

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201803Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 201803	Submission Date: 6/30/10
Submission Type; Code:	Original; 505(b)(2);
Brand/Code Name:	To be determined
Generic Name:	Sodium Ibuprofen Dihydrate
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP2
ORM Division:	Division of Nonprescription Clinical Evaluation
Sponsor:	Pfizer Consumer Healthcare
Relevant IND(s):	-
Formulation; Strength(s):	Tablet; 256 mg sodium ibuprofen dehydrate (ibuprofen 200 mg)
Proposed Indication:	For temporarily relieves minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, minor pain of arthritis, and temporarily reduces fever
Proposed Dosage	<ul style="list-style-type: none">Adults and children 12 years and over: take 1 tablet every 4 to 6 hours while symptoms persist;
Regimen:	<ul style="list-style-type: none">If pain or fever does not respond to 1 tablet, 2 tablets may be used;Do not exceed 6 tablets in 24 hours, unless directed by a doctor;Children under 12 years: ask a doctor;Do not take more than directed;The smallest effective dose should be used

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the NDA 201-803 submitted on 6/30/10. From OCP perspective, the information contained in the Application is acceptable.

1.2 Phase IV Commitments – Not applicable

1.3 Summary of CPB Findings

Pfizer Consumer Healthcare submitted NDA 201803, sodium ibuprofen dehydrate 256 mg tablets/caplets, equivalent to 200 mg of ibuprofen free acid, accordance with 505(b)(2) provisions of the Food, Drug and Cosmetic Act, for the use of sodium ibuprofen dehydrate for temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular pain, backache, the minor pain of arthritis, for the pain of menstrual cramps, and for reduction of fever.

This application refers to the following NDAs for general safety and efficacy of ibuprofen: Motrin IB (NDA 19-012), Advil Liqui-Gels (NDA 20-402), and Advil Tablets, Caplets and Gel-Caplets (NDA 18-989). This application also refers to the following NDAs for safety and efficacy of ibuprofen in the pediatric population to support a partial waiver of pediatric studies in children under the age of 12 and the proposed pediatric plan for adolescents age 12-17: Children’s Advil Suspension (NDA 20-589 and NDA 19-833) and Infant’s Advil Drops (NDA 20-812).

Initially, the sodium ibuprofen dehydrate tablet was developed by Wyeth Consumer Healthcare, which is now a wholly-owned subsidiary of Pfizer Inc. doing business as Pfizer Consumer Healthcare. The products will be manufactured, tested, and released by the Wyeth Pharmaceuticals Company, Consumer Site located in Guayama, Puerto Rico. The Wyeth Consumer Site located in Guayama, Puerto Rico will package products into bottle configurations. The products will also be packaged into pouches by Wyeth Pharmaceuticals (b) (4), will be responsible for packaging the product into vials.

The current submission contains results from two pharmacokinetic (PK) studies. The first study (AH-08-07) is a pilot PK study exploring the prototype formulations. A cursory review was done for this study and concluded that the results do not have any impact on the overall NDA assessment.

The second study (AH-09-08) was a pivotal PK study comparing the ibuprofen sodium tablet to Advil Liqui-Gel. Additionally, ibuprofen sodium tablet was compared to Motrin IB tablet. Food effect was also assessed. Inspections for clinical and analytical sites were requested through Division of Scientific Investigation. The results from the inspection did not find any issues precluding the acceptance of the data (see review by Dr. Abhijit Raha dated 01/25/11).

Ibuprofen sodium tablet was bioequivalent to Advil Liqui-Gel. Ibuprofen extent of absorption (AUC) from ibuprofen sodium tablet was bioequivalent to Motrin IB tablets in fasted state; however, ibuprofen C_{max} was 35% greater for ibuprofen sodium tablet compared to Motrin IB tablet.

Under fed conditions (high-fat, high-caloric breakfast), ibuprofen C_{max} and AUC values decreased by 38% and 11%, respectively, for ibuprofen sodium tablet. Advil Liqui-gel produced similar decrease in C_{max} and AUC values (30% in C_{max} and 11% in AUC_{0-inf}) under fed conditions and its use has no food related dosing restrictions. In line with this, ibuprofen sodium tablet also can be taken with or without food.

Overall, the provided information in this application is acceptable.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

The sponsor stated that the development rationale for sodium ibuprofen dihydrate tablet is that the tablet is expected to provide more rapid pain relief than standard ibuprofen

tablets, and thereby provide consumers with another therapeutic option for pain relief. However, data to support rapid pain relief is not provided and therefore is speculative.

Ibuprofen is a racemate. The sodium salt is a (b) (4)

The drug substance is a virtually white, crystalline powder that is freely soluble in water.

Sodium Ibuprofen Tablets

Sodium Ibuprofen Tablets, 200 mg are round, beige film-coated tablets, printed with black ink, containing 256 mg of sodium ibuprofen dihydrate per dosage unit (equivalent to a 200 mg dose of ibuprofen). Sodium Ibuprofen Tablets, 200 mg were manufactured at the PCH facility located in Guayama, PR.

The excipients utilized in the manufacture of tablet along with the functionality of each excipient are listed in the table below (Table 1).

Table 1: Excipients for Sodium Ibuprofen Tablets, 200 mg

Excipient	Function
	(b) (4)
Colloidal Silicon Dioxide	
Mannitol	
Microcrystalline Cellulose	
Sodium Lauryl Sulfate	
(b) (4)	
Acesulfame Potassium	
(b) (4)	
Sucralose	
Carnauba Wax	
(b) (4)	

Three prototype formulas were manufactured to support a screening biostudy. The formulations evaluated in the screening biostudy are listed in Table 2.

Table 2: Screening Biostudy Formulas WH-1373-0002, WH-1373-0004, and WH-1373-0005

(b) (4)			
Raw Material	WH-1373-0002	WH-1373-0004	WH-1373-0005
	mg/tablet	mg/tablet	mg/tablet
Sodium Ibuprofen Dihydrate	256.25	256.25	256.25
Colloidal Silicon Dioxide	(b) (4)		
Mannitol			
Crospovidone			
(b) (4)			
Microcrystalline Cellulose			
(b) (4)			
Sodium Lauryl Sulfate			
Stearic Acid			
(b) (4)			
(b) (4)			
Total Weight	450	450	450

The results of the screening biostudy indicated that all three formulas were bioequivalent to each other and to Advil® Liqui-gels. All three sodium ibuprofen dihydrate formulations resulted in very similar C_{max}, AUC, and T_{max} values. Formula WH-1373-0002 with a (b) (4) ratio of microcrystalline cellulose to mannitol as the primary (w) (4) yielded the same *in vivo* performance as formula WH-1373-0004 with a (b) (4) ratio. (b) (4)

(b) (4)

The final formulation for Sodium Ibuprofen Tablets, 200 mg is listed in Table 3.

Table 3: Composition of Sodium Ibuprofen Tablets, 200 mg Drug Product

Ingredient	Grade/Quality Standard	Unit Dose (mg/du)	Function		
Sodium Ibuprofen Dihydrate	DMF	256.25	Active Ingredient		
Colloidal Silicon Dioxide	NF, Ph. Eur.		(b) (4)		
Mannitol	USP, Ph. Eur.				
Microcrystalline Cellulose	NF, Ph. Eur.				
Sodium Lauryl Sulfate	NF, Ph. Eur.				
(b) (4)	DMF				
Acesulfame Potassium	NF, Ph. Eur.				
Sucralose	NF				
(b) (4)	DMF				
Carnauba Wax	NF, Ph. Eur.				
(b) (4)	DMF				
(b) (4)	USP, Ph. Eur.				
(b) (4)	USP, Ph. Eur.				
Total:				446.2	

a. Essentially removed during processing.

2.1.2 What are the proposed mechanism of action and therapeutic indication(s)?

Ibuprofen is indicated for temporarily relieves minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, minor pain of arthritis, and temporarily reduces fever.

Ibuprofen, an orally-administered propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic activity. The exact mechanism of action is not known for ibuprofen; however, it is believed to include inhibition of cyclooxygenase mediated prostaglandin formation. Ibuprofen inhibits both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) activities and thereby synthesis of prostaglandins and thromboxanes.

The oral formulation was first approved in the United States in 1974 and was afterward approved for nonprescription status in 1984. Ibuprofen was approved for use in the United States as an antipyretic in children in 1989, and soon after for over-the-counter (OTC) status in the mid-1990s.

2.1.3 What are the proposed dosage and route of administration?

Sodium ibuprofen tablet/caplet will be administered via the oral route. The following dosage regimen is proposed, which is currently used for the over-the-counter ibuprofen products.

- Adults and children 12 years and over: take 1 tablet every 4 to 6 hours while symptoms persist;
- If pain or fever does not respond to 1 tablet, 2 tablets may be used;
- Do not exceed 6 tablets in 24 hours, unless directed by a doctor;
- Children under 12 years: ask a doctor;
- Do not take more than directed;
- The smallest effective dose should be used.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials?

No efficacy studies have been conducted using the tablet. The clinical development plan consisted of one pilot (formulation development and selection) and one pivotal (relative bioavailability and food effect using the commercial formulation) pharmacokinetic studies. The sponsor wishes to utilize the Agency’s safety and efficacy findings of ibuprofen to the following NDAs: Motrin IB (NDA 19-012), Advil Liqui-Gels (NDA 20-402), and Advil Tablets, Caplets and Gel-Caplets (NDA 18-989). This application also refers to the following NDAs for safety and efficacy of ibuprofen in the pediatric population to support a partial waiver of pediatric studies in children under the age of 12 and the proposed pediatric plan for adolescents age 12-17: Children’s Advil Suspension (NDA 20-589 and NDA 19-833) and Infant’s Advil Drops (NDA 20-812).

2.2.2 Exposure-response – Not applicable

2.2.3 What are the single dose PK parameters?

The pivotal pharmacokinetic study, AH-09-08, was an open label, 5-way crossover, BE and food effects trial was performed in the US in 2009. The following treatment groups were administered to healthy subjects (Table 4).

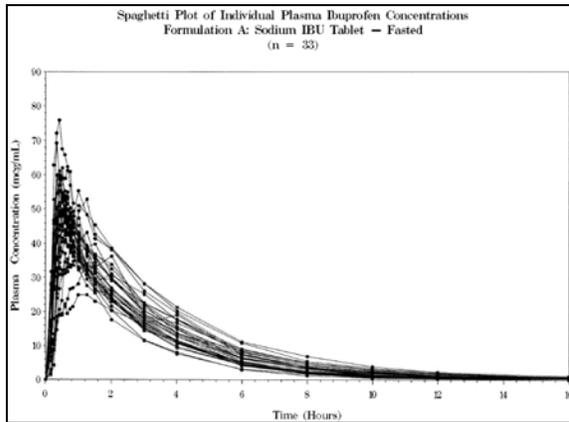
Table 4: Treatments groups in pivotal PK study

Treatment Group	Drug	Lot #	Food	Per Unit	Total mg
A	IBU Na tablets	(WH-1373-0010-004)	Fasted	Ibuprofen 200 mg	400 mg
B	IBU Na tablets	(WH-1373-0010-004)	Fed	Ibuprofen 200 mg	400 mg
C Reference	Advil Liqui-Gels	(WH-0693-0001-007)	Fasted	Solubilized Ibuprofen 200 mg	400 mg
D Reference	Advil Liqui-Gels	(WH-0693-0001-007)	Fed	Solubilized Ibuprofen 200 mg	400 mg
E Reference	Motrin IB tablets	(WH-0001-0483-003)	Fasted	Ibuprofen 200 mg	400 mg

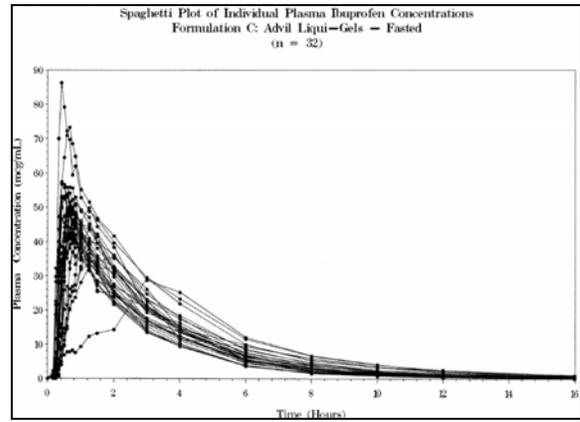
A total of 36 subjects (18 females and 18 males), 18-45 years of age, were enrolled in the study; 35 were dosed. The average age and BMI were 27.4 years and 23.9 kg/m² (range: 19-28 kg/m²), respectively. The majority of subjects were White (31 subjects, 86.1%) and 4 (11.1%) were Black, and 1 (2.8%) was Asian. Seventeen (47.2% were of Hispanic/Latino ethnicity. Thirty-two (32) subjects provided evaluable data, as four subjects discontinued during or after completing period I. The blood samples (3 mL) were taken at the following time intervals: pre-dose (0 hour) and 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90 minutes and 2, 3, 4, 6, 8, 10, 12 and 16 hours post-dose. The obtained pharmacokinetic parameters (log transformed) were analyzed using an analysis of variance (ANOVA; 90% two-sided confidence intervals for the ratio of reference vs. test formulation for each of the comparisons) with effects for subject, period, and treatment.

