)	(92.95, 103.9)

The data in the table above indicate that ibuprofen capsules 200 mg are not bioequivalent to Advil liquigels under fed conditions because the 90% CI for the ratio of population geometric means of Cmax based on log transformed data is not contained within the Agency criteria of 80-125%. However, the 90% CI for the ratio of population geometric means of AUC were contained within the Agency criteria of 80-125%, indicating that there was no food effect on the extent of absorption. The observed increase in mean Cmax of ibuprofen capsules was only ~12.2% higher than that of Advil liquigels, but lower (~30%) than the Cmax obtained in the fasted state. This implies that the food effect is highly unlikely to be of any clinical relevance. This food effect is also relatively small (< 20 %). Also the proposed labeling for the ibuprofen capsules 200 mg does not recommend administration with food except when stomach upset occurs, which is consistent with the current labeling for the approved reference Advil liquigel capsule.

Do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The proposed dissolution method and specifications used for the Advil Cold and Sinus Liquid Suspension is reproduced in the Table below:

Table: Dissolution Method and Specifications

Apparatus	USP Apparatus I Type- Baskets
Speed	— RPM
Media	900 mL 50mM phosphate buffer, pH 7.2
Temperature	37.0°C ± 0.5°C
Specification	Q = — in 30 minutes

Since the subject drug product contains solubilized active ingredients in a soft gelatin capsule, one would expect dissolution to be complete and rapid after the gelatin shell ruptures. The proposed speed of — rpm appears too high to allow for discriminating power to detect products with poor in vivo performance. However, the dissolution method for the Advil liquigels was developed to be consistent with the USP requirements for dissolution testing of immediate release ibuprofen tablets (USP XXII, 1990). The current USP requirements

considered after [redacted] dissolution of both products and this method is most suitable for dissolution comparisons when three to four or more dissolution time points are available. Therefore, the utilization of the f2 value [redacted] obtained using all the sampling time points is not useful since they do not meet the standard for the test.

4.4 Analytical

How was ibuprofen isolated and measured in plasma in the clinical pharmacology and biopharmaceutics studies?

[redacted]

Were the analytical methods used for the determination of ibuprofen in biological fluids validated?

Yes, the method validation results (see details in table below) demonstrate that the analytical method used for the quantitative determination of ibuprofen in human plasma was reliable and reproducible for the intended use. Reproduced in the Table below are the analytical validation results for ibuprofen:

Table: Analytical Validation Results

Compound	**Ibuprofen**
Accuracy	[redacted]
Precision (CV%)	
Standard Curve Range	
Sensitivity (LOQ)	
Selectivity	
Recovery (mean ± CV%)	
Stability	

5 Appendix

5.1 Proposed Annotated labeling

5.2 Individual Study Reviews

5.2.1 NDA 21-472: Study No. ROO-133 Synopsis

Title of Study: Single dose bioequivalence study of ibuprofen liquid solution in soft gelatin capsules under fasting conditions

Investigator: [redacted]

Study Centers: [redacted] Analytical Site: [redacted]

Study Period: Period I: June 6, 2001
Period II: June 20, 2001

Objectives: To evaluate the bioequivalence of ibuprofen capsules, 200 mg by Banner Pharmacaps, Inc. with that of Advil® Liqui-gels® 200 mg Capsules distributed by Whitehall-Robins healthcare following a single oral dose (1x200 mg capsule) in healthy adult volunteers under fasting conditions.