Mean plasma IBU concentrations from 0-16 hours for each of the treatment groups are presented below.

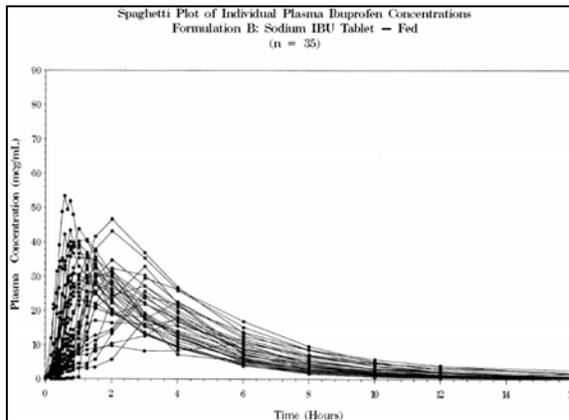
Plot of Treatment A:



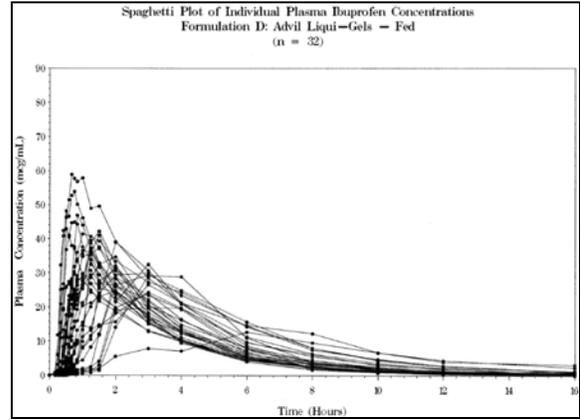
Plot of Treatment C:



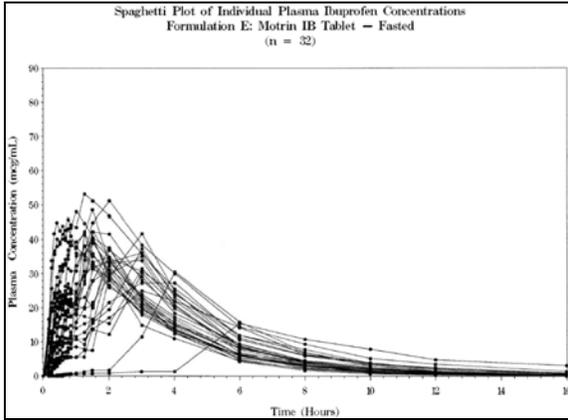
Plot of Treatment B:



Plot of Treatment D:

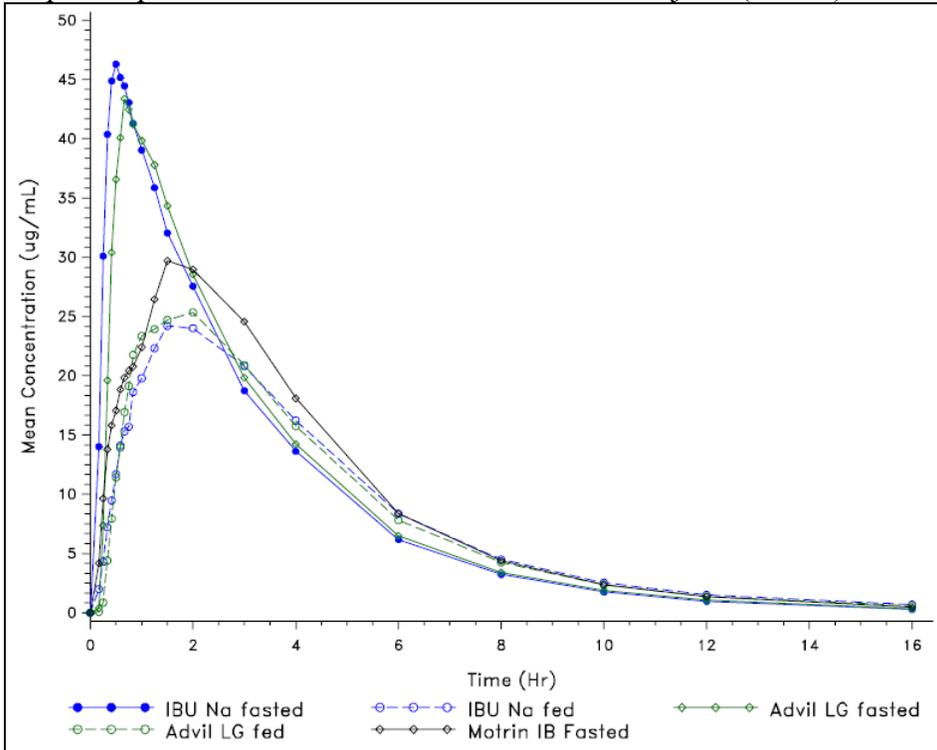


Plot of Treatment E:

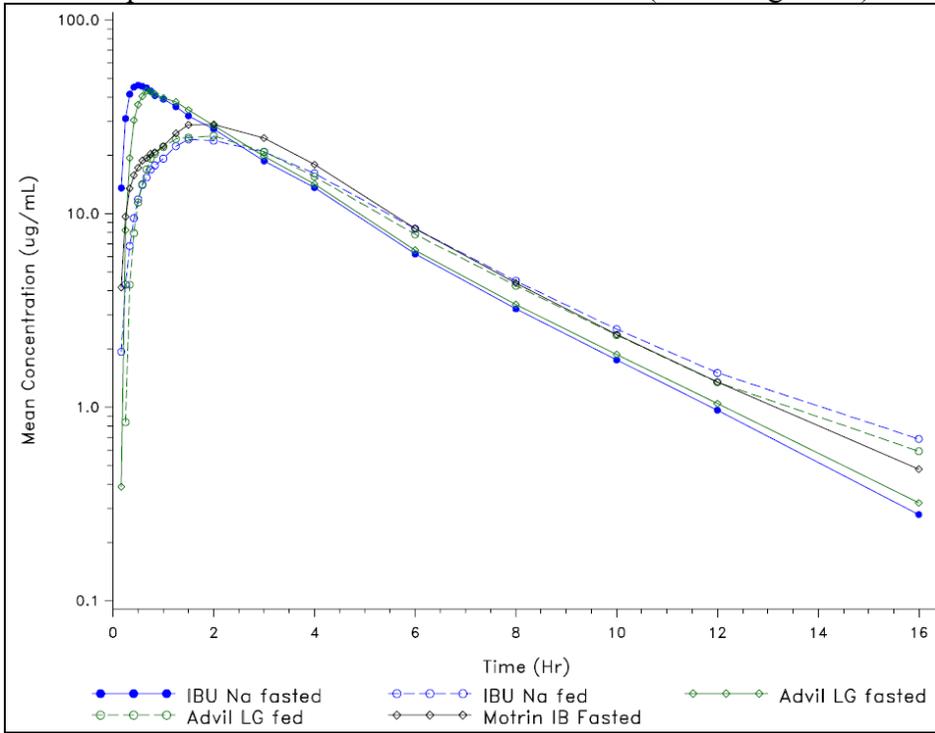


Mean ibuprofen plasma concentration profiles are presented below.

Ibuprofen plasma concentration over Time - All Subjects (Linear)



Mean Ibuprofen Plasma Concentration over Time (Semi-Log Scale)



Ibuprofen pharmacokinetic parameters are presented below (Table 5), as well as 90% confidence interval (Table 6).

Table 5: Ibuprofen Pharmacokinetic Parameters (Mean, Standard Deviation, Median*)

Treatment			AUC _{0-t} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC _{0-inf} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C _{max} ($\mu\text{g}/\text{mL}$)	T _{max} (min)
			Mean (SD)			
A	IBU Na Tablet	Fasted	145.7 (29.6)	147.2 (30.1)	50.6 (10.3)	35.1 (14.3) [30.4]
B	IBU Na Tablet	Fed	127.2 (28.6)	130.6 (29.2)	31.5 (8.8)	115.1 (72.5) [90.0]
C	Advil Liqui-Gels	Fasted	143.8 (32.6)	145.5 (33.2)	48.6 (11.2)	50.1 (29.7) [40.5]
D	Advil Liqui-Gels	Fed	125.9 (29.7)	128.9 (30.6)	34.2 (9.7)	111.0 (67.9) [90.0]
E	Motrin IB Tablet	Fasted	143.4 (32.2)	145.6 (32.4)	37.4 (7.8)	126.5 (66.9) [120.0]

Table 6: 90% Confidence Intervals

Ratios			
	AUC0-t (µg•h/mL)	AUC0-inf (µg•h/mL)	Cmax (µg/mL)
A/C† Ratio (%) 90% CI	102.0 (99.1-105.0)	102.0 (99.1-105.0)	104.2 (96.6-112.4)
A/E† Ratio (%) 90% CI	102.4 (99.5-105.4)	101.8 (98.9-104.8)	135.0 (125.2-145.5)
B/D† Ratio (%) 90% CI	101.7 (98.8-104.7)	102.1 (99.2-105.1)	91.2 (84.6-98.3)

*Median presented for Tmax only

^Based on fitted log-transformed parameters.

†Reference product

Ibuprofen exposure from ibuprofen sodium tablet was bioequivalent to Advil Liqui-Gels in fasted state. Ibuprofen extent of absorption (AUC) from ibuprofen sodium tablet was bioequivalent to Motrin IB tablets in fasted state. However, ibuprofen Cmax was 35% greater from ibuprofen sodium tablet.

2.3 Intrinsic Factors

2.3.1 What is the status of pediatric studies and/or any pediatric plan for study?

The Na IBU tablet will have the same labeled indications and is intended for the same consumer population as currently-marketed ibuprofen tablets and liquigels. Thus, the proposed product is indicated for use by consumers 12 years of age and older. The sponsor wishes to cross-reference NDAs 19-833 and 20-402 and the literature for clinical support for use of Na IBU in adolescents age 12-17.

The proposed product is not indicated for use by children less than 12 years of age. The sponsor wishes to request for a partial waiver of pediatric studies for this age group. The sponsor does not believe that pediatric studies in the 2 month to 11 year age group are necessary for a Na IBU tablet product. The proposed Na IBU tablets do not represent a meaningful therapeutic benefit over existing therapies and are not likely to be used in a substantial number of children 2 months to 11 years of age. The sponsor presented the following rationale to request for a partial waiver of pediatric studies in the 2 month to 11 year old pediatric population:

1. Children's IBU products have been approved and marketed OTC for the treatment of pain and fever in children 2 to 11 years of age for 15 years, and for children 6-23 months for over 10 years. During this time pediatric IBU products have compiled an excellent overall record of safety and efficacy. IBU use in children of these age groups has been extensively studied. Data supporting the efficacy and safety in pediatric age groups were submitted in NDAs 19-833 and 20-589. Furthermore, recent reviews/meta-analyses of clinical trials, including children down to 2 months of age, indicate that IBU is as or more

efficacious than acetaminophen in the treatment of pain and fever and has a similar safety profile that is comparable to placebo.

2. Na IBU will provide almost identical effectiveness compared to the currently available IBU products. It will not eliminate or reduce potential drug reactions, or enhance compliance in a new subpopulation. In the pivotal pharmacokinetic study submitted herein, Na IBU tablets were bioequivalent to IBU liquigels (Advil® Liqui- Gels®) for both the rate and extent of IBU absorption. Previous clinical studies have demonstrated that IBU liquigels are bioequivalent to currently-marketed Children’s Advil Suspension for both the rate and extent of absorption (PV-96-02 submitted to IND (b)(4) and PV-96-08 submitted to IND (b)(4)). Therefore, Na IBU would not provide greater safety or efficacy than currently-marketed pediatric IBU products. As such, Na IBU does not represent a meaningful therapeutic benefit over existing therapies for this population.