Study Design: A randomized, single dose, two-way crossover study

Number of Subjects (planned/analyzed): The study was completed by 24 of 26 subjects enrolled Subject 02 elected to withdraw prior to Period II secondary to car problems. Subject 06 was dropped by the clinical investigators prior to Period II dosing, secondary to tonsilitis. There were 14 males and 12 females. The majority of the subjects were Caucasians (92.3%). There was 1 American Indian (#16) and 1 Black subject (# 02). Demographics are reproduced in the table below:

	Females	Males	All
Age			
Mean	33	26.9	29.7
SD	13.8	12.4	13.2
Range	18-61	18-66	18-66
Weight			
Mean	68	77.9	73.3
SD	10.5	11.0	11.7
Range	50.7-88.3	64.3-97.8	50.7-97.8
Height			
Mean	165.7	174.5	170.5
SD	8.0	5.0	7.8
Range	154.9-177.8	162.6-182.9	154.9-182.9

The applicant stated that weight range was not more than ± 15% from normal for height and body frame as per the "Desirable Weights for Men or Women-1983 Metropolitan Height and Weight table".

Race: The number of subjects in each racial group was insufficient to conduct any meaningful analysis.

Treatments: Subjects received one of two treatments following an overnight fast (# of hours not clear from submission report): *Treatment A:* Ibuprofen Capsules, 200 mg (Banner Pharmacaps, Inc. Lot No. — 21020622-C; Exp.date: none shown. DOM: Feb. 2001, batch size ——— capsules); *Treatment B:* Advil Liqui-gels 200 mg Capsules (Whitehall-Robins Healthcare Lot No. 3002475, Exp. Date: 7/02). Capsules were administered with 240 mLs of water. There was a seven-day washout period between periods. Subjects fasted for 4.25 hours following dose administration. Subjects consumed 240mL of water 2-hours post-dosing.

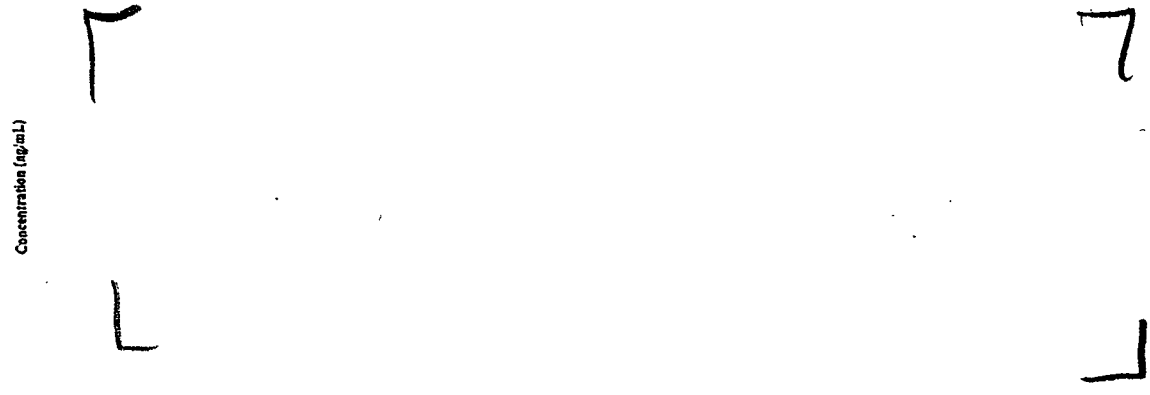
Pharmacokinetic Blood Sampling: Blood samples were taken by venipuncture or by catheter at the following times: pre-dose (0 hr), and 0.167, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post-dose. Each blood sample was centrifuged at — rpm and — for — minutes and the plasma pipetted into ——— The plasma samples were placed in the — within — hour of collection and stored at — until transferred to ——— for analysis of ibuprofen.

Analytical Methodology: ———

[ ]

Pharmacokinetic Parameters and Statistical Methods: All pharmacokinetic parameters were derived using WinNonlin ® version 3.1 (Scientific Consulting, Inc.). Statistical analysis was done using SAS®, Version 8.1 for windows. AUCL, AUCI, and Cmax (both log transformed and untransformed) were analyzed for differences among treatments using analysis of variance (ANOVA) containing factors for sequence of treatments, subjects within sequence, periods and treatment was utilized in comparing the