3. Na IBU is not likely to be used in a substantial number of pediatric patients because of the number of already approved and labeled OTC products (both name brand and store brand equivalents) with pain reliever/fever reducer indications for the pediatric population. Many of these products contain the same active ingredient (IBU) as the subject of this application (Na IBU). Retrospective review of information submitted and actions taken in response to PREA 2003 indicated that a number of already approved and labeled products in a particular class for a particular indication would be an appropriate reason to believe that a product would not be expected to be used in a substantial number of patients.

4. As there is no meaningful therapeutic benefit for Na IBU compared to IBU in children, PCH does not intend to either pursue approval of an NDA or commercialize pediatric formulations of Na IBU.

Table 1: Examples of Marketed Pediatric Analgesic/Antipyretic Products*

Product Name	Active Ingredient	Strength	Approved Age Range
Infants’ Advil® Concentrated Drops	Ibuprofen	50 mg/1.25 mL	6-23 months
Children’s Advil Suspension	Ibuprofen	100 mg/5 mL	2-11 years
Infants’ Motrin® Concentrated Drops	Ibuprofen	50 mg/1.25 mL	6-23 months
Children’s Motrin Suspension	Ibuprofen	20 mg/mL	2-11 years
Junior Strength Motrin Caplets	Ibuprofen	100 mg	6-11 years
Junior Strength Motrin Chewable Tablets	Ibuprofen	100 mg	2-11 years
Infants’ Concentrated Tylenol® Drops	Acetaminophen	160 mg/1.6 mL	2-3 years
Children’s Tylenol Suspension	Acetaminophen	160 mg/5 mL	2-11 years
Junior Tylenol Orally-Dissolvable Tablets	Acetaminophen	160 mg	6-12 years

* there are also numerous additional marketed generic (private label) products equivalent to several of the branded products above

This pediatric plan was discussed at the PERC meeting on 02/16/11. Committee discussed at length where there was sufficient data to support that the product is not likely to be used in a substantial number of pediatric patients. Committee recommended deferring studies in patients less than 12 years of age and that the sponsor needs to submit use data to support that the product is not likely to be used in a substantial number of pediatric patients to qualify for a waiver.

2.4 Extrinsic Factors – Not applicable

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The pivotal pharmacokinetic study (relative bioavailability) was conducted with the commercial formulation.

2.5.2 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 food effect was assessed from the pivotal pharmacokinetic study, AH-09-08, as presented previously. The table (Table 7) below contains the C_{max} and AUC values of ibuprofen sodium tablet and Advil Liqui-Gel.

Table 7: Ibuprofen Pharmacokinetic Parameters (Mean, Standard Deviation, Median*, and 90% Confidence Intervals)

Treatment			AUC _{0-t} (µg•h/mL)	AUC _{0-inf} (µg•h/mL)	C _{max} (µg/mL)	T _{max} (min)
			Mean (SD)			
A	IBU Na Tablet	Fasted	145.7 (29.6)	147.2 (30.1)	50.6 (10.3)	35.1 (14.3) [30.4]
B	IBU Na Tablet	Fed	127.2 (28.6)	130.6 (29.2)	31.5 (8.8)	115.1 (72.5) [90.0]
C	Advil Liqui-Gels	Fasted	143.8 (32.6)	145.5 (33.2)	48.6 (11.2)	50.1 (29.7) [40.5]
D	Advil Liqui-Gels	Fed	125.9 (29.7)	128.9 (30.6)	34.2 (9.7)	111.0 (67.9) [90.0]

*Median presented for T_{max} only

^Based on fitted log-transformed parameters.

†Reference product

The point-estimate ratios of Cmax and AUC values from fasted and fed treatments are presented (Table 8) below.

Table 8: Ratios of Mean Ibuprofen Cmax and AUC Parameters in fed vs. fasted treatments

	Fed/fasted Cmax	Fed/fasted AUC0-inf
IBU Na Tablet	0.62	0.89
Advil Liqui-Gel	0.70	0.89

Under fed conditions (high-fat, high-caloric breakfast), ibuprofen Cmax and AUC values decreased by 38% and 11%, respectively, for ibuprofen sodium tablet. Advil Liqui-gel produced similar decrease in Cmax and AUC values (30% in Cmax and 11% in AUC0-inf) under fed conditions and its use has no food related dosing restrictions. In line with this, ibuprofen sodium tablet also can be taken with or without food.

2.6 Analytical Section

2.6.1 What active moieties were measured in the plasma in the clinical pharmacology and biopharmaceutics studies and what bioanalytical methods are used to assess concentrations?

Plasma samples were analyzed for racemic ibuprofen using a validated method of high performance liquid chromatography with tandem mass spectrometry/mass spectrometry (HPLC MS/MS) detection.

Blood sample handling: Each blood sample was inverted at least eight times to ensure mixing, cooled in a cryo block, and centrifuged within 30 minutes of collection. Each tube was labeled with the protocol number, period number, date, time of collection, and subject number. The blood was centrifuged at 2,500 revolutions per minute (rpm) for 15 minutes. The plasma was removed and divided into two equal aliquots and transferred to plain tubes. The plain tubes were sealed with a cap and labeled appropriately as above. The clinical site stored the plasma samples at -20°C or lower until shipped to ^{(b) (4)} [REDACTED].

Method Description: A 100-μL sample aliquot is fortified with 25 μL of 25 μg/mL internal standard working solution and diluted with 100 μL of 0.1 M phosphoric acid. Analytes are isolated by a liquid/liquid extraction using 90:10 hexane/isopropyl alcohol, v/v. The organic layer is transferred to another 96-well plate and evaporated under a nitrogen stream at room temperature. The remaining residue is reconstituted with 250 μL of 0.01% formic acid in acetonitrile / 1.0 mM ammonium formate, 50:50 v/v. The final extract is analyzed via HPLC with MS/MS detection.

2.6.1.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Validation of the analytical method showed acceptable values for average back calculated calibration standards; eight calibration standards were analyzed in duplicate over the nominal concentration ranges of 0.20 to 50.0 µg/mL during the analytical assay runs. A linear, 1/concentration squared weighted, least-squares regression algorithm was used to plot the peak area ratio of the analyte to its internal standard versus concentration. The results from average back calculated calibration standards are acceptable (Table 9).

Table 9: Average back calculated calibration standards from the assay method validation:

Average back calculated calibration standards Ibuprofen									
Run ID	CAL 1 (µg/mL)	CAL 2 (µg/mL)	CAL 3 (µg/mL)	CAL 4 (µg/mL)	CAL 5 (µg/mL)	CAL 6 (µg/mL)	CAL 7 (µg/mL)	CAL 8 (µg/mL)	
1XWP2-A	0.201	0.343	0.581	1.85	5.00	15.2	41.1	51.8	
	0.206	0.348	0.599	1.93	4.84	15.4	41.0	51.6	
2XWP2-A	0.212	0.347	0.575	2.01	4.86	15.5	40.4	52.1	
	0.198	0.330	0.609	1.97	4.96	15.2	40.0	49.7	
3XWP2-A	0.203	0.333	0.594	1.97	4.96	15.1	41.0	52.5	
	0.205	0.350	0.591	1.94	5.04	14.3	40.1	51.7	
5XWP2-A	0.198	0.351	0.588	1.94	4.94	15.2	41.4	50.6	
	0.205	0.354	0.590	1.92	4.96	15.2	40.5	50.6	
N	8	8	8	8	8	8	8	8	
Theoretical Concentration	0.200	0.350	0.600	2.00	5.00	15.0	40.0	50.0	
Mean	0.203	0.344	0.591	1.94	4.95	15.2	40.7	51.3	
S.D.	0.00477	0.00852	0.0104	0.0465	0.0678	0.348	0.502	0.920	
%C.V.	2.34	2.48	1.77	2.40	1.37	2.29	1.23	1.79	
% Difference from Theoretical	1.72	-1.60	-1.52	-2.90	-1.10	1.00	1.76	2.63	

The results from average back calculated calibration standards from the PK study plasma sample analytical runs are acceptable (Table 10).

Table 10: Average back calculated calibration standards from the PK study plasma sample runs:

N	84	85	86	84	85	85	86	86
Theoretical Concentration	0.200	0.350	0.600	2.00	5.00	15.0	40.0	50.0
Mean	0.201	0.350	0.593	1.98	4.95	15.0	40.4	50.9
S.D.	0.0102	0.0189	0.0221	0.0665	0.151	0.483	1.28	1.64
%C.V.	5.08	5.40	3.72	3.36	3.05	3.23	3.16	3.22
% Difference from Theoretical	0.480	0.0957	-1.17	-1.04	-1.02	-0.250	1.10	1.78

2.6.1.2 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

The lower limit of quantitation was the lowest non-zero concentration level that was quantified with acceptable accuracy and precision. For this validation, the lower limit of quantitation was 0.200 µg/mL for ibuprofen. The upper limit of quantitation was 50 µg/mL for ibuprofen.

2.6.1.3 What is the QC sample plan? What is the accuracy and precision?

During the method validation, precision and accuracy were evaluated by analyzing quality control pools prepared at 0.200, 0.500, 1.00, 3.00, 10.0, and 37.5 µg/mL. Precision was expressed as the percent coefficient of variation (%CV) of each pool. Accuracy was measured as the percent difference from theoretical. The typical results are presented below (Tables 11 and 12). The results are acceptable.

Table 11: A typical intra-assay precision and accuracy (from assay method validation run 1XWP2-A)

Intra-Assay precision and accuracy Ibuprofen						
Run ID	QC 0 (µg/mL)	QC 1 (µg/mL)	QC 2 (µg/mL)	QC 3 (µg/mL)	QC 4 (µg/mL)	QC 5 (µg/mL)
1XWP2-A	0.210	0.504	0.972	2.83	10.1	39.5
	0.216	0.499	0.955	2.90	10.1	39.1
	0.215	0.502	0.958	2.88	10.1	39.5
	0.208	0.504	0.969	2.75	10.3	39.5
	0.217	0.510	0.964	2.84	10.1	39.1
	0.218	0.511	0.961	2.88	10.0	38.8
N	6	6	6	6	6	6
Theoretical Concentration	0.200	0.500	1.00	3.00	10.0	37.5
Mean	0.214	0.505	0.963	2.85	10.1	39.2
S.D.	0.00401	0.00469	0.00637	0.0547	0.0774	0.293
%C.V.	1.87	0.929	0.661	1.92	0.764	0.748
% Difference from Theoretical	6.92	1.03	-3.70	-5.10	1.25	4.63
Low Limit	0.160	0.425	0.850	2.55	8.50	31.9
High Limit	0.240	0.575	1.15	3.45	11.5	43.1

Table 12: A typical inter-assay precision and accuracy

Inter-Assay precision and accuracy Ibuprofen						
Run ID	QC 0 (µg/mL)	QC 1 (µg/mL)	QC 2 (µg/mL)	QC 3 (µg/mL)	QC 4 (µg/mL)	QC 5 (µg/mL)
1XWP2-A	0.210	0.504	0.972	2.83	10.1	39.5
	0.216	0.499	0.955	2.90	10.1	39.1
	0.215	0.502	0.958	2.88	10.1	39.5
	0.208	0.504	0.969	2.75	10.3	39.5
	0.217	0.510	0.964	2.84	10.1	39.1
	0.218	0.511	0.961	2.88	10.0	38.8
2XWP2-A	0.200	0.490	0.915	2.81	10.2	39.3
	0.208	0.496	0.967	2.86	10.1	39.3
	0.206	0.506	0.938	2.91	10.2	38.2
	0.203	0.493	0.968	2.83	10.1	39.5
	0.204	0.491	0.961	2.86	10.3	39.0
	0.209	0.491	0.952	2.84	10.3	39.6
3XWP2-A	0.197	0.499	0.971	2.88	10.2	39.0
	0.217	0.502	0.957	2.83	10.3	39.0
	0.213	0.504	0.982	2.95	10.1	38.9
	0.208	0.505	0.958	2.91	10.2	39.9
	0.206	0.499	0.982	2.75	9.88	39.3
	0.212	0.501	0.948	2.90	10.2	38.9
5XWP2-A	0.199	0.500	0.941	2.86	10.1	38.4
	0.209	0.509	0.971	2.76	10.0	39.2
	0.209	0.493	0.968	2.86	10.1	38.8
	0.209	0.492	0.972	2.70	9.98	38.3
	0.200	0.488	0.979	2.82	10.1	38.8
	0.208	0.516	0.974	2.88	9.74	38.4
N	24	24	24	24	24	24
Theoretical Concentration	0.200	0.500	1.00	3.00	10.0	37.5
Mean	0.208	0.500	0.962	2.84	10.1	39.1
S.D.	0.00582	0.00743	0.0151	0.0591	0.132	0.435
%C.V.	2.79	1.49	1.57	2.08	1.30	1.11
% Difference from Theoretical	4.21	0.0493	-3.82	-5.17	1.20	4.14
Low Limit	0.160	0.425	0.850	2.55	8.50	31.9
High Limit	0.240	0.575	1.15	3.45	11.5	43.1

The results from the overall inter-assay information from the PK study plasma sample analytical runs are also acceptable (Table 13).