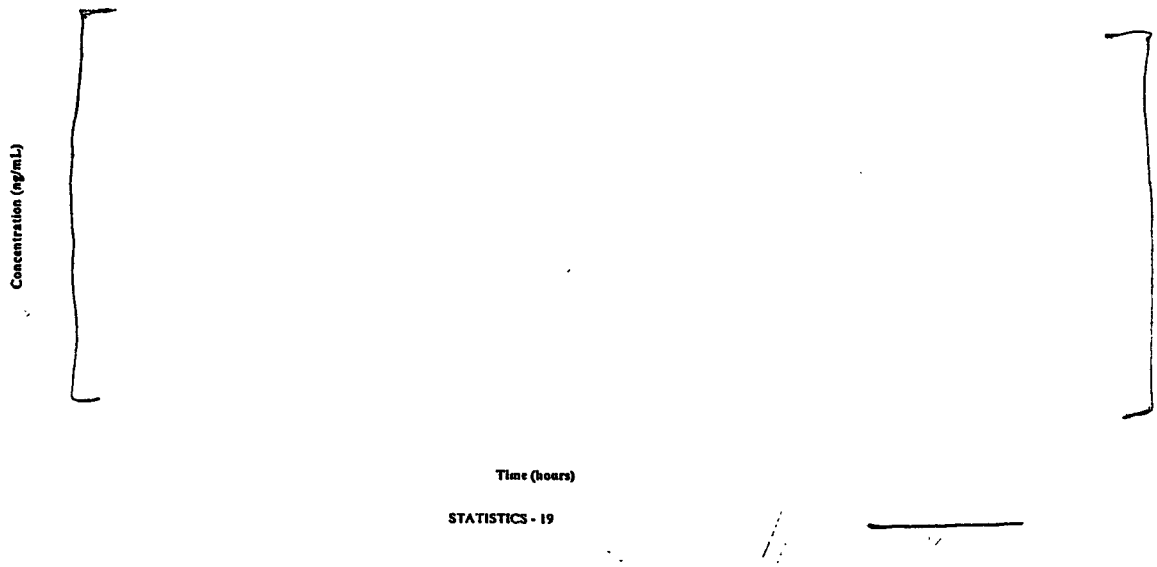
Figure 2.2
Plasma Concentration (0 - 12 hours) for Each Subject - Reference Product
N=24



difference between test and reference. A 90% two-sided confidence interval about the ratio of the mean test value to mean reference value was calculated for AUC_{0-12}, AUC_{inf} and Cmax.

Results:
Spaghetti plots of plasma-concentration time profiles

Figure 2.1
Plasma Concentration (0 - 12 hours) for Each Subject - Test Product
N=24



The plasma concentrations for both test and reference were all > than the effective concentration (6 mcg/mL) for Ibuprofen, although it appeared that the test product had lower concentrations generally. Subject #08 (42 year old Caucasian female subject weighing 52.5 kg) had pre-dose concentrations of ibuprofen for period I and II however, the percent ratio (0 hour/Cmax were 0.79 and 1.07 % respectively) was < 5% of the Cmax values obtained in this subject therefore this subject's data was included in all PK calculations.

Pharmacokinetic Parameters:

Summary of Mean Pharmacokinetic Parameters for Ibuprofen (n=24)

Parameters	Formulation (Arithmetic Mean ±SD)	
	Banner Pharmacaps (test)	Advil Liquigel (reference)
C_{max} (ng/mL)	23044.43 (5333.15)	25552.49 (6845.93)
$AUC_{(0-\infty)}$ ng*hr/mL)	72929.54 (18143.73)	72360.63 (17186.51)
$AUC_{(0-12)}$ ng*hr/mL)	71152.54 (17380.03)	70770.67 (16525.79)
T_{max} (hr)	1.43 (0.88)	0.78 (0.32)
$T_{1/2}$ (hr)	2.05 (0.27)	2.09 (0.32)
Kel (1/h)	0.344 (0.05)	0.339 (0.05)
MRT (hr)	3.40 (0.62)	3.03 (0.33)

The following tables summarize the results of the analyses performed on the pharmacokinetic parameters.

Ibuprofen	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
Test Product Geometric Mean	22611.47	69441.33	71099.22
Reference Product Geometric Mean	24724.70	68917.63	70391.27
% Ratio	91.45	100.76	101.01
90% Confidence Interval	(84.24, 99.29)	(97.61, 104.01)	(97.87, 104.25)

The power of the ANOVA was 99.3 % for Cmax and 100 % for AUC.

Safety Results: The applicant reported that 4 AE's were reported by one subject (#06) over the course of the study. These were headache, swollen glands, sore throat, and tonsillitis. These were considered to be unrelated to study investigation by the clinical investigator. However, subject 06 was dropped prior to Period dose II secondary to tonsillitis.

Conclusions: An evaluation of the confidence intervals for the log transformed AUC inf and Cmax for the comparison of the Banner Pharmacaps VS. Advil Liquigels were within the Agency acceptance criteria of 80 – 125 %. Therefore it can be concluded that the Banner Pharmacaps are BE to the Advil Liquigels under fasted conditions.

5.2.2 NDA 21-472: Study No. ROO-134 Synopsis

Title of Study: Single dose bioequivalence study of ibuprofen liquid solution in soft gelatin capsules under non-fasting conditions

Investigator:

Study Centers: Clinical Site: Analytical Site:

Study Period: Period I: June 12, 2001; Period II: June 19, 2001

Objectives: To evaluate the bioequivalence of ibuprofen capsules, 200 mg by Banner Pharmacaps, Inc. with that of Advil® Liqui-gels® 200 mg Capsules distributed by Whitehall-Robins healthcare following a single oral dose (1x200 mg capsule) in healthy adult volunteers under non-fasting conditions.

Study Design: A randomized, single dose, two-way crossover study

Number of Subjects (planned/analyzed): The study was completed by 17 of 18 subjects enrolled Subject # 13 elected to withdraw prior to Period II dosing. There were 7 males and 11 females. All of the subjects were Caucasians. Since all the subjects were Caucasian no analysis on the effect of race could be conducted. Demographic data is reproduced in the table below:

	Females	Males	All
Age			
Mean	31.3	22.4	27.8
SD	12.1	3.4	10.5
Range	21-53	18-27	18-53
Weight			
Mean	69.3	81.8	74.2
SD	8.6	12.9	11.9
Range	59.3-87.9	65.2-105.5	59.3-105.5
Height			
Mean	165.5	178.9	170.7
SD	7.8	10.1	10.8
Range	149.9-177.8	165.1-193.0	149.9-193.0

Treatments: Subjects received one of the following two treatments (# of hours not clear from submission report) according to a randomized crossover design: *Treatment A:* Ibuprofen Capsules, 200 mg (Banner Pharmacaps, Inc. Lot No. — 21020622-C; Exp.date: none shown. DOM: Feb. 2001); *Treatment B:* Advil Liqui-gels 200 mg Capsules (Whitehall-Robins Healthcare Lot No. 3002475, Exp. Date: 7/02). Subjects were dosed 30 minutes after the initiation of a standardized, high fat breakfast preceded by an overnight fast. There was a seven-day washout period between doses. The breakfast consisted of the following: 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 2-4 oz. of hash brown potatoes, 6oz. (180 mL) of orange juice and 8oz. (240 mL) of whole milk. This corresponds to the modified FDA high fat diet (originally developed by the Office of Generic drugs). In terms of the nutritional content this diet has Protein (28.9g), Fat (26.7g) and Carbohydrate (72.9g). The total number of calories is 648 representing 75% of the official FDA high fat diet (i.e. 859 calories). Following consumption of the high fat breakfast, subjects were sequentially dosed at 1-minute intervals. Drug administration was administered with 240 mL of room temperature water. Subjects fasted for 4.25 hours following dose administration. Subjects consumed 240mL of water 2-hours post-dosing.