Table 13: Intra-assay precision and accuracy from PK study plasma sample runs:

N	86	86	86	86	86
Theoretical Concentration	0.500	1.00	3.00	10.0	37.5
Mean	0.498	0.987	2.97	9.92	37.9
S.D.	0.0229	0.0406	0.0940	0.345	1.27
%C.V.	4.61	4.11	3.17	3.48	3.36
% Difference from Theoretical	-0.486	-1.26	-1.14	-0.805	1.10
Low Limit	0.425	0.850	2.55	8.50	31.9
High Limit	0.575	1.15	3.45	11.5	43.1

2.6.1.4 What is the sample recovery and stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

During the method validation, sample recovery and stability information was collected. The typical results from the recovery and stability information are presented below. The results are acceptable (Tables 14 – 24).

Recovery

A general extraction recovery of the analytes from human plasma was evaluated by comparing analyte responses of pre-extraction spiked samples to those of post-extraction spiked samples.

Table 14: General Extraction Recovery for Ibuprofen and Internal Standard

Theoretical Concentration (µg/mL)	Sample ID (pre-extraction fortified)	Analyte Response	Int. Std. Response	Sample ID (post-extraction fortified)	Analyte Response	Int. Std. Response
0.200	PRE 0-1	1947.25	23027.08	POST 0-1	2791.21	32803.18
	PRE 0-2	1967.37	22848.31	POST 0-2	3136.62	36856.84
	PRE 0-3	2015.11	24147.78	POST 0-3	3157.07	36712.53
	Mean	1977	23341	Mean	3028	35458
	%CV	1.76%	3.02%	%CV	6.79%	6.49%
				%Recovery	65.3%	65.8%
3.00	PRE 3-1	29272.33	22832.76	POST 3-1	45261.58	36052.09
	PRE 3-2	30620.25	24632.15	POST 3-2	46698.63	36738.36
	PRE 3-3	31475.37	25052.42	POST 3-3	46168.26	36384.63
	Mean	30456	24172	Mean	46043	36392
	%CV	3.65%	4.88%	%CV	1.58%	0.943%
				%Recovery	66.1%	66.4%
37.5	PRE 5-1	360993.97	23336.73	POST 5-1	519600.25	33429.09
	PRE 5-2	356274.59	23115.29	POST 5-2	526170.94	33926.58
	PRE 5-3	364707.88	23317.21	POST 5-3	515043.97	33346.98
	Mean	360659	23256	Mean	520272	33568
	%CV	1.17%	0.527%	%CV	1.08%	0.934%
				%Recovery	69.3%	69.3%

Recovery was evaluated as part of Runs 4XWP2-A (0.200 and 3.00 µg/mL) and 5XWP2-A (37.5 µg/mL).

Stability

Freeze/thaw stability (F/T) was evaluated by analyzing low- and high-level quality controls that were subjected to three and four freeze/thaw cycles. Samples were thawed at room temperature.

Table 15: Freeze/thaw Stability (Three Cycles)

Run ID	3F/T 1 (µg/mL)	3F/T 5 (µg/mL)
3XWP2-A	0.500	38.6
	0.494	36.2
	0.494	39.2
	0.474	38.7
	0.473	38.9
	0.489	39.1
N	6	6
Theoretical Concentration	0.500	37.5
Mean	0.487	38.4
S.D.	0.0111	1.13
%C.V.	2.27	2.93
% Difference from Theoretical	-2.54	2.49

Table 16: Freeze/thaw Stability (Four Cycles)

Run ID	4F/T 1 (µg/mL)	4F/T 5 (µg/mL)
5XWP2-A	0.507	38.4
	0.496	39.3
	0.504	39.0
	0.503	38.5
	0.507	37.7
	0.496	38.7
N	6	6
Theoretical Concentration	0.500	37.5
Mean	0.502	38.6
S.D.	0.00504	0.566
%C.V.	1.00	1.47
% Difference from Theoretical	0.419	2.92

Analyte stability in thawed matrix (TM)

Analyte stability in thawed matrix was evaluated by allowing a set of low- and high-level quality controls to thaw and remain at room temperature for 24 hours prior to extraction and analysis.

Table 17: Analyte stability in thawed matrix

Run ID	24TM 1 (µg/mL)	24TM 5 (µg/mL)
2XWP2-A	0.487	38.1
	0.490	36.7
	0.484	38.2
	0.483	37.9
	0.484	38.5
	0.463	38.7
N	6	6
Theoretical Concentration	0.500	37.5
Mean	0.482	38.0
S.D.	0.00939	0.724
%C.V.	1.95	1.90
% Difference from Theoretical	-3.64	1.40

Reinjection reproducibility (RR)

Reinjection reproducibility (RR) was evaluated by analyzing calibration standards and quality controls that were extracted and injected as part of Run 1XWP2-A and stored at room temperature prior to and during reanalysis as Run 6XWP2-A.

Table 18: Reinjection reproducibility

Limits / Levels for RR Ibuprofen					
Run ID	RR 1 (µg/mL)	RR 2 (µg/mL)	RR 3 (µg/mL)	RR 4 (µg/mL)	RR 5 (µg/mL)
6XWP2-A	0.515	0.960	2.84	10.2	39.2
	0.503	0.965	2.93	10.1	39.7
	0.485	0.947	2.79	10.2	38.5
	0.503	0.968	2.80	10.2	39.7
	0.511	0.966	2.80	10.1	40.0
	0.510	0.977	2.90	10.1	39.1
N	6	6	6	6	6
Theoretical Concentration	0.500	1.00	3.00	10.0	37.5
Mean	0.505	0.964	2.84	10.2	39.3
S.D.	0.0109	0.00985	0.0579	0.0689	0.544
%C.V.	2.15	1.02	2.04	0.679	1.38
% Difference from Theoretical	0.912	-3.61	-5.19	1.55	4.91

Post-preparative extract stability (ES)

Post-preparative extract stability (ES) was evaluated by analyzing quality controls that were extracted, injected as part of Run 1XWP2-A and stored at room temperature for approximately 129 hours prior to and during reinjection. These samples were quantified versus the original calibration curve analyzed on the day of extraction.

Table 19: Post-preparative Extract Stability

Run ID	ES 1 (µg/mL)	ES 2 (µg/mL)	ES 3 (µg/mL)	ES 4 (µg/mL)	ES 5 (µg/mL)
7XWP2-A	0.515	0.960	2.83	10.2	39.1
	0.503	0.964	2.93	10.1	39.7
	0.485	0.947	2.79	10.2	38.4
	0.503	0.968	2.80	10.2	39.6
	0.511	0.965	2.80	10.0	39.9
	0.510	0.976	2.90	10.1	39.0
N	6	6	6	6	6
Theoretical Concentration	0.500	1.00	3.00	10.0	37.5
Mean	0.505	0.963	2.84	10.1	39.3
S.D.	0.0109	0.00984	0.0578	0.0689	0.544
%C.V.	2.15	1.02	2.04	0.679	1.38
% Difference from Theoretical	0.901	-3.66	-5.26	1.46	4.81

Post-preparative extract stability was demonstrated by analyzing quality controls that were extracted, injected as part of Run 1XWP2-A and stored at room temperature for approximately 129 hours prior to and during reinjection in Run 6XWP2-A. These samples were quantified versus the original calibration curve (Run 1XWP2-A) analyzed on the day of extraction. The combined data (reinjected QC and original injected calibrator responses) are reported as Run 7XWP2-A.

Analyte stability in frozen matrix

Analyte stability in frozen matrix (for a period of seven days at -20°C) was evaluated by analyzing QCs versus freshly prepared calibration standards at the end of the validation.

Table 20: Analyte stability in frozen matrix

Intra-Assay precision and accuracy Ibuprofen							
Run ID	QC 0 (µg/mL)	QC 1 (µg/mL)	QC 2 (µg/mL)	QC 3 (µg/mL)	QC 4 (µg/mL)	QC 5 (µg/mL)	
5XWP2-A	0.199	0.500	0.941	2.86	10.1	38.4	
	0.209	0.509	0.971	2.76	10.0	39.2	
	0.209	0.493	0.968	2.86	10.1	38.8	
	0.209	0.492	0.972	2.70	9.98	38.3	
	0.200	0.488	0.979	2.82	10.1	38.8	
	0.208	0.516	0.974	2.88	9.74	38.4	
N	6	6	6	6	6	6	
Theoretical Concentration	0.200	0.500	1.00	3.00	10.0	37.5	
Mean	0.206	0.500	0.967	2.81	10.0	38.7	
S.D.	0.00479	0.0107	0.0133	0.0692	0.138	0.358	
%C.V.	2.33	2.15	1.38	2.46	1.38	0.925	
% Difference from Theoretical	2.86	-0.0459	-3.25	-6.20	0.0492	3.09	
Low Limit	0.160	0.425	0.850	2.55	8.50	31.9	
High Limit	0.240	0.575	1.15	3.45	11.5	43.1	

Quality controls were analyzed versus freshly prepared calibration standards at the end of the validation. No apparent abnormalities associated with storage for up to seven days at -20 °C were observed.

Table 21: Long-term Stability in Frozen Sodium Heparin Human Plasma (389 Days at -20 °C)

Stability Notebook Reference	8367-10-03	8367-10-03	
Stability Sample Prep Date	03-JUL-06	03-JUL-06	
Date Samples Extracted	27-JUL-07	27-JUL-07	
Approx. Stability Evaluation Days	389	389	
Status	Final Report		
Report #	1333314		
	Run ID	STAB 2 (µg/mL)	
		STAB 6 (µg/mL)	
	6XWP4-A	0.507	38.9
		0.538	38.9
		0.498	38.8
		0.524	38.3
		0.510	41.7
		0.503	38.5
	N	6	6
	Theoretical Concentration	0.500	37.5
	Mean	0.513	39.2
	S.D.	0.0148	1.23
	%C.V.	2.88	3.13
	% Difference from Theoretical	2.63	4.52

Table 22: Long-term Stability in Frozen Sodium Heparin Human Plasma (266 Days at -70 °C)

Stability Notebook Reference	8894-17-05	8894-17-05
Stability Sample Prep Date	04-MAY-07	04-MAY-07
Date Samples Extracted	25-JAN-08	25-JAN-08
Approx. Stability Evaluation Days	266	266
Status	Final Report	
Report #	1411721	
	Run ID	STAB 1 (µg/mL)
		STAB 5 (µg/mL)
	8XWP4-A	0.466
		36.1
		0.486
		35.9
		0.488
		35.4
		0.453
		38.3
		0.460
		37.0
		0.498
		36.6
	N	6
	Theoretical	
	Concentration	0.500
		37.5
	Mean	0.475
		36.6
	S.D.	0.0181
		1.01
	%C.V.	3.81
		2.75
	% Difference	
	from Theoretical	-4.95
		-2.52

Table 23: Long-term Stability in Frozen Lithium Heparin Human Plasma (21 Days at -20 °C)

Stability Notebook Reference	NB1024-94-02	NB1024-94-02
Stability Sample Prep Date	19-JUN-08	19-JUN-08
Date Samples Extracted	10-JUL-08	10-JUL-08
Approx. Stability Evaluation Days	21	21
Status	Final Report	
Report #	1482295	
	Run ID	STBT 2 (µg/mL)
		STBT 6 (µg/mL)
	10XWP4-A	0.464
		36.0
		0.408
		36.5
		0.474
		36.6
		0.477
		36.7
		0.478
		36.9
		0.480
		36.7
	N	6
	Theoretical	
	Concentration	0.500
		37.5
	Mean	0.464
		36.5
	S.D.	0.0278
		0.318
	%C.V.	5.99
		0.871
	% Difference	
	from Theoretical	-7.30
		-2.54

Table 24: Long-term (266 days) Stability in Frozen Lithium Heparin Human Plasma (21 Days at -70 °C)

Stability Notebook Reference	NB1024-93-45	NB1024-93-45
Stability Sample Prep Date	19-JUN-08	19-JUN-08
Date Samples Extracted	10-JUL-08	10-JUL-08
Approx. Stability Evaluation Days	21	21
Status	Final Report	
Report #	1482294	
	Run ID	STBT 1 (µg/mL)
		STBT 5 (µg/mL)
	10XWP4-A	0.463
		35.9
		0.472
		36.9
		0.463
		36.4
		0.473
		37.3
		0.473
		36.0
		0.474
		37.0
	N	6
	Theoretical	
	Concentration	0.500
		37.5
	Mean	0.470
		36.6
	S.D.	0.00527
		0.561
	%C.V.	1.12
		1.53
	% Difference	
	from Theoretical	-6.04
		-2.41

3 Detailed Labeling Recommendations

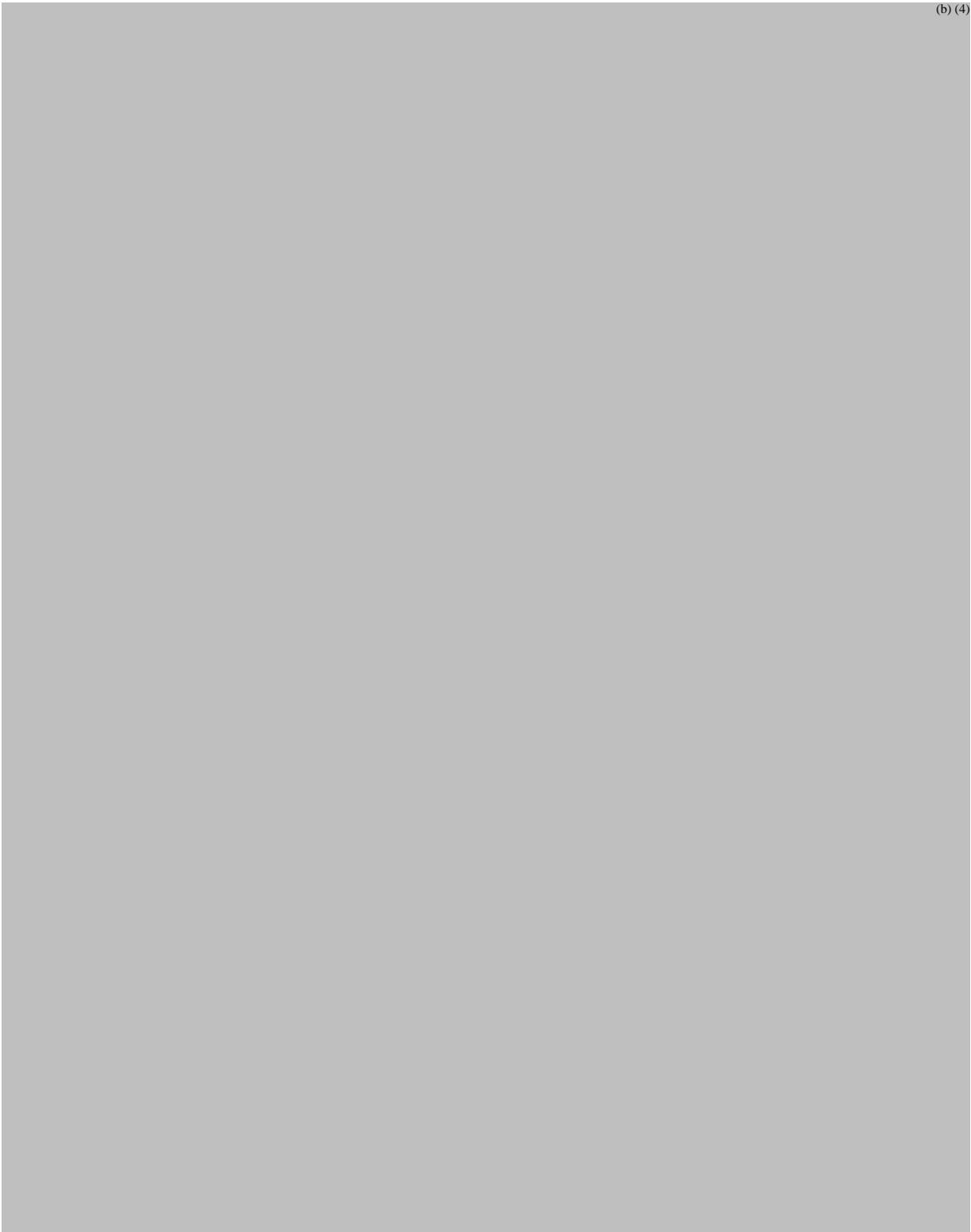
The sponsor's proposed labeling is acceptable.

4 Appendices

4.1 Proposed Package Insert (Original and Annotated)

The proposed labeling is based on the approved class labeling for pain relievers/fever reducers, specifically on the approved labeling for Advil Tablets (NDA 18-989) and Advil Liqui-Gel (NDA 20-402).





4.2 Individual Study Review

4.2.1 Pilot STUDY AH-08-07: A Pilot Study to Compare the Absorption of Ibuprofen Sodium Prototype Tablets to Ibuprofen Liquigels

INVESTIGATOR: Aziz L. Laurent, MD

Clinical Site: PPD Development, LP; 7551 Metro Center Drive; Suite 200; Austin, Texas 78744

Analytical Site: (b) (4)

OBJECTIVES:

To compare the rate and extent (up to 6 hours) of ibuprofen absorption from ibuprofen sodium prototype tablets to ibuprofen liquigels.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Healthy male and female non-smoking volunteers between 18 – 45 years of age, and with a body mass index (BMI) of 18 – 29.

NUMBER OF PATIENTS (PLANNED, ENROLLED, ANALYZED):

Healthy, non-smoking male and female subjects; All 17 subjects that received study medication were analyzed for safety.

DURATION OF TREATMENT: Six hours post-dose for each treatment period, with each of the individual treatment periods separated by a washout period of at least 48 hours.

STUDY DRUG, DOSE, AND MODE OF ADMINISTRATION, BATCH NUMBER:

- Treatment A: 2 x ibuprofen sodium 256 mg prototype tablets formulation I (equivalent to 400 mg ibuprofen)(WH-1373-0002-002) under fasted conditions;
- Treatment B: 2 x ibuprofen sodium 256 mg prototype tablets formulation II (equivalent to 400 mg ibuprofen)(WH-1373-0004-002) under fasted conditions;
- Treatment C: 2 x ibuprofen sodium 256 mg prototype tablets formulation III (equivalent to 400 mg ibuprofen)(WH-1373-0005-001) under fasted conditions.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

- Treatment D: 2 x Advil® Liqui-Gels® 200 mg (total dose = 400 mg)(WH-0693-0001-004) under fasted conditions.

PHARMACOKINETICS AND STATISTICAL METHODS:

The AUCL and C_{max} data, both log transformed and untransformed, were analyzed for differences between treatments using an analysis of variance (ANOVA) with effects for gender, subject (gender), period, treatment, and treatment-by-gender interaction. The two one-sided hypotheses were tested at 5% level for \ln AUCL, $\ln C_{max}$, AUCL and C_{max} by constructing 90% two-sided confidence intervals for the ratio of reference vs. test formulation for each of the comparisons.

SUBJECT POPULATION:

A total of 17 subjects (8 [47.1%] males and 9 [52.9%] females) participated in the trial. The average age, and body mass index of the population were 30.6 years (range 23-44 years) and 24.3 kg/m² (range 20.0 – 28.0 kg/m²). Eleven (64.7%) of the subjects were White, followed by 3 (17.7%) Black, 2 (11.8%) Asian, and 1 (5.9%) classified as 'Other' race. Eight (47.1%) subjects were of Hispanic ethnicity.

RESULTS

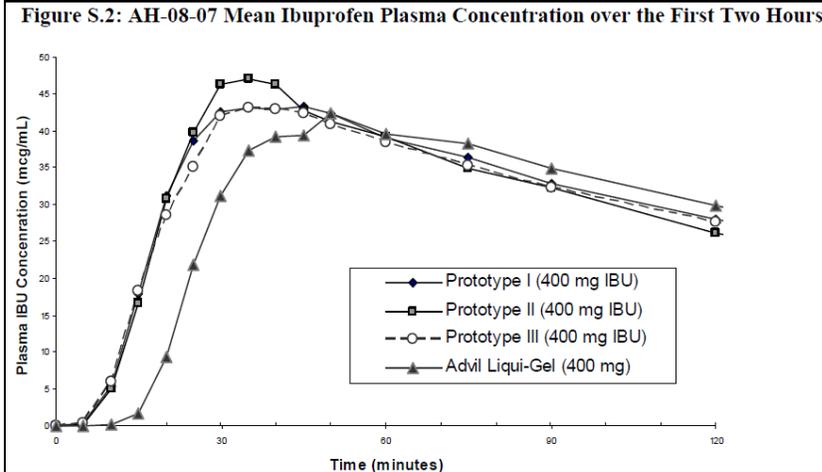
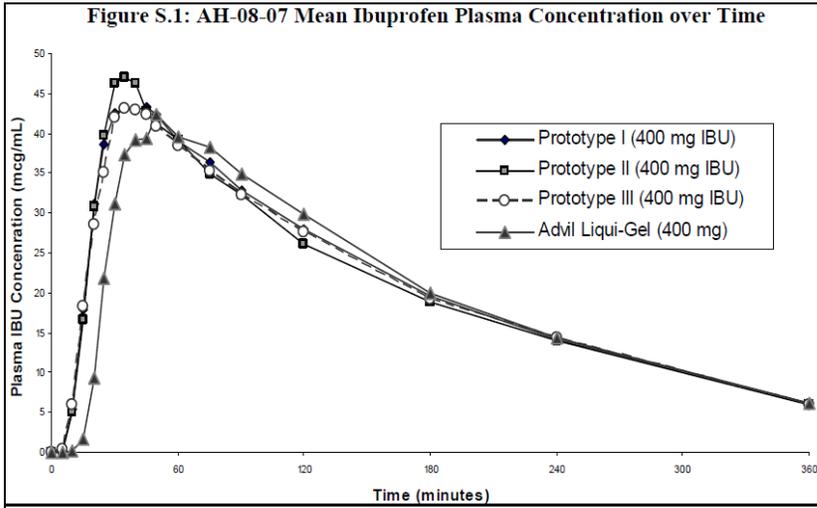
Table S.1: AH-08-07 Summary of Results – IBU Pharmacokinetic Parameters (Mean, Standard Deviation, and 90% Confidence Intervals)

Treatment	AUCL (mcg•h/mL)	C _{max} (mcg/mL)	T _{max} (min)	T _{mec} (min)	T ₂₀ (min)
A: IBU prototype I	125.80(21.5)	47.41(8.6)	38.75(10.8)	11.36(4.3)	17.74(6.4)
B: IBU prototype II	123.98(20.0)	49.58(7.8)	32.76 (6.1)	10.77(4.4)	16.31(5.0)
C: IBU prototype III	123.44(16.5)	47.06(9.0)	36.70(12.3)	11.72(5.3)	18.16(7.6)
D†: Advil Liqui-Gels	121.52(18.8)	47.61(8.9)	52.36 (16.7)	22.18(8.5)	28.94(12.6)
A/D Ratio [^] (%)	103.26	99.73	--	--	--
90% CI [^]	100.7-105.9	93.0-106.9			
B/D Ratio [^] (%)	101.93	104.62	--	--	--
90% CI [^]	99.4-104.6	97.6-112.2			
C/D Ratio [^] (%)	101.87	98.74	--	--	--
90% CI [^]	99.3-104.5	92.1-105.8			

† Reference product

[^]Based on fitted log-transformed parameters.

Note: Each formulation contained a molar equivalent of 400 mg of ibuprofen.



CONCLUSION:

Based on the PK data from these prototypes, intermediate between Prototypes I and II was developed for further investigation.

4.2.2 STUDY AH-08-08:

Title: A Pharmacokinetic Study Comparing Sodium Ibuprofen Tablets to Ibuprofen Liquigels and Tablets

INVESTIGATOR: Aziz L. Laurent, MD

Clinical Site: PPD Development, LP; 7551 Metro Center Drive; Suite 200; Austin, Texas 78744

Analytical Site: (b) (4)

STUDY OBJECTIVES:

Primary: To compare the rate and extent of ibuprofen absorption from treatments in *fasted* state.

NUMBER OF PATIENTS (PLANNED, ENROLLED, ANALYZED): 32 subjects completed the study.

DURATION OF TREATMENT: 16 hours post-dosing for each treatment period with each of the individual treatment periods separated by a washout period of at least 48 hours.

DOSAGE:

Treatment Group	Per Unit	Per Dose/Route
Treatment A: IBU Na tablets, fasted (WH-1373-0010-004)	ibu 200 mg	2 IBU Na tablets orally in the fasted state
Treatment B: IBU Na tablets, fed (WH-1373-0010-004)	ibu 200 mg	2 IBU Na tablets orally in the fed state
Treatment C (Reference): Advil Liqui-Gels, fasted (WH-0693-0001-007)	solubilized ibu 200 mg	2 liquid capsules orally in the fasted state
Treatment D (Reference): Advil Liqui-Gels, fed (WH-0693-0001-007)	solubilized ibuprofen 200 mg	2 liquid capsules orally in the fed state
Treatment E (Reference): Motrin IB tablets, fasted (WH-0001-0483-003)	ibuprofen 200 mg	2 tablets orally in the fasted state

For Treatments B and D, the following high fat breakfast will be served within 20 minutes prior to dosing: 2 eggs fried in butter, 2 pieces of bacon, 2 pieces of toast with butter, 4 oz. hash browns, and 8 oz. whole milk

SAMPLING TIMES:

Three milliliters (3 mL) of blood drawn at the following time intervals: pre-dose (0 hour) and 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90 minutes and 2, 3, 4, 6, 8, 10, 12 and 16 hours post-dose.

ANALYTICAL:

Plasma samples were frozen at -20°C or below and analyzed subsequently for racemic ibuprofen using a validated method of liquid chromatography with tandem mass-spectrometry (LC/MS/MS). Each blood sample was inverted at least eight times to ensure mixing, cooled in a cryo block, and centrifuged within 30 minutes of collection. Blood was centrifuged at 2,500 revolutions per minute (rpm) for 15 minutes. The plasma was removed and divided into two equal aliquots and transferred to plain tubes. The clinical site stored the plasma samples at -20°C or lower until shipped to analytical site. Plasma samples were analyzed for racemic ibuprofen.

STATISTICAL ANALYSIS:

Pharmacokinetic parameters, AUC_{0-t}, AUC_{0-inf}, and, C_{max}, both log transformed and untransformed, were analyzed for differences between treatments using an analysis of variance (ANOVA) with effects for subject, period, and treatment.

RESULTS

SUBJECT POPULATION: Equal numbers of males and females were enrolled (18 [50%] males and 18 [50%] females). Thirty-one (86.1%) of the subjects were White, 4 (11.1%) Black, and 1 (2.8%) Asian. Seventeen (47.2%) subjects were of Hispanic/Latino ethnicity. The average age, BMI, height, and weight were 27.4 years (range 18.0-45.0 years), 23.9 kg/m² (range 19.0-28.0 kg/m²), 169.1 cm (range 155.0-190.0 cm), and 68.4 kg (range: 50.8-94.3 kg), respectively.

Subjects excluded from the PK analysis: Four subjects (Subject 10004, 10020, 10021, and 10022) discontinued during or after completing Treatment Period 1. Since these subjects did not provide data for at least two treatment periods, per protocol, they were excluded from all pharmacokinetic analyses. Three other subjects also had data excluded for specific periods because they missed two or more consecutive blood draws: Subject 10026 (Treatment Period 2), 10032 (Treatment Period 1), and 10034 (Treatment Periods 1 and 3).

Description of Assay Method and Instrumentation Used: Table 6-2: AH-09-08 Assessment of Accuracy and Precision of Assay Methodologies for Racemic Ibuprofen

	Analyte---Ibuprofen
Intra-Assay Accuracy	-5.10% to 6.92%
Intra-Assay Precision	0.542% to 3.36%
Inter-Assay Accuracy	-5.17% to 4.21%
Inter-Assay Precision	1.11% to 2.79%
Lower Limit of Quantitation	0.2 mcg/mL

Discussion on enantiomer analysis:

The following discussion is intended to address a specific question raised at the pre-NDA meeting on December 15, 2009, related to the PK of individual IBU enantiomers with Na IBU vs. standard IBU acid tablets. In pharmacokinetic studies, Na IBU was administered as the racemic mixture. Since it has a chiral center, IBU exists as two enantiomers, an R- and S-isomer. The former is the inactive form, whereas the latter is pharmacologically active (as a COX-1 and COX-2 inhibitor). When IBU is administered to humans as the racemic mixture, R-IBU undergoes unidirectional chiral conversion to S-IBU (Lee et al, 1985).

In this study, IBU was analyzed only as the racemic mixture, so the actual levels of R and S-IBU are not known. However, there is no reason to believe that the levels of R- and S-IBU following administration of Na IBU would be any different than those following administration of a standard immediate-release IBU acid tablet. A previous study found that AUC values for both R-IBU and S-IBU were not significantly altered after administration of a 600 mg immediate-release racemic IBU tablet vs after a 600 mg sustained release formulation, and levels of S-IBU were higher than those for R-IBU with both formulations (Ding et al, 2007). Furthermore, the S/R ratios for AUC values of the two enantiomers did not differ between the two formulations, and the S/R ratio of serum concentrations was higher for the sustained-release formulation at only a single time point (6 hour). These results suggest that the levels of R-IBU, and more importantly, S-IBU, following administration of Na IBU would not be different from those following ingestion of a standard IBU tablet.

PHARMACOKINETICS RESULTS: The mean plasma ibuprofen concentration curves for the five formulations are presented in Figure S.1. The results for the different comparisons are summarized in Table S.1. Means and standard deviations are presented for the pharmacokinetic parameters AUCL, AUCI, C_{max}, and T_{max}. The median is also presented for T_{max}.

Figure S.1: AH-09-08 Mean Ibuprofen Plasma Concentration over Time - All Subjects (Linear)

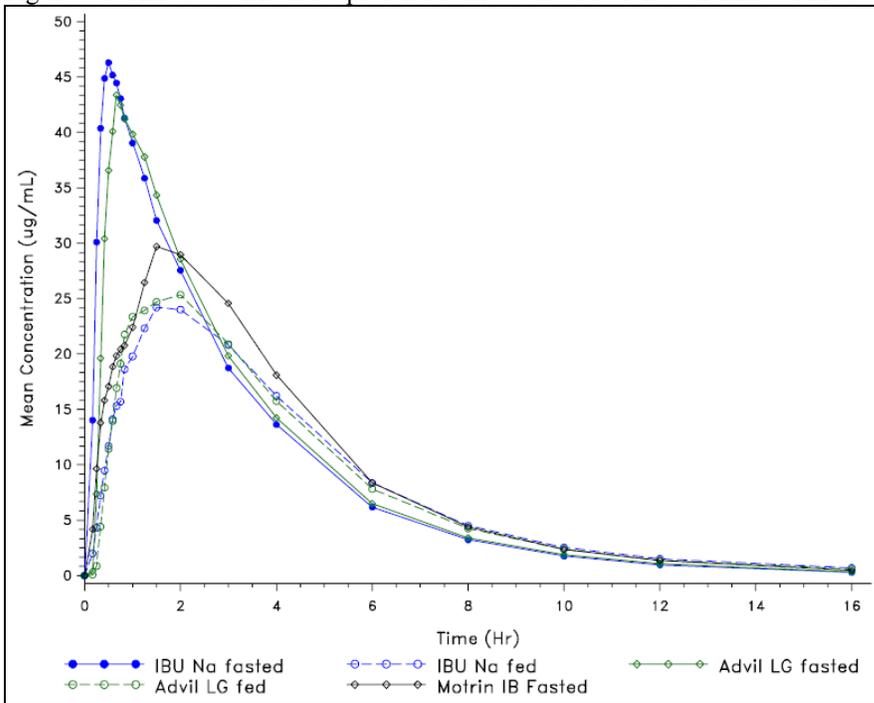
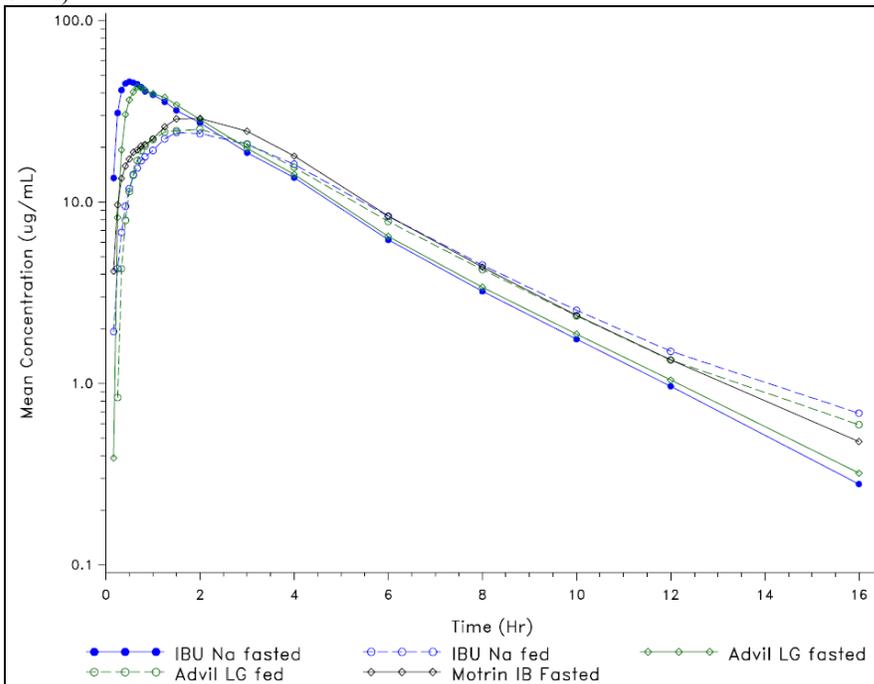
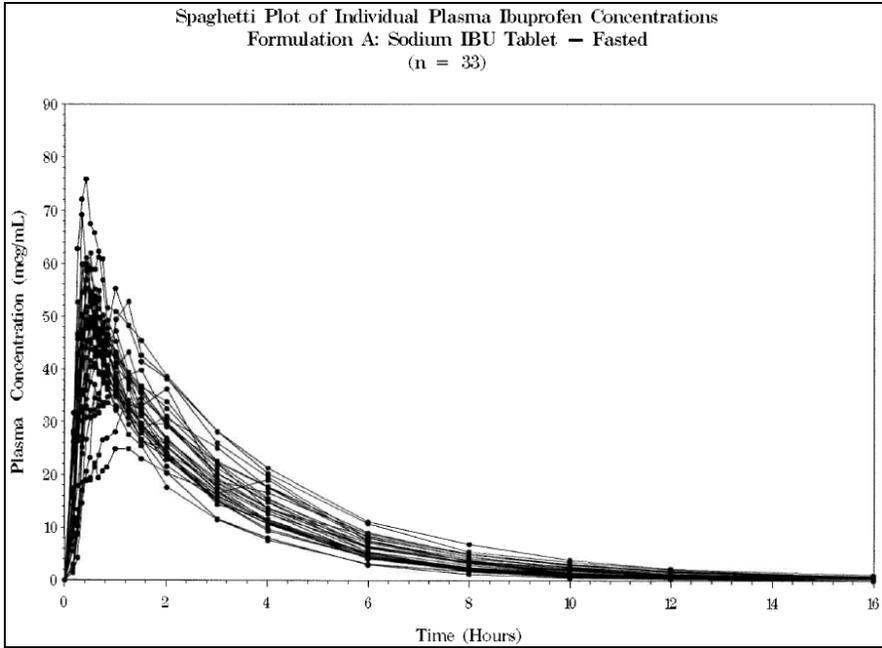


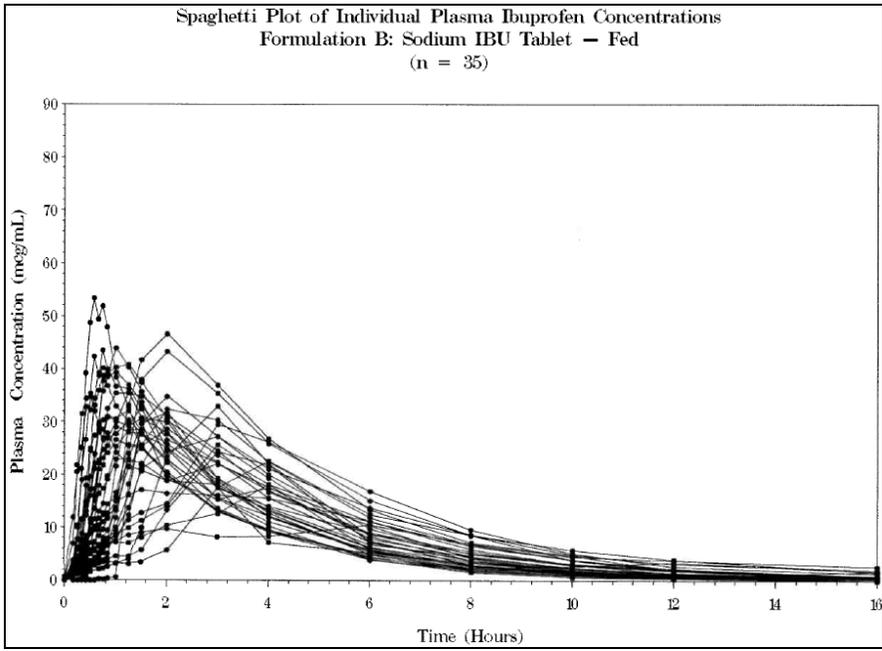
Figure 9-2: AH-09-08 Mean Ibuprofen Plasma Concentration over Time (Semi-Log Scale)



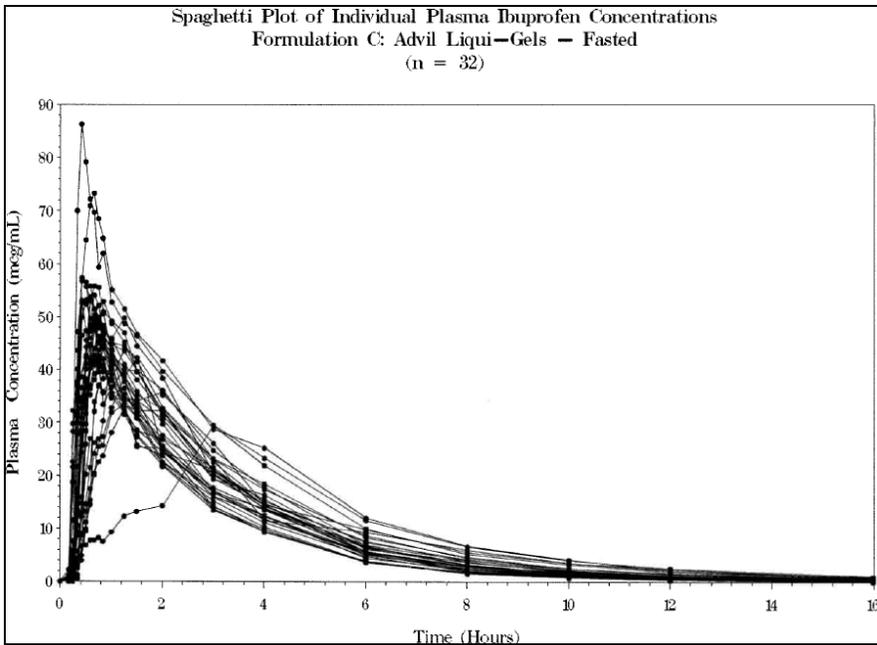
Plot of Treatment A:



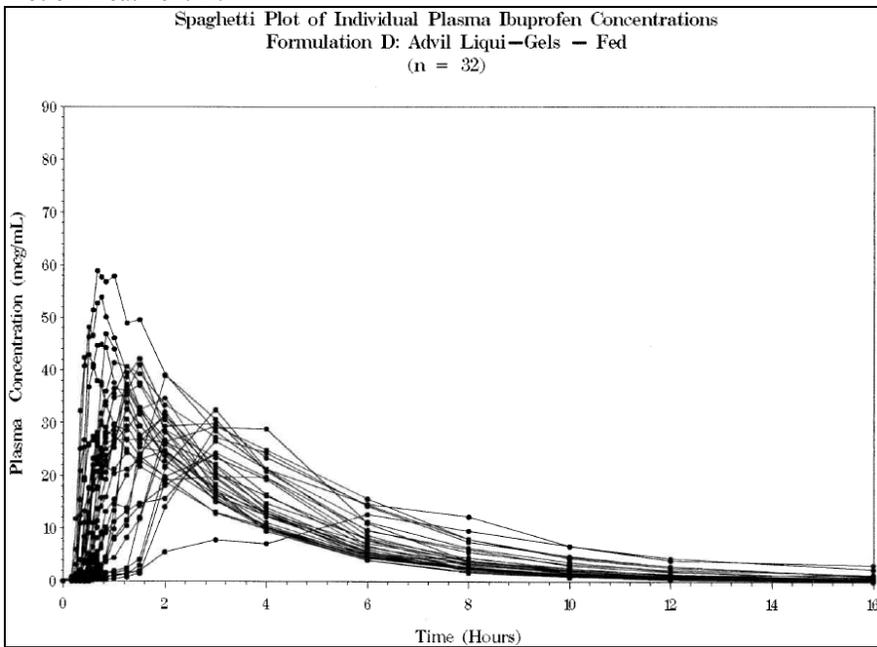
Plot of Treatment B:



Plot of Treatment C:



Plot of Treatment D:



Plot of Treatment E:

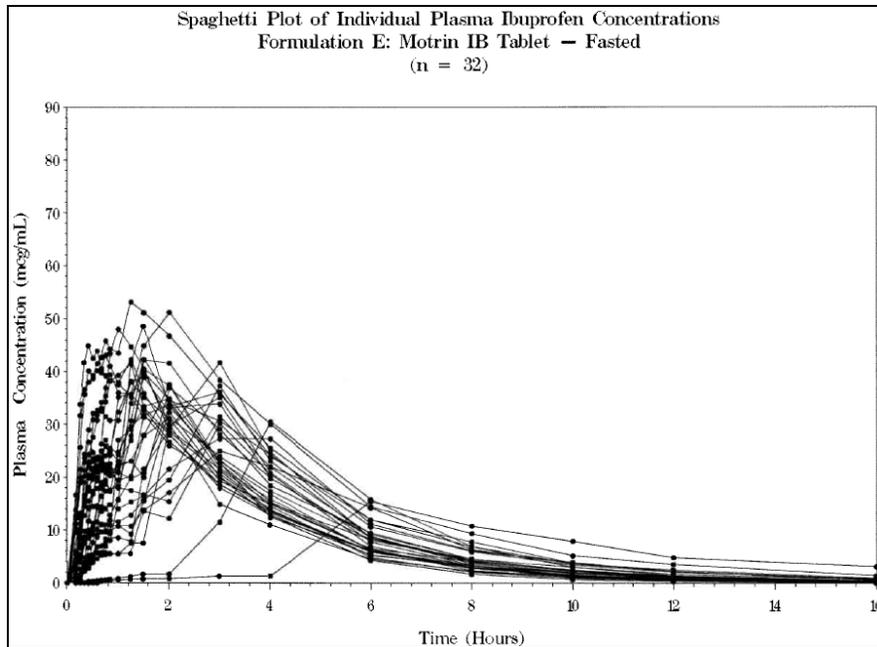


Table S.1: AH-09-08 Summary of Results - Ibuprofen Pharmacokinetic Parameters (Mean, Standard Deviation, Median*, and 90% Confidence Intervals)

Treatment				AUCL (mcg•h/mL)	AUCI (mcg•h/mL)	Cmax (mcg/mL)	Tmax (min)
				Mean (SD)			
A	IBU Tablet	Na	Fasted	145.7 (29.6)	147.2 (30.1)	50.6 (10.3)	35.1 (14.3) [30.4]
B	IBU Tablet	Na	Fed	127.2 (28.6)	130.6 (29.2)	31.5 (8.8)	115.1 (72.5) [90.0]
C	Advil Liqui- Gels		Fasted	143.8 (32.6)	145.5 (33.2)	48.6 (11.2)	50.1 (29.7) [40.5]
D	Advil Liqui- Gels		Fed	125.9 (29.7)	128.9 (30.6)	34.2 (9.7)	111.0 (67.9) [90.0]
E	Motrin IB Tablet		Fasted	143.4 (32.2)	145.6 (32.4)	37.4 (7.8)	126.5 (66.9) [120.0]
Ratio (90% CI)^							
A/C† Ratio (%) 90% CI				102.0 (99.1-105.0)	102.0 (99.1-105.0)	104.2 (96.6-112.4)	--
A/E† Ratio (%) 90% CI				102.4 (99.5-105.4)	101.8 (98.9-104.8)	135.0 (125.2-145.5)	--

B/D† Ratio (%) 90% CI	101.7 (98.8-104.7)	102.1 (99.2-105.1)	91.2 (84.6-98.3)	--
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*Median presented for Tmax only

^Based on fitted log-transformed parameters.

†Reference product

IBU Na tablets (fasted) (Treatment A) versus Advil Liqui-Gels (fasted) (Treatment C) - Primary: The two formulations were bioequivalent with respect to both the extent [A/C ratio for AUCL = 102.0%, 90% CI = (99.1, 105.0%)] and the rate [A/C ratio for Cmax = 104.2%, 90% CI = (96.6, 112.4%)] of ibuprofen absorption.

IBU Na tablets (fasted) (Treatment A) versus Motrin IB tablets (fasted) (Treatment E): The two formulations were bioequivalent with respect to the extent of absorption [A/E ratio for AUCL = 102.5%, 90% CI = (99.6, 105.5%)] but IBU Na tablets (fasted) had a faster rate of ibuprofen absorption [A/E ratio for Cmax = 135.0%, 90% CI = (125.2, 145.5%)] relative to Motrin IB tablets.

IBU Na tablets (fed) (Treatment B) versus Advil Liqui-Gels (fed) (Treatment D): The two formulations were bioequivalent with respect to both the extent [B/D ratio for AUCL = 101.7%, 90% CI = (98.8, 104.7%)] and the rate [B/D ratio for Cmax = 91.2%, 90% CI = (84.6, 98.3%)] of ibuprofen absorption.

The mean half-life, elimination rate, clearance, and volume of distribution were the same across the five treatments (about 2.5 hr, 0.30 hr⁻¹, 3 L/hr, and 10 L, respectively).

CONCLUSION: Sodium ibuprofen tablets were bioequivalent to Advil Liqui-Gels in the fasted state.

4.3 Consult Review (including Pharmacometric Reviews) – Not applicable

4.4 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form					
General Information About the Submission					
	Information		Information		
NDA Number	201803		Brand Name	To be determined	
OCP Division (I, II, III)	II		Generic Name	Ibuprofen sodium dehydrate	
Medical Division	DNCE		Drug Class	NSAIDs	
OCPB Reviewer	David Lee		Indication(s)	Pain	
OCPB Team Leader	Suresh Doddapaneni		Dosage Form	Immediate release tablet	
			Dosing Regimen	1 to 2 tablets Q4 to 6	
Date of Submission	6/30/10		Route of Administration	Oral	
Estimated Due Date of OCP Review	2/28/11		Sponsor	Pfizer	
Medical Division Due Date			Priority Classification	S	
PDUFA Due Date	5/1/11				
Clin. Pharm. and Biopharm. Information					
	“X” included if 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	1	1	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	x			
Blood/plasma ratio:	x			
Plasma protein binding:	x			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	2	2	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
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:				Waiver
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 2/3:				
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 -	x			
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				

BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Filability and QBR comments				
	"X" if yes	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?		

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/s/

DAVID J LEE
02/28/2011

SURESH DODDAPANENI
03/01/2011

ADDENDUM to ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	201-803/N-000
Submission Date:	02/25/11
Brand Name:	Advil (b) (4)
Generic Name:	Sodium ibuprofen dihydrate (256 mg)
Formulation:	Oral immediate release (IR) tablet and capsule-shaped (Caps-Shaped) IR tablet
Strength:	200 mg Ibuprofen
Sponsor:	Pfizer
Type of submission:	Proposed Dissolution Specifications
Reviewer:	Tien-Mien Chen, Ph.D.

The above NDA was reviewed on 02/15/11 and the following comment has been sent to the sponsor on 02/17/11 to revise the dissolution specification for Advil (b) (4):

**Change from Q= (b) (4) % at (b) (4) min
to Q= (b) (4) % at 15 min.**

On 02/25/11, the sponsor counter-proposed: Q= (b) (4) % at (b) (4) min. On 02/28/11, a teleconference between the Agency and the sponsor was held earlier today to resolve the above issue.

At the end of the teleconference, the sponsor agreed with the Agency's proposal and will revise and implement the specifications of Q= (b) (4) % at 15 min for Advil (b) (4).

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/s/

TIEN MIEN CHEN
02/28/2011

PATRICK J MARROUM
02/28/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	201-803/N-000
Submission Date:	06/30/10
Brand Name:	Advil- (b) (4)
Generic Name:	Sodium ibuprofen dihydrate (256 mg)
Formulation:	Oral immediate release (IR) tablet and capsule-shaped (Caps-Shaped) IR tablet
Strength:	200 mg Ibuprofen
Sponsor:	Pfizer
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Advil IR tablet (ibuprofen 200 mg) under NDA 18-989 was approved on 05/18/84. Ibuprofen is a nonsteroidal, anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic activity.

On 06/30/10, Pfizer submitted an original NDA 201-803 to the Agency seeking approval for sodium ibuprofen dihydrate 256 mg (equivalent to ibuprofen 200 mg) in two different tablet shapes; Advil- (b) (4) IR tablets (round shape) and Advil- (b) (4) IR Caps-Shaped tablets. It was filed under 505(b)(2) referencing NDA 18-989 (Advil IR tablet, Ibuprofen 200 mg). The proposed dosing and indications are identical to those of currently marketed over the counter (OTC) Ibuprofen 200 mg, Advil IR tablet.

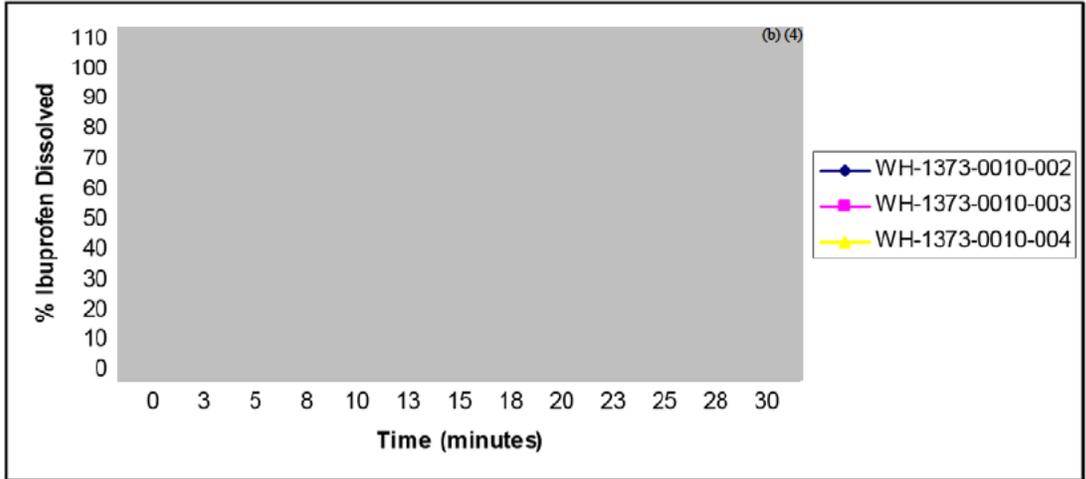
Under NDA 201-803, a pivotal bioequivalence (BE) study (No. 09-08) was conducted using the to be-marketed (TBM) Advil- (b) (4) IR tablet formulation in order to link to Advil IR tablets (200 mg ibuprofen). Also submitted for review were 1). The proposed dissolution methodology and specifications, 2). The dissolution data of three registration batches of both IR tablets and IR Caps-Shaped tablets, and 3). The dissolution development report. The pivotal BE study is currently under review by the Office of Clinical Pharmacology (OCP). The dissolution development report, the proposed dissolution methodology and specifications, and the dissolution data are reviewed here.

The dissolution development report was reviewed and the sponsor's conclusion and justifications on the selection of the dissolution methodology below were found acceptable.

Media/Temperature (Units Tested)	Dissolution Apparatus	Speed of Rotation
900 mL of 50mM phosphate buffer, pH 7.2 37°C ± 0.5°C (6 units tested)	USP Apparatus I Baskets	100 rpm

The mean dissolution profiles of the three registration batches of IR tablets using the above proposed dissolution method are shown below.

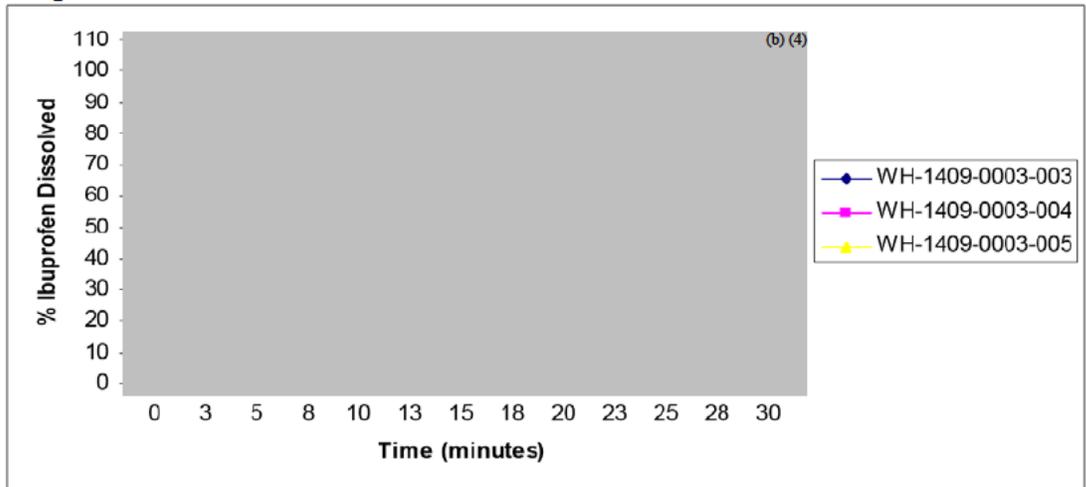
Mean Dissolution Profiles of the Three Registration Batches of Advil- (b) (4) IR Tablets



Note: Batch No. WH-1373-0010-004 is also a biobatch used in the BE study No. 09-08.

The mean dissolution profiles of the three registration batches of IR Caps-Shaped tablets using the above proposed dissolution method are shown below.

Mean Dissolution Profiles of the Three Registration Batches of Advil- (b) (4) IR Caps-Shaped Tablets



Advil- (b) (4) IR Caps-Shaped tablets showed comparable mean dissolution profiles with those of Advil (b) (4) IR tablets. It provides a link to the BE data since the IR Caps-Shaped tablets had not been tested clinically.

Finally, the sponsor proposed specifications, $Q = \frac{(b) (4)}{(4)}\%$ at $\frac{(b) (4)}{(4)}$ min, for both Advil IR tablets and IR Caps-Shaped tablets need to be $\frac{(b) (4)}{(4)}$ since $\frac{(b) (4)}{(4)}$ of Ibuprofen dissolved in 15 min.

RECOMMENDATION

From the Biopharmaceutics perspective, the proposed dissolution methodology and dissolution data were reviewed and found acceptable for both Advil-^{(b)(4)} IR tablets and IR Caps-Shaped tablets, however, the proposed dissolution specifications need further revisions. The following comment needs to be conveyed to the sponsor.

COMMENT (Needs to be sent to the sponsor)

Your proposed dissolution methodology as shown below is acceptable.

Media/Temperature (Units Tested)	Dissolution Apparatus	Speed of Rotation
900 mL of 50mM phosphate buffer, pH 7.2 37°C ± 0.5°C (6 units tested)	USP Apparatus I Baskets	100 rpm

However, your proposed dissolution specifications need to be tightened since >90% of Ibuprofen dissolved in 15 min, i.e.,

**Change from Q= ^{(b)(4)}% at ^{(b)(4)} min
to Q= ^{(b)(4)}% at 15 min.**

Prior to approval, you should update your specifications to reflect the newly recommended dissolution specifications.

BACKGROUND

Ibuprofen, an orally-administered propionic acid derivative, is an NSAID with analgesic, anti-inflammatory, and antipyretic activity. Like all traditional non-selective NSAIDs, the putative mechanism of action is attributed to reduction of prostaglandin biosynthesis via non-selective inhibition of two isoenzymes: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Advil IR tablet (ibuprofen 200 mg) under NDA 18-989 was approved on 05/18/84.

CURRENT SUBMISSION

On 06/30/10, Pfizer submitted an original NDA 201-803 to the Agency for review seeking approval for sodium ibuprofen dihydrate 256 mg (equivalent to ibuprofen 200mg) in two different tablet shapes; Advil (b) (4) IR tablets (round shape) and Advil- (b) (4) IR Caps-Shaped tablets. It was filed under 505(b)(2) referencing NDA 18-989 (Advil IR tablet, Ibuprofen 200 mg).

The proposed dosing is identical to that of currently marketed OTC Ibuprofen 200 mg, Advil IR tablet: one tablet every 4-6 hrs while symptoms persist, or if pain or fever does not respond to one tablet, two tablets may be used, with a maximum daily dose of 1200 mg in adults and children 12 years of age and over.

The proposed indications are also identical to that of currently marketed OTC Ibuprofen 200 mg tablets/caplets/liqui-gels: for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, and the minor pain of arthritis, as well as the temporary reduction of fever.

Under NDA 201-803, a pivotal BE study (No. 09-08) was conducted using the final, commercial/TBM IR tablet formulation in order to link to NDA 18-989 (Advil IR tablets; 200 mg ibuprofen). Also submitted for review are 1). The proposed dissolution methodology and specifications, 2) The dissolution data of the three registration batches of both IR tablets and IR Caps-Shaped tablets, and 3). The dissolution development report. The pivotal BE study is currently under review by the Office of Clinical Pharmacology. The dissolution development report, the proposed dissolution methodology and specifications, and the dissolution data are reviewed here.

FORMULATION COMPARISONS

The final formulation as shown below is the same for Advil- (b) (4) IR tablets and Caps-Shaped tablets. The only difference is the shape of the tablets.

Table 1. Final TBM Formulation of Sodium Ibuprofen Dihydrate 256 mg IR Tablets and IR Caps-Shaped Tablets (Ibuprofen 200 mg)

Ingredient	Grade/Quality Standard	Unit Dose (mg/du)	
Sodium Ibuprofen Dihydrate	DMF	256.25	
Colloidal Silicon Dioxide	NF, Ph. Eur.	(b) (4)	
Mannitol	USP, Ph. Eur.		
Microcrystalline Cellulose	NF, Ph. Eur.		
Sodium Lauryl Sulfate	NF, Ph. Eur.		
(b) (4)	DMF		
Acesulfame Potassium	NF, Ph. Eur.		
Sucralose	NF		
(b) (4)	DMF		
Carnauba Wax	NF, Ph. Eur.		
(b) (4)	DMF		
	USP, Ph. Eur.		
	USP, Ph. Eur.		
Total:			446.2

a. Essentially removed during processing.

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The development of dissolution methodology involved dissolution testing using various conditions as summarized below. Please see the dissolution development report No. 09GTR006.01 for details.

Table 2. Summary of the Development of Dissolution Testing Method

Experiment	Dissolution Parameters	Samples and Conditions
Different Rotational Speeds	(b) (4)	(b) (4)
Different Apparatus		
Different Vessel		
Different Medium pH		
Different Apparatus and Medium pH		

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Tien-Mien Chen, Ph.D.
Reviewer
ONDQA Biopharmaceutics

02/14/11
Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

02/14/11
Date

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

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