Pharmacokinetic Blood Sampling: Blood samples were taken by venipuncture or by catheter at the following times; pre-dose (0 hr), and 0.167, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post-dose. Each blood sample was centrifuged at [redacted] minutes and the plasma pipetted into [redacted] The plasma samples were placed in the freezer within 1 hour of collection and stored at ~-20°C until transferred to [redacted] for analysis of ibuprofen.

Analytical Methodology: [redacted]

Pharmacokinetic Parameters and Statistical Methods: All pharmacokinetic parameters were derived using WinNonlin ® version 3.1 (Scientific Consulting, Inc.). Statistical analysis was done using SAS®, Version 8.1 for windows. AUCL, AUCI, and Cmax (both log transformed and untransformed) were analyzed for differences among treatments using analysis of variance (ANOVA) containing factors for sequence of treatments, subjects within sequence, periods and treatment was utilized in comparing the difference between test and reference. A 90% two-sided confidence interval about the ratio of the mean test value to mean reference value was calculated for AUC_{0-12}, AUC_{inf} and Cmax.

Results:

Spaghetti plots of plasma-concentration time profiles

Figure 2.1
Plasma Concentration (0 - 12 hours) for Each Subject - Test Product
N=17

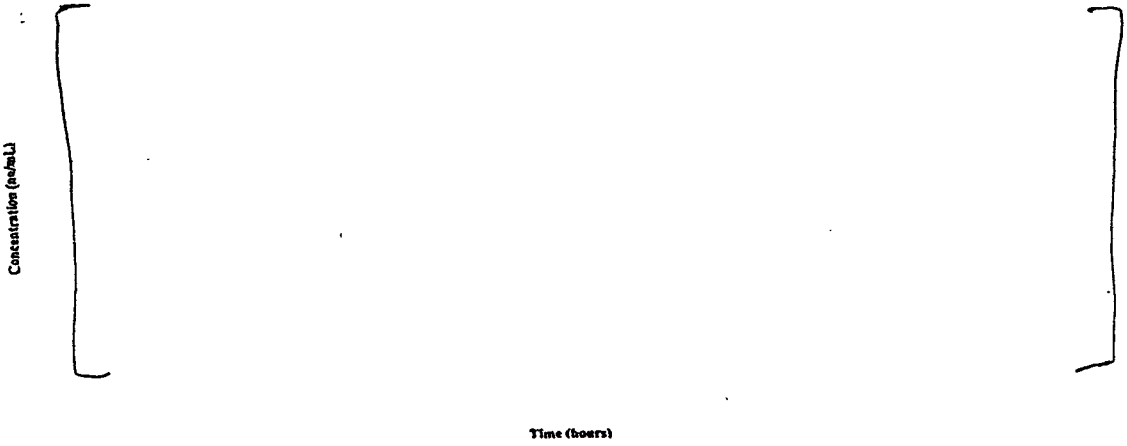
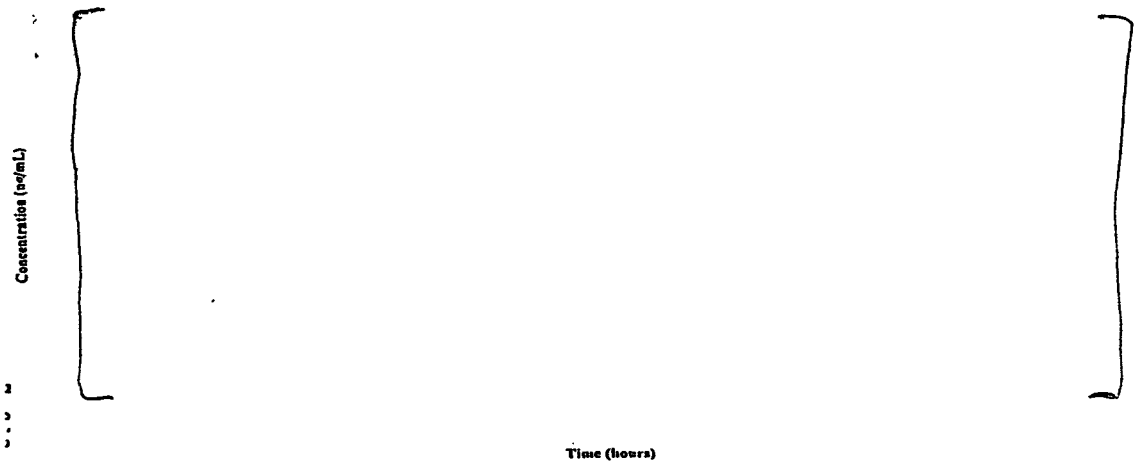


Figure 2.2
Plasma Concentration (0 - 12 hours) for Each Subject - Reference Product
N=17



The plasma concentrations for both test and reference were all > than the effective concentration (6 mcg/mL) for Ibuprofen, although it appeared that the test product had higher concentrations generally. Subject #14 (21 year old Caucasian female subject weighing 59.3 kg) had pre-dose concentrations of ibuprofen for period II with the reference product however, the percent ratio (0 hour/Cmax was 0.94 %) was < 5% of the Cmax values obtained in this subject therefore this subject's data was included in all PK calculations. The applicant gave no reason for this pre-dose concentration. The profiles indicate a lag time in absorption of 0.5-1 hour, for both test and reference products.

Pharmacokinetic Parameters:

Summary of Mean Pharmacokinetic Parameters for Ibuprofen (n=24)

Parameters	Formulation (Arithmetic Mean ±SD)	
	Banner Pharmacaps (test)	Advil Liquigel (reference)
C_{max} (ng/mL)	16917.89 (6642.24)	14398.67 (2743.35)
$AUC_{(0-\infty)}$ ng*hr/mL)	56950.35 (14357.63)	57371.88 (13356.27)
$AUC_{(0-12)}$ ng*hr/mL)	54796.24 (13563.40)	55320.82 (12450.28)
T_{max} (hr)	2.32 (1.26)	2.13 (0.88)
$T_{1/2}$ (hr)	2.20 (0.37)	2.16 (0.33)
Kel (1/h)	0.32 (0.05)	0.33 (0.05)
MRT (hr)	4.00 (0.91)	4.01 (0.65)

The Cmax for the test is somewhat higher than that of the reference product with greater variability. It appears one subject #14 was causing this shift with the test product with a Cmax value of 32585.18. The range of Cmax values was 9654.46-32585.18 ng/mL for the Test product and 8980.92-18813.11 ng/mL for the reference product.

The following tables summarize the results of the analyses performed on the pharmacokinetic parameters.

Ibuprofen	Ln-Transformed C_{max}	Ln-Transformed AUC_{0-t}	Ln-Transformed AUC_{inf}
Test Product Geometric Mean	15756.56	53174.94	55190.30
Reference Product Geometric Mean	14044.85	54218.89	56159.56
% Ratio	112.19	98.07	98.27
90% Confidence Interval	(98.36, 127.96)	(92.81, 103.64)	(92.95, 103.9)

The power of the ANOVA for Cmax was 79.3% whereas for AUC it was 100%.

Safety Results: The applicant reported that 4 AE's were reported by four subjects (#01, 02, 15, and 18) over the course of the study. They all reported headaches. These were considered to be unrelated to study investigation by the clinical investigator. Only the report of one AE was considered by the investigator to be possibly related to the study medication.

Conclusions: The two products had a similar extent of absorption in the fed state. An evaluation of the confidence intervals for the log transformed Cmax for the comparison of the Banner Pharmacaps versus Advil Liquigels were not within the Agency acceptance criteria of 80 – 125 %. Therefore it can be concluded that the Banner Pharmacaps are not BE to the Advil Liquigels under non-fasting (fed) conditions. ***However the Cmax of the test product is only about 12% greater than that of the ref product which is unlikely to be clinically significant considering the broad therapeutic index of ibuprofen.***

5.2.3 Dissolution Study # PD01-287

Title: Comparative Dissolution of Ibuprofen Soft Gelatin Capsules

Objective: To compare the dissolution performance of ibuprofen soft gelatin capsules (200mg) manufactured at the Banner High Point plant with the Advil® Liqui-Gels® product containing the same strength.

Methods: Dissolution testing using the proposed method below (——— was conducted on the ibuprofen capsules 200 mg (lot # 21020622-A) and the Advil Liquigels ® (Lot # 3002475) that were used to perform a bio-equivalence clinical study:

Apparatus	USP Apparatus I Type- Baskets
Speed	— RPM
Number of units	———
Sampling times (minutes)	15, 30, 45 and 60
Media	900 mL 50mM phosphate buffer, pH 7.2
Temperature	37.0°C ± 0.5°C
Acceptance criteria	Similarity Factor (f2) value between 50 and 100 indicates that the two dissolution profiles are similar

Date of Study: Nov 13th, 2001

Results: Inserted below

4.0 RESULTS

SUMMARY OF DISSOLUTION RESULTS

Dissolution Results for High Point Lot# 21020622-A

Time	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Ave. (R)	Range	Std. Dev.
15													86		6.52
30													96		2.57
45													97		2.22
60													97		2.22

Notebook

Dissolution Results for Advil Lot# 3002475

Time	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Ave. (T)	Range	Std. Dev.
15													97		1.22
30													98		0.58
45													98		0.72
60													99		0.51

Notebook

Time	R - T	(R - T)²
15		
30		
45		
60		

0 CALCULATIONS AND CONCLUSIONS

Conclusions: F2 is between 50 and 100, but more than one measurement after — dissolved was used for f2 calculations and less than three sampling points available before — dissolved, therefore calculations not useful.

5.3 OCPB Filing/Review Form

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

General Information About the Submission

	Information		Information
NDA Number	**21-472**	**Brand Name**	**NA**
OCPB Division (I, II, III)	**III**	**Generic Name**	**Ibuprofen Capsules, 200mg**
Medical Division	**HFD-550**	**Drug Class**	**Analgesic/Antipyretic**
OCPB Reviewer	**Abi Adebowale**	**Indication(s)**	**OTC use in temporarily relieving the minor aches and pains due to common cold, headache, toothache, muscular aches, backache, minor pain arthritis, menstrual cramps, and fever.**
OCPB Team Leader	**Dennis Bashaw**	**Dosage Form**	**Soft gel capsules**
IND Number	**62,553**	**Dosing Regimen**	**1capsules Q 4-6 hrs for adults and children ≥ 12 years old**
Date of Submission	**18th December, 2002**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**14th August , 2002**	**Sponsor**	**Banner Pharamcaps**
PDUFA Due Date	**18th October, 2002**	**Priority Classification**	**3S**

Division Due Date	6th September, 2002		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				

III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		8		
Total Number of Studies		2		

Filability and QBR comments

	"X" if yes	
		No Comments
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	Yes	Attachment included.
QBR questions (key issues to be considered)	Is the new formulation of ibuprofen capsules bioequivalent to the RLD in the fasting state? Is the pharmacokinetics of the new formulation of ibuprofen capsules comparable to the RLD in the fed state? Are the dissolution profiles comparable?	
Other comments or information not included above	Sponsor replied on 10/03/02 committing to conduct dissolution studies at lower speeds and submitting the data to the Agency by December 1st, 2002.	
Primary reviewer Signature and Date	Abi Adebowale (08/09/02)	
Secondary reviewer Signature and Date		

CC: NDA 21-373, HFD-850 (P. Lee), HFD-860 (M. Mehta), HFD-550 (B. Gould), HFD-880 (D. Bashaw, J.Lazor, A. Selen), CDR

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Abi Adebowale
10/8/02 12:44:29 PM
BIOPHARMACEUTICS

Dennis Bashaw
10/9/02 09:54:08 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL