

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75661

BIOEQUIVALENCY REVIEW(S)

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA #: 75-661

①

SPONSOR: BASF corp.

DRUG AND DOSAGE FORM: **Ibuprofen Tablet**

STRENGTH(S): **200mg**

TYPES OF STUDIES: Single dose fasting and fed, Dissolution

CLINICAL STUDY SITE(S): (

ANALYTICAL SITE(S): (

SUMMARY: Bio-studies acceptable.

DISSOLUTION: Acceptable

DSI INSPECTION STATUS

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

PRIMARY REVIEWER: Pradeep M. Sathe, Ph.D.

BRANCH: II

INITIAL: _____

[Signature]

DATE: _____

11/6/07

TEAM LEADER: Shrinivas G. Nerurkar, Ph.D.

BRANCH: II

INITIAL: _____

[Signature]

DATE: _____

11/6/2001

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

INITIAL: _____

[Signature]

DATE: _____

11/6/01

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-661

APPLICANT: BASF

DRUG PRODUCT: Ibuprofen tablet, 200mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

CC: ANDA 75-661
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer (P.Sathe)

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Printed in final on 11/06/01

Endorsements: (Final with Dates)
HFD-655/ Reviewer *PS* 11/6/01
HFD-655/ Bio team Leader
HFD-650/ D. Conner *APB* 11/6/01

PS 11/6/01

BIOEQUIVALENCY - ACCEPTABLE

submission date: Oct. 9, 2001

1. **FASTING STUDY (STF)**
Clinical:

Strengths: 200mg

Analytical:(

Outcome: AC

2. **FOOD STUDY (STP)**
Clinical:(

Strengths: 200mg

Analytical:(

Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:

Ibuprofen
200 mg film coated Tablet
ANDA 75-661
Reviewer: Pradeep M. Sathe, Ph.D.

BASF Corporation
Shreveport, LA-77136
Submission Dates:
June 30, August 16, 1999

REVIEW OF TWO BIO-STUDIES AND DISSOLUTION

BACKGROUND/CURRENT APPLICATION: The firm has approved 400 mg, 600 mg and 800 mg strengths on the market. These are prescription strengths. The Orange Book lists the 200 mg strength tablet as the OTC product. The Orange Book recommended Innovator product is Nuprin^R 200 mg strength by McNeil Labs. The application consists of two bioequivalence studies (fasting and fed) involving the test product and the comparative dissolution. Though the dissolution information may be considered barely acceptable, the information, data and results pertaining to the bio-studies are inadequately presented and deficient in many areas. The submitted information has been reviewed where possible. The firm is however referred to the deficiencies and is requested to submit the data, results and information using the suggested format.

Note: In an amendment dated August 16, 1999, (Attachment 1), the firm clarified a couple of points related to the bio-studies conducted on the other strengths and the use of the innovator product Motrin^{IB} 200 mg OTC tablet.

Table 1

<u>Drug Moiety, Indication</u>	<u>Ibuprofen, Non-steroidal anti-inflammatory</u>
<u>Reported Kinetics</u>	Rapid and complete absorption, T _{max} : 1-2 hr, T _{1/2} : 2 hours, F: 0.8-1, Protein Binding: 0.99, V _d : 0.1L/kg
<u>Reference Product, Other Generics</u>	Motrin ^{IB} ; (Nuprin ^R) by McNeil Labs. OTC product, Other approved generics, Not a first generic
<u>Current Application, Studies</u>	A 'fasting' bioequivalence study, a 'food challenge' bioequivalence study, comparative dissolution
<u>Relation to food</u>	Absorption is slightly affected by co-administration with food.

Table 2: Test Product

Ingredients	200 mg Strength (mg/tab)
<i>Ibuprofen</i>	200
✓ <i>Microcrystalline Cellulose</i>	
✓ <i>Crosscarmallose Sodium</i>	
✓ <i>Polysorbate 80</i>	
✓ <i>Colloidal Silicon Dioxide</i>	
✓ <i>Magnesium Stearate</i>	
Compressed Tablet Weight	220.0
Coating Solution	
✓ <i>Polydextrose FCC</i>	
✓ <i>Hydroxypropyl Methyl Cellulose,</i>	
✓ <i>Hydroxypropyl Methyl Cellulose,</i>	
✓ <i>Hydroxypropyl Methyl Cellulose,</i>	
✓ <i>Polyethylene Glycol</i>	
✓ <i>Carnauba Wax</i>	
✓ <i>Titanium Dioxide</i>	
✓ <i>Synthetic Red Iron Oxide</i>	
✓ <i>FD & C Yellow #10</i>	
✓ <i>FD & C Yellow #6</i>	
Total Film Weight Gain Per Tablet	
Total Weight of the Film Coated Tablet	229.57

* = Removed during processing

Tablet Characteristics	Reference Product	Test Product
Shape	Round	Yet to be determined**
Color	White	Yet to be determined
Imprint	Motrin ^{IB} in black	Yet to be determined
Scoring	No	Yet to be determined

** = Page 022, volume 1.1

DISSOLUTION: Currently, there is a compendial (USP XXIII) dissolution procedure for this product. The firm has conducted comparative dissolution as per the USP monograph.

Table 3

<i>In-Vitro</i> Dissolution Testing						
I. Conditions for Dissolution Testing:						
Apparatus: USP XXIII apparatus II (Paddle) RPM: 50						
No. Units Tested: 12						
Medium: pH 7.2 phosphate buffer at 37°C					Volume: 900 ml	
Specifications: NLT (Q) % (Q) in 30 minutes						
Reference Drug: Motrin ^R IB by McNeil						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product: Ibuprofen Tablet, Lot # WO11421, Strength (200 mg)			Reference Product: Motrin ^R tablet by McNeil, Lot # 39CAM, Strength (200 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	98		2.14	96		2.7
20	99		2.29	99		1.24
30	100		2.23	99		1.46
40	100		2.14	100		1.31

F2=91.2

DEFICIENCIES:

1. To avoid confusion, the two bio-studies (fasting and 'food challenge', should be preferably presented separately in two volumes. Each study should be addressed through the following focal points:

STUDY NUMBER AND CATEGORY e.g. SINGLE DOSE FASTING STUDY:

A. TITLE:

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

1. Principal Investigator:
2. Bio-Study Site:
3. Analytical Investigator:
4. Analysis Site:
5. Study Dates: Period I: Period II:
6. Analysis Dates:

C. STUDY OBJECTIVE:

D. STUDY DESIGN AND NUMBER OF SUBJECTS:

E. SUBJECT SELECTION/EXCLUSION CRITERIA:

F. SUBJECT RESTRICTIONS:

G. TREATMENTS:

1. TEST: ***** Tablet, **** mg (firm name), Lot # *****, Assay Potency= ****%, Batch Size=***** tablets
2. REFERENCE: ***** Tablet, **** mg (Innovator), Lot # *****, Potency= ****%, Expiry date: *****

H. STUDY SCHEDULES:

1. Methods:
2. Randomization Scheme:

	Treatments		
	Period I	Period II	Volunteer Number
Sequence	A	B	*****
	B	A	*****

3. **Blood Samples:** Number of samples drawn, total volume of blood collected, sample scheme, collection and storage.

I. ASSAY: Type of assay, detection mode.

1. Extraction:
2. Run Conditions:

Analytical Column:

Mobile Phase:

Flow rate:

Injection Volume:

Detector:

Integrator:

Internal Standard:

Approximate Retention Times:

3. Calibration: equation:

4. Analytical Validation: The analytical validation information reports should be presented in tables for the following:

Specificity:

Recovery:

Limit of Quantitation:

Intra-assay variability:

Inter-assay variability:

Linear Dynamic Range:

Freeze Thaw Cycles:

Room Temperature Stability:

In-Process Stability:

Long-Term Stability: Must cover at least the duration of the study.

J. PHARMACOKINETICS AND STATISTICS: Methods should be provided. The statistical data should be arranged with respect to each treatment. The mean standard deviation and coefficient of variation of the data should be provided. If a General Linear Model is used for the statistical analysis; it should have the following classes and structure: Response Parameter= Sequence Sequence(Subject) Period Treatment

K. ADVERSE EVENTS: Please provide a table with probable possible or definite relationship of the adverse events to the administered drug product.

L. RESULTS:

1. A Table with time, Mean (n=24, say) Plasma levels with %CV's and the ratio of the means:
2. A Table of Mean Pharmacokinetic Parameters (with and without log conversion) and the 90% confidence intervals using the two-one sided test procedure.

3. Plasma profiles (plots) of the two treatments (in the case of the 'food challenge' study, three treatments) with respect to each subject and mean profiles (plots).
4. The plasma levels of each treatment should be tabulated and presented with their mean, standard deviation and coefficient of variation information. The pharmacokinetic parameters should be submitted in an ASCII format (on a 3.5" diskette) with the following variables. Please provide a separate file for each study.

Subject	Sequence	Period	Treatment	AUCt	AUCinf	Cmax	Tmax	TI/2
1.	***	***	***	***	***	***	***	***
2	***	***	***	***	***	***	***	***
3	***	***	***	***	***	***	***	***

A similar format should be used to present the results of the 'food challenge' study.

2. It is not clear why the firm has used the MIXED EFFECTS model instead of the GENERAL LINEAR model for the statistical analysis of the fasting study data. Please explain.
3. It is not understood why the 'food challenge' study was conducted using only 12 subjects leading to only 2 subjects per sequence.
4. The firm should complete the "How Supplied" section of the labelling. It is pointed out that the firm *may not* make changes such as 'scoring' to the test product, unless it is also seen with the innovator product.

RECOMMENDATIONS:

1. The dissolution testing conducted by BASF Pharmaceuticals on its Ibuprofen 200 mg Tablet, Lot # WO11421, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 ml of pH 7.2 phosphate buffer at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

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

2. The fasting and 'food challenge' bioequivalence studies conducted by BASF Pharmaceuticals on its 200 mg Ibuprofen tablet, lot # WO11421, comparing it to McNeil's, 200 mg Motrin^R tablet Lot # 39CAM, have been found deficient and

incomplete by the Division of Bioequivalence.

3. At present, from the bioequivalence point of view, the application is incomplete. Deficiencies 1-4 should be forwarded to the firm.

/S/
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II.

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

/S/

9/20/1999

Concur:

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

Date: 11/4/99

cc: ANDA 75-661 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

Ibuprofen
200mg Tablet
ANDA 75-661
Reviewer: Pradeep M. Sathe, Ph.D.

4.1
JPD
BASF Corp.
Shreveport, LA-71106
Submission Date:
October 9, 2001

REVIEW OF TWO BIO-STUDIES AND THE DISSOLUTION

<u>Drug Moiety, Indication</u>	<i>Ibuprofen, Non-steroidal anti-inflammatory</i>
<u>Reported Kinetics</u>	Rapid and complete; absorption, Tmax: 1-2 hr, T1/2: 2 hours, F: 0.8-1, Protein Binding: 0.99, Vd: 0.1L/kg
<u>Reference Product, Other Generics</u>	Motrin [®] IB, (Nuprin [®]) by McNeil Labs. OTC product. Other approved generics. Not a first generic
<u>Current Application, Studies</u>	A 'fasting' bioequivalence study, a 'food challenge' bioequivalence study, comparative dissolution
<u>Relation to food</u>	Absorption is slightly affected by co-administration with food.

Background/Current Amendment:

The firm has approved 400 mg, 600 mg and 800 mg strengths on the market. These are prescription strengths. As per the 'Orange Book', 200mg strength tablet is an OTC product. The Orange Book lists Nuprin[®] 200mg tablet (McNeil Labs) as the innovator product. The amendment consists of reanalyzed results of two bio-equivalence studies (fasting and fed). The firm has conducted re-validation of the assay methodology, and conducted reanalysis of the bio-study samples in response to the Division's recommendation. The firm's reanalysis results are reviewed together with the information from the original submissions, which were dated July 30, 1999 and August 16, 1999. These included a single dose fasting, and a single dose post-prandial bioequivalence study comparing firm's Ibuprofen Film-Coated Tablets USP, 200 mg, with McNeil's Motrin[®] 200 mg Ibuprofen Tablets. The applications also included comparative dissolution data on the test and RLD products.

History:

1. June 30, 1999 and August 16, 1999.

The bio-study data could not be analyzed because it was not presented in a proper format. The firm was informed of the proper format to present the bio-study data (review date November 4, 1999).

2. April 13 and April 20, 2000.

This was not the firm's response to the item 1.

The submission had

- i) results of the inspection conducted by the Division of Scientific Investigation (DSI),
- ii) the form 483 that described the deficiencies, and
- iii) a response to every deficiency cited on form 483.

The review of the submission indicated that the responses had serious flaws. The firm was informed (review date May 31, 2000) of sixteen deficiencies.

3. June 23, 2000

This was a response to item 2.

The firm responded to the 16 deficiencies cited above. The firm's responses were evaluated. The responses were not totally satisfactory (review date September 29, 2000). Seven new deficiencies were communicated to the firm.

4. October 31, 2000

This is a response to the item 3

The firm's responses to the seven deficiencies were evaluated. The firm was notified that

- 1) The 'OGD' has concerns about the assay validation.
- 2) bio-study data was therefore not statistically evaluated.

5. October 9, 2001 (Current Amendment):

In response to the Division's recommendation, in the amendment, the firm has conducted 1) re-validation of the assay methodology and 2) re-assayed plasma samples of the fasting and 'fed' studies.

Table I: Test Product

Ingredients	200 mg Strength (mg/tab)
Ibuprofen	200
✓ Microcrystalline Cellulose	
✓ Crosscarmallose Sodium	
✓ Polysorbate 80	
✓ Colloidal Silicon Dioxide	
✓ Magnesium Stearate	
Compressed Tablet Weight	220.0
Coating Solution	
✓ Polydextrose FCC	
✓ Hydroxypropyl Methyl Cellulose,	
✓ Hydroxypropyl Methyl Cellulose,	
✓ Hydroxypropyl Methyl Cellulose,	
✓ Polyethylene Glycol	
✓ Carnauba Wax	
✓ Titanium Dioxide	
✓ Synthetic Red Iron Oxide	
✓ FD & C Yellow #10	
✓ FD & C Yellow #6	
Total Film Weight Gain Per Tablet	
Total Weight of the Film Coated Tablet	229.57

* = Removed during processing

Table 2

Tablet Characteristics	Reference Product	Test Product
Shape	Round	Round
Color	White	Brown
Imprint	Motrin ^{IB} in black	"IBU 200" in black
Scoring	No	No

SINGLE DOSE FASTING STUDY (#IBU200, phase I):

A. TITLE: In-vivo Bioequivalence study for IBU200 (In-vivo fasted single dose bioequivalence study of ibuprofen tablets, USP, 200mg film coated tablets by BASF.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

1. Principal Investigator: ()

2. Bio-Study Site: []

3. Analytical Investigator: ()

4. Analytical Site: []

5. Assay Dates: June 8 through June 22, 2001

C. STUDY OBJECTIVE: To conduct (re-assay and analyze the plasma samples for) a fasting in-vivo bio-equivalence study to compare the bioequivalence of the test product IBU® 200 by BASF, to the reference listed drug product Motrin®.

D. STUDY DESIGN AND NUMBER OF SUBJECTS: A two-period, two-sequence crossover study in 24 healthy volunteers with a 36-hour washout period. Twenty-four subjects entered the study. All 24 completed the study. There were no drop-outs.

Demographics: Age: 33.4±7.3 years, Sex (Female:Male): 17:7, Race (African American:White:Other: 3:21:0)

E. SUBJECT SELECTION/EXCLUSION CRITERIA: Page numbers 102-103 volume 1.2, original application.

F. SUBJECT RESTRICTIONS: Page Number 103 volume 1.2 original application

G. DRUG TREATMENTS:

1. TREATMENT A (TEST PRODUCT): Ibuprofen Tablets, 200mg (BASF Labs.), Lot #WO11421, Assay Potency = 101.8%, Batch Size= tablets

2. TREATMENT B (REFERENCE PRODUCT): Motrin^R Tablets, 200mg (McNeil), Lot #39CAM, Assay Potency=98.2%, Expiry date: 12/2002

H. STUDY SCHEDULES:

1. **Methods:** Page number 102, volume 1.2 of the original application

2. **Randomization Schedule:**

Treatment		Volunteer Number
Phase I	Phase II	
A	B	1, 5, 6, 7, 9, 10, 11, 14, 18, 21, 24
B	A	2, 3, 4, 8, 12, 13, 15, 16, 17, 19, 20, 22, 23

3. **Blood Sampling:** 0.0 (pre-dose) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0 and 12.0 hr post-dose.

I. Reanalysis Assay Methodology: by

Assay procedure:

Run Conditions:

Type: at 220nm

Column: Waters C18 (4.6*150mm) with a C18 guard-column of (3.9*20mm)

Mobile Phase: 40% water pH 2.6 (adjusted with phosphoric acid):60% acetonitrile

Flow Rate: 2.0 ml/min

Injection Volume: 25 microliters

Column Temperature: 40°C

Integrator: Waters Millenium 32 Chromatography manager

Internal Standard: Naproxen

Retention Times: Ibuprofen 3.1 minutes, Naproxen 1.7 minutes

NOTE: In the reanalysis, each set of calibration curve standards was included each analytical run. The QC samples of Low, Medium and High concentrations were () mcg/mL and () mcg/mL for the pre-study validation and () mcg/mL () mcg/mL and () mcg/mL for the during study validation.

Assay Specificity: acceptable

Limit of Quantitation: 1.56 mcg/mL was determined based on the criterion that the limit of quantitation response is >5 times the response of the blank. Any concentration below this limit was reported as zero.

Linearity: Standard Curve 0.78-100.0 mcg/mL (0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, and 100mcg/mL).

Reproducibility:

Pre-Study validation:

Intra-day precision: CV 2.74% at 4.50 mcg/mL (n=6), 2.39% at 40.0 mcg/mL (n=6) and 2.66% at 85.0 mcg/mL (n=6).

Inter-day Accuracy: 98.8% at 4.50 mcg/mL (n=6), 99.8% at 40.0 mcg/mL (n=6) and 99.9% at 85.0 mcg/mL (n=6).

During Study Validation:

Intra-day CV (precision): 5.2% at 4.50 mcg/mL (n=54), 13.3% at 30.0 mcg/mL (n=54) and 8.6% at 65.0 mcg/mL(n=54).

Inter-day Accuracy: 95.6% at 4.50 mcg/mL (n=54), 96.7% at 30.0 mcg/mL (n=54) and 98.5% at 65.0 mcg/mL(n=54).

Recovery:

Pre-study: From ()% for concentrations of () micrograms per ml.

Stability Studies:

Long-term stability study: Plasma standards prepared before or on the day the study samples were collected (50.0 and 10.0 mcg/mL on 12/7/98 and 30.0 and 100 mcg/mL on 2/12/99), stored -70°C, were analyzed shortly before the sample reanalysis (6/5/01) and at the end of the sample reanalysis (8/8/01). The results were compared with the nominal values and summarized below.

	<u>50 mcg/mL(n=3)</u>	<u>10 mcg/mL(n=3)</u>
12/7/98 to 6/5/01 (910 days)	88.6%(CV=2.22%)	90.8% (CV=2.78%)
12/7/98 to 8/8/01 (974 days)	95.3% (CV=3.40%)	93.6% (CV=2.82%)
	<u>30 mcg/mL(n=3)</u>	<u>100 mcg/mL(n=3)</u>
2/12/99 to 6/5/01 (843 days)	95.0% (CV=1.65%)	-----
2/12/99 to 8/8/01 (907 days)	100.1% (CV=1.78%)	98.8% (CV=4.37%)

Ibuprofen has been shown above to be stable in frozen plasma @ -70C for the maximum storage duration of the study samples (from 2/1/99 (first dosing date of the Non-Fasting Study which preceded the Fasting Study) to 7/25/01 (last date of the sample reanalysis) or 904 days).

Short-term stability: 24 hours at room temperature (unprocessed samples); 48 hours at room temperature (processed samples in auto sampler)

Freeze-thaw: 3 cycles

Repeat Samples: Two samples from the reanalysis of both studies were repeated for analytical reasons.

J. PHARMACOKINETICS AND STATISTICS: Page 572-573 of volume 4.3 of the amendment. Parameters: AUC_t, AUC_{inf}, C_{max}; with and without log conversion

K. ADVERSE EVENTS: No adverse events are reported directly related to the study. Two adverse events reported not related to the study, headache, mild intensity, non-

serious, resolved spontaneously.

L. RESULTS OF THE FASTING STUDY: Mean (n=24) Plasma ibuprofen levels with %CV's are given in Table 3. Mean Pharmacokinetic Parameters are given in Table 4.

Table 3

Time (hr)	Test	Reference	Ratio (T/R)
0.0	0.0 (---)	0.0 (---)	
0.5	9.8 (52.6)	11.8 (57.5)	0.83
1.0	15.1 (41.7)	14.9 (47.6)	1.01
1.5	15.3 (39.7)	15.7 (30.3)	0.97
2.0	14.9 (32.8)	14.4 (28.3)	1.03
2.5	13.8 (27.5)	11.6 (30.5)	1.19
3.0	10.4 (33.5)	10.7 (23.1)	0.97
3.5	9.4 (33.6)	8.3 (30.2)	1.13
4.0	8.0 (29.0)	7.3 (33.6)	1.10
6.0	3.9 (35.7)	3.4 (30.6)	1.15
8.0	2.4 (24.7)	2.6 (52.8)	0.92
12.0	0.0 (---)	0.0 (---)	

Table 4

Parameter	Test	Reference	Ratio	90% Con. Interval
C _{max} (mcg/ml)	18.4	18.9	0.977	90.1-106
T _{max} (hr)	1.6	1.3		
AUC(0-t) [^] (mcg·hr/ml)	58.6	57.9	1.01	94.5-108.1
AUC(0-inf) (mcg·hr/ml)	65.8	66.3	0.99	92.8-108.6
K _{el} (per hour)	0.39	0.39		
T _{1/2} (hr)	1.8	1.9		

[^] Geometric means

FOOD CHALLENGE STUDY, (Number: IBU 200 phase II)

A. TITLE: In-vivo bioequivalence study for Ibuprofen tablets USP (200mg film coated tablets by BASF) under 'fed' conditions.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

1. Principal Investigator: Same as the previous study
2. Bio-Study Site: Same as the previous study
3. Analytical Investigator: Same as the previous study
4. Study Dates: Period I: 12/14/98, Period II: 12/16/98, Period III: 12/18/98 (10 subjects), 01/04/99 (1 subject), 01/11/99 (1 subject).

C. STUDY OBJECTIVE: To (re-assay and analyze the plasma samples) evaluate the in-vivo bioequivalence of Ibuprofen tablets, USP 200mg film coated tablets by BASF with Motrin IB (Nuprin) compared to Ibuprofen tablets, USP, 200mg by McNeil Consumer Products Company, under 'fed' conditions.

D. STUDY DESIGN: This was a three period, three treatment, six sequence crossover design in 12 subjects. There was a 36-hour washout period between the study phases. Twelve subjects entered the study. All of them completed the study. There were no drop-outs. The above twelve subjects had also participated in the fasting study.

E. SUBJECT SELECTION CRITERIA: same as the previous study.

Demographics: Age: 33.8 ± 7.9 years, Sex (Female:Male): 9:3, Race (African American:White:Other: 1:11:0)

F. SUBJECT RESTRICTIONS: same as the previous study:

G. DRUG TREATMENTS:

1. TREATMENT A: Ibuprofen tablet, 200mg (BASF) fasting, Lot # WO11421, Assay Potency=101.8%, Batch Size= () units
2. TREATMENT B: Ibuprofen Tablet, 200mg (BASF) with food, Lot # WO11421, Assay Potency=101.8%, Expiry date: N/A
3. TREATMENT C: Motrin^R Tablet, 200mg (McNeil) with food, Lot #39CAM, Assay Potency=98.2%. Expiry Date= 12/2002

H. STUDY SCHEDULES:

1. **Methods:** Food: FDA recommended standard breakfast. Page 83-84, volume 1.2 original application.

2. **Randomization Schedule:**

Treatments			Volunteer Number
Phase I	Phase II	Phase III	
A	B	C	3, 9
B	C	A	1, 7
C	A	B	5, 11
A	C	B	4, 10
B	A	C	2, 8
C	B	A	6, 12

3. **Blood Sampling Scheme:** Same as the previous study.

I. ASSAY METHOD AND ANALYTES: Same as the previous study.

J. PHARMACOKINETICS AND STATISTICS: Pharmacokinetic parameter calculation similar to the previous study. Point estimates were used and evaluated for a ()% difference between test and reference means.

K. ADVERSE EVENTS: No adverse events are reported related to the study. Three adverse events reported not related to the study, cough, muscle-spasm, itchy-eyes. Mild intensity, non-serious, resolved spontaneously.

L. RESULTS OF THE POST PRANDIAL STUDY: Mean (n=12) ibuprofen plasma levels are given in table 5. Mean pharmacokinetic parameters are listed in table 6.

Table 5

Time (hr)	Test (fasted)	Test (fed)	Reference (fed)	Ratio (Tfed/Refed)
0.0	0.0 (---)	0.0 (---)	0.0 (---)	
0.5	11.5 (55.5)	10.2 (57.5)	10.6 (55.5)	0.96
1.0	15.9 (37.4)	10.5 (47.8)	11.6 (69.6)	0.91
1.5	16.5 (32.2)	10.1 (44.1)	13.6 (84.1)	0.74
2.0	14.4 (28.0)	8.6 (34.3)	11.3 (37.6)	0.76
2.5	11.5 (28.7)	7.7 (33.1)	9.9 (31.9)	0.79
3.0	9.6 (30.9)	7.3 (30.4)	8.9 (31.7)	0.83
3.5	8.1 (30)	7.0 (32.6)	7.9 (30.2)	0.96
4.0	7.0 (33.6)	7.8 (58.3)	6.1 (29.9)	1.28
6.0	3.9 (50.3)	5.4 (65.3)	3.5 (25.1)	1.54
8.0	2.6 (35.1)	3.3 (61.0)	1.9 (11.5)	1.73
12.0	0.0 (---)	2.2 (12.9)	0.0 (---)	

Table 6

Parameter	Test (fasted)	Test (fed)	Reference (fed)	Ratio
C _{max} (mcg/ml)	18.6	14.0	16.1	0.869
T _{max} (hr)	1.5	2.3	1.5	
AUC _(0-t) (mcg·hr/ml)	58.3	51.6	48.7	1.06
AUC _(0-∞) (mcg·hr/ml)	67.9	64.3	55.0	1.17
K _{el} (per hour)	0.38	0.29	0.34	
T _{1/2} (hr)	2.2	3.1	2.1	

DISSOLUTION: USP 24 specifies a dissolution method for this product. The firm has conducted comparative dissolution as per the USP monograph. The results (reproduced from the original application) are given in Table 7.

Table 7

<i>In-Vitro</i> Dissolution Testing						
I. Conditions for Dissolution Testing:						
Apparatus: USP 24, apparatus II (Paddle) RPM: 50						
No. Units Tested: 12						
Medium: pH 7.2 phosphate buffer at 37°C					Volume: 900 ml	
Specifications: NLT()% (Q) in 60 minutes						
Reference Drug: Motrin [®] IB by McNeil						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product: Ibuprofen Tablet, Lot # WO11421, Strength (200 mg)			Reference Product: Motrin [®] tablet by McNeil, Lot # 39CAM, Strength (200 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	98	┌	2.14	96	┌	2.7
20	99		2.29	99		1.24
30	100		2.23	99		1.46
40	100		2.14	100		1.31

COMMENTS:

1. The validation for the reanalysis assay method is acceptable. The fasting and non-fasting bioequivalence studies are found acceptable. The studies demonstrate that the test and reference products are equivalent in the rate and extent of absorption as measured by log-transformed CMAX and AUC's of ibuprofen under fasting and non-fasting conditions.

2. The dissolution testing is acceptable.

RECOMMENDATIONS:

1. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by BASF Corp. on the test product, Ibuprofen Tablets, 200 mg, lot # WO11421, comparing it with the reference product, McNeil's Motrin^R 200 mg Tablets, lot # 39CAM, have been found **acceptable** by the Division of Bioequivalence. The test product, BASF's Ibuprofen Tablets, 200 mg, is deemed bioequivalent to the reference product, McNeil's Motrin 200 mg Tablets under fasting and non-fasting conditions.
2. The in-vitro dissolution testing conducted by BASF on its Ibuprofen Tablets, 200 mg has been found **acceptable**. The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of pH 7.2 phosphate buffer at 37°C using USP XXIV apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than ()% of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

JSI
11/6/01
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II. *11/6/2001*

RD/FT INITIALED BY SGNERURKAR *JSI*

Concur: *JSI*
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: *11/6/01*

cc: ANDA 76-661 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

CC: ANDA 75-661
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer (P.Sathe)

Printed in final on 11/06/01

Endorsements: (Final with Dates)
HFD-655/ Reviewer *JS 11/6/01*
HFD-655/ Bio team Leader
HFD-650/ D. Conner *MS 11/6/01*

MS 11/6/01

BIOEQUIVALENCY - ACCEPTABLE

submission date: Oct. 9, 2001

1. **FASTING STUDY (STF)**
Clinical:

✓ Strengths: 200mg

Analytical:

Outcome: AC

2. **FOOD STUDY (STP)**
Clinical:

✓ Strengths: 200mg

Analytical:

Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:

Ibuprofen
200 mg film coated Tablet
ANDA 75-661
Reviewer: Pradeep M. Sathe, Ph.D.

BASF Corporation
Shreveport, LA-77136
Submission Date:
January 19, 2001

REVIEW OF AN AMENDMENT

BACKGROUND HISTORY:

1. June 30, 1999 and August 16, 1999.

The bio-study data could not be analyzed because it was not presented in a proper format. The firm was informed of the proper format to present the bio-study data (review date November 4, 1999).

2. April 13 and 20, 2000.

This was not the firm's response to the item 1.

The submission had

- i) results of the inspection conducted by the Division of Scientific Inspection (DSI),
- ii) the form 483 that described the deficiencies, and
- iii) responses of the firm to every deficiency on the form 483.

The review of the application indicated that the responses had serious flaws. The firm was informed (review date May 31, 2000) of sixteen deficiencies.

3. June 23, 2000

This was a response to item 2.

The firm responded to the 16 deficiencies cited above. The firm's responses were evaluated. The responses were not totally satisfactory (review date September 29, 2000). The firm was communicated seven new deficiencies and was recommended to conduct a new bio-study if possible.

4. October 31, 2000

This is a response to the item 3

The firm's responses to the seven deficiencies were evaluated. The evaluation indicated that the firm's responses were not satisfactory. The firm had made new claims about the previously submitted information on the assay validation. To verify the new information and its impact on the overall validation, the application was referred to DSI.

5. January 19, 2001 (current amendment)

This appears to be a response to item 3.

The amendment consists of firm's response to 'chemistry' deficiencies as well as 'an analytical protocol to address the outstanding bioequivalence deficiencies'. The firm is requesting a reclassification of the amendment from 'major' to 'minor' status and is seeking an expedited review due to the economic considerations.

Method: The firm plans to reanalyze the bioequivalence analytical samples using the attached protocol (Attachment I). The re-analysis is intended to confirm the demonstration of bioequivalence for the fasting and limited food effect studies that are the subject of the application amendment dated April 20, 2000. It will be using three QC controlled samples as suggested in the FDA's draft guidance, "Bioanalytical method validation for human studies." The firm is planning re-analysis of analytical samples for 6 subjects of the fasting study and analytical samples for the 6 subjects of the 'food challenge' study. By doing this, the firm plans to confirm the validity of results of the original analysis that used one QC sample versus the reanalysis using three QC samples as referenced in the draft guidance document.

DEFICIENCY COMMENTS:

1. The analytical protocol "addresses (only) the 'in-study' validation to demonstrate the reproducibility of the assay method using the quality control samples and calibration curves for each analytical run during the analysis for ibuprofen in human plasma samples." Also the protocol refers to analysis of samples from only 6 subjects from each fasting and food challenge studies. There is no pre-study validation and the analysis does not cover samples from all subjects. Due to these two reasons the analytical protocol is incomplete.
2. The firm is requested to conduct the entire assay validation which includes pre and during study validations. Validation of the method should include specificity, sensitivity, accuracy, precision, linearity, recovery and stability. The firm may consult the *draft* guidance titled "Bioanalytical Methods Validation for Human Studies (Issued 12/1998, Posted 1/5/1999)", before starting the analytical validation. As of today, the above guidance is not finalized.
3. The samples from each and every subject in the two studies should be reanalyzed using the new completely validated assay methodology.
4. The firm should demonstrate stability of the drug in plasma samples, under the experimental storage conditions, for the duration covering the period from the first sample collection to the last sample analysis. It is expected that the firm has been storing the samples appropriately until the reanalysis (temperature and other storage conditions should be appropriate).
5. It is suggested that the firm should be careful not to repeat any of the deficiencies cited in the DSI 483 for the earlier assay validation methodology and results.

6. The DBE has not yet statistically analyzed the bio-study data due to deficiencies in the assay validation. Following the newly conducted assay validation and bio-study subject plasma sample analysis, the new data will be statistically analyzed for determining bioequivalence.
7. Instead of the above exercise, the firm has an option of conducting new bio-studies with proper assay validation.

RECOMMENDATION:

Deficiency Comments 1-7 should be forwarded to the firm.

ISI 4/11/01
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

ISI

4/27/2001

Concur: *ISI*
fn Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: 4/30/2001

cc: ANDA 75-661 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

CC: ANDA 75-661
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer (P.Sathe) *PS 4/11/01*
HFD-655/Bio Team Leader (SG Nerurkar)
HFD-617/Project Manager
HFD-650/Dale Conner *for Rev 4/30/2001*

BIOEQUIVALENCY - DEFICIENCIES

Submission Date: Jan. 19, 2001

1. **STUDY AMENDMENT (STA)**

Strengths: 200mg

Outcome: **IC**

Outcome: **IC**

Outcome Decisions:

IC - Incomplete

WinBio Comments

BIOEQUIVALENCY DEFICIENCIES

ANDA:75-661

APPLICANT: BASF Corporation

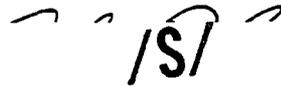
DRUG PRODUCT: Ibuprofen 200mg film coated tablet

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

1. The analytical protocol "addresses (only) the 'in-study' validation to demonstrate the reproducibility of the assay method using the quality control samples and calibration curves for each analytical run during the analysis for ibuprofen in human plasma samples." Also, the protocol refers to analysis of samples from only 6 subjects from each fasting and food challenge studies. Due to these reasons the protocol is incomplete.
2. You are requested to conduct the entire assay validation. Validation of the method should include Specificity, Sensitivity, Accuracy, Precision, Linearity, Recovery and Stability. All samples from all subjects in the two studies should be reanalyzed using the new completely validated assay methodology. You should submit all validation and within-study data. You may consult the **draft** guidance titled "Bioanalytical Methods Validation for Human Studies (Issued 12/1998, Posted 1/5/1999)", before starting the analytical validation. As of today, the above guidance is not finalized.
3. You should demonstrate the stability of the drug in plasma samples under the storage conditions selected from the time of first sample collection to the time of last sample analysis.
4. It is expected that you are storing the samples appropriately until the reanalysis (temperature and other storage conditions should be appropriate).

5. You are requested to be careful not to repeat any of the deficiencies cited by the DSI for the previous assay validation methodology and results.

Sincerely yours,

A handwritten signature in black ink, appearing to be "D.P. Conner", with a stylized flourish above the letters.

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

Ibuprofen
200 mg film coated Tablet
ANDA 75-661
Reviewer: Pradeep M. Sathe, Ph.D.

OLD
Revised version
BASF Corporation
Shreveport, LA-77136
Submission Date:
January 19, 2001
4/30/01

REVIEW OF AN AMENDMENT

BACKGROUND: As per the 'Orange Book', the firm has had approved 400 mg, 600 mg and 800 mg strengths on the market. These are prescription strengths. The 'Orange Book' lists 200mg strength tablet as an OTC product. The ('Orange Book') recommended innovator product is Nuprin^R 200 mg strength by McNeil Labs. In applications dated June 30 and August 16, 1999, the firm submitted ANDA application consisting of two bioequivalence studies (fasting and fed) and comparative dissolution involving the test product and the reference (200mg strength Motrin^{IB}) products. Though the dissolution information was considered barely acceptable, the bio-study information, data and results were found to be inadequate and deficient in many areas. In a review dated Nov. 4, 1999, the firm was notified of the deficiencies. In addition, an inspection of the bioequivalence studies (bio-studies were conducted by () under the direction of () was requested from DSI.

As per DBE's request, DSI conducted an audit of the fasting and food challenge bioequivalence studies involving 200mg and 800mg strengths, between Jan 24-27, 2000. Following the inspection, an FDA Form 483, was issued to ()

In a DBE review of the 'EIR reviews' dated April 13 and April 20, 2000, the Division evaluated the DSI and Firm's positions/responses. Due to objectionable observations like: a) the incomplete/inadequate () assay validation, b) the use of a single standard curve in the assay validation, and c) the use of horse serum instead of human blank plasma for calibration/control standards for assay validation, the DBE concluded that the reported data and study results may not be relied upon for approval. The reported bio-equivalence studies and results were therefore declared unacceptable towards demonstrating bioequivalence of the BASF 200mg Ibuprofen tablet with the corresponding 200mg reference Nuprin^R or Motrin^{IB} tablet.

Subsequently, in an amendment dated June 23, 2000, the firm tried to clarify its position. In a review dated 09/29/00, the Division found the firm's position unacceptable and in a facsimile dated 10/3/2000 the firm was notified of the Division's opinion. In another amendment dated November 2, 2000, firm once again attempted to clarify their position by providing additional information. The amendment was reviewed by the

Division and was sent to DSI to verify the newly clarified information.

CURRENT AMENDMENT: The amendment consists of firm's response to OGD's facsimile dated 12/5/2000. The firm is requesting a reclassification of the amendment from 'major' to 'minor' status and is seeking an expedited review due to the economic considerations. The firm has included response to 'chemistry' deficiencies as well as 'an analytical protocol to address the outstanding bioequivalence deficiencies'.

The firm plans to reanalyze the bioequivalence analytical samples using the attached protocol (Attachment I). The re-analysis is intended to confirm i) the demonstration of bioequivalence for the fasting and limited food effect studies that are the subject of the application amendment dated April 20, 2000, and ii) in response to the deficiency letter dated November 20, 2000. It will be using three QC controlled samples as suggested in the FDA's draft guidance, "Bioanalytical method validation for human studies." The firm is planning re-analysis of analytical samples for 6 subjects of the fasting study and analytical samples for the 6 subjects of the 'food challenge' study. By doing this, the firm plans to confirm the validity of results of the original analysis that used one QC sample versus the reanalysis using three QC samples as referenced in the draft guidance document.

DEFICIENCY COMMENTS:

1. The analytical protocol "addresses (only) the 'in-study' validation to demonstrate the reproducibility of the assay method using the quality control samples and calibration curves for each analytical run during the analysis for ibuprofen in human plasma samples." Also the protocol refers to analysis of samples from only 6 subjects from each fasting and food challenge studies. Due to these reasons the protocol is incomplete.
2. The firm is requested to conduct the entire assay validation. Validation of the method should include specificity, sensitivity, accuracy, precision, linearity, recovery and stability. All samples from all subjects in the two studies should be reanalyzed using the new completely validated assay methodology. The firm should submit all validation and within-study data. The firm may consult the *draft* guidance titled "Bioanalytical Methods Validation for Human Studies (Issued 12/1998, Posted 1/5/1999)", before starting the analytical validation. As of today, the above guidance is not finalized.
3. The firm should demonstrate the stability of the drug in plasma samples under the storage conditions selected from the time of first sample collection to the time of last

sample analysis.

4. It is expected that the firm has been storing the samples appropriately until the reanalysis (temperature and other storage conditions should be appropriate).

5. It is suggested that the firm should be careful not to repeat any of the deficiencies cited by the DSI for the previous assay validation methodology and results.

RECOMMENDATION:

Deficiency Comments 1-5 should be forwarded to the firm.

/S/
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II.

for RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

/S/ 2/12/01

Conc: */S/*
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: *2/12/01*

cc: ANDA 75-661 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

CC: ANDA 75-661
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer (P.Sathe) *to 1/26/01*
HFD-655/Bio Team Leader (SS Nerurkar) *for 1/26/01*
HFD-617/Project Manager
HFD-650/Dale Conner *SK 2/12/01*

BIOEQUIVALENCY - DEFICIENCIES

Submission Date: Jan. 19, 2001

1. **STUDY AMENDMENT (STA)**

Strengths: 200mg

Outcome: **IC**

Outcome: **IC**

Outcome Decisions:

IC - Incomplete

WinBio Comments

Ibuprofen
200 mg film coated Tablet
ANDA 75-661
Reviewer: Pradeep M. Sathe, Ph.D.

BASF Corporation
Shreveport, LA-77136
Submission Dates:
October 31,2000

REVIEW OF AN AMENDMENT

BACKGROUND HISTROY:

1. June 30, 1999 and August 16,1999.

The biostudy data could not be analyzed because it was not presented in a proper format. The firm was informed of the proper format to present the biostudy data (review date November 4, 1999).

2. April 13 and 20, 2000.

This was not the firm's response to the item 1.

The submission had

- i) results of the inspection conducted by the Division of Scientific Inspection (DSI),
- ii) the form 483 that described the deficiencies, and
- iii) the responses of the firm to every deficiency on the form 483.

The review of the application indicated that the responses had serious flaws. The firm was informed (review date May 31, 2000) of sixteen deficiencies.

3. June 23, 2000

This was a response to item 2.

The firm responded to the 16 deficiencies cited above. The firm's responses were evaluated. The responses were not totally satisfactory (review date September 29, 2000). Seven new deficiencies were communicated to the firm.

4. October 31, 2000 (current submission)

This is a response to the item 3

The firm's responses to the seven deficiencies were evaluated. The evaluation has the following format. The deficiency is stated, followed by the firm's response to that deficiency, and then DBE's evaluation of the response is given.

Deficiency 1:

The firm has not stated whether the validation information reported in response 1 refers to a pre- or post- study validation. In all likelihood it appears to be a post-

study validation, which is not acceptable. This is a serious flaw.

Firm's response 1:

It was not post study validation; it was a pre-study validation.

Our evaluation 1:

The response is unsatisfactory because the DSI did not confirm the firm's response (see DSI memo on page 5)

Deficiency 2:

The firm has given an explanation for using only one standard curve. This explanation is not sufficient for the acceptance of the validation results. This is a serious flaw.

Firm's response 2:

The firm's response mentions pre study validation. However, it does not categorically state how many standard curves were run to analyze all study samples. It mentions that the samples from half of the subjects in the biostudy on the 200 mg tablet (ANDA 75-661) were estimated along with the samples from the subjects enrolled in the biostudy on the 800 mg Tablet (ANDA 75-682).

Our evaluation 2:

The firm has not clearly stated how many standard curves were used for analyzing all plasma samples from all the subjects for the bio-equivalence study involving 200 mg tablet product (ANDA 75-661). The response is unsatisfactory until the firm provides results of individual curves and the mean data (experimentally determined concentrations of calibration standards and QC samples).

Deficiency 3:

The firm has provided the information comparing the horse and human serums. The correlation between the animal (in this case horse) and the human data have never been accepted by the Division as a substitute for adequate assay validation using only human plasma samples. This is a serious flaw.

Firm's response 3:

The horse serum data was only for information purposes. It was never used in validation. Human plasma was used for validation.

Our Evaluation 3:

The response is unsatisfactory because the DSI did not confirm the firm's response (see DSI memo on page 5).

Deficiency 4:

Please refer to Comment 2 above.

Firm's response 4:

See the response 2.

Our evaluation 4:

See Evaluation 2

Deficiency 5:

The firm has not satisfactorily answered why only one QC sample with a concentration only near the mid-range of the standard curve was used in the original validation.

Firm's response 5:

See the response 2.

Our evaluation 5:

See Evaluation 2

Deficiency 6:

The firm has not satisfactorily answered why the original validation reported a standard curve lower limit of quantitation as () mcg/ml instead of () mcg/ml.

Firm's response 6:

The firm insists the lower limit of quantitation is () mcg/ml.

Our evaluation 6:

The response is unsatisfactory because the DSI did not confirm the firm's response (see DSI memo on page 5)

Deficiency 7:

The firm has accepted responsibility for deficiencies 8 through 16. Even though not the serious flaws, they refer to the inadequate and loose practices related to the assay conduct and data reporting. The firm has accepted responsibility and stated that these practices would be avoided in future studies.

Firm's response 7:

The firm states these are minor deficiencies and may not influence the study results.

Our evaluation 7:

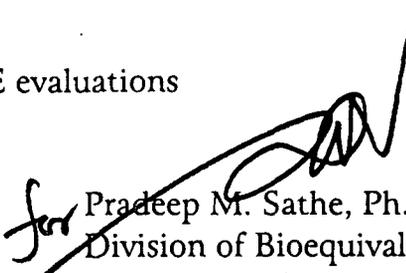
The Division agrees with the firm.

IMPORTANT NOTES:

1. THE AGENCY STILL HAS DOUBTS ABOUT THE ASSAY VALIDATION.
2. THE BIOSTUDY DATA HAS NOT BEEN EVALUATED AT ALL.

RECOMMENDATION:

The firm should be informed of the DBE evaluations

for 
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II. ⁿ

5/14/2001

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

TSI

Concur:

TSI

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

Date: 5/22/2001

cc: ANDA 75-661 EIR (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 9, 2001

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an ANDA 75-661 Amendment
Ibuprofen Tablets, 200 mg
Sponsored by BASF Corporation, Shreveport, LA

TO: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence (HFD-650)

BASF Corporation submitted to HFD-650 an amendment to ANDA 75-661 (Ibuprofen Tablets, 200 mg) on October 31, 2000. This amendment (see Attachment 1) provided the response to the deficiencies that HFD-650 communicated to BASF on October 3, 2000. In a recent meeting with Drs. Pradeep M. Sathe, and Shrinivas G. Nerurkar of HFD-650, the amendment was forwarded to HFD-48 for consultation, as the deficiencies were originally identified by HFD-48 following an inspection of _____ (Jan 24-27, 2000) at the _____

After a review of the October 31, 2000 amendment, we have the following comments:

DSI Comment - Deficiency 1.

The accuracy, precision, stability, specificity and recovery data summarized by BASF in the June 23, 2000 submission (Attachment 2) were obtained using an ibuprofen concentration of 10 ng/mL. As cited in the Form FDA-483, validation data near the high (40 ng/mL) and low (1 ng/mL) ends of the standard curve (with standard points ranged from _____ ng/mL) were not generated at the analytical site _____

It should be noted that in the June 23, 2000 submission, BASF had also provided some information concerning the accuracy, precision, and recovery of the () assay at the high and low ends of the standard curve. However, these data were generated by () and not by (). BASF should be informed that to adopt assay validation results from a different analytical site or laboratory is not acceptable.

DSI Comment - Deficiency 2

The written response from BASF is unsatisfactory and does not resolve the deficiencies concerning the standard curve and QC samples.

During the inspection, we found that only one standard curve (Curve IBU-2) was generated by () during the pre-study assay validation. Moreover, for the analysis of subject plasma samples, only one standard curve (Curve_1) was used for all analytical runs in the 200 mg study. Another single standard curve (Curve_100) was used for all analytical runs in the 800 mg study.

The quality control (QC) samples used in all analytical runs were also deficient. Specifically, there were no QC samples to monitor the performance of each analytical run near the low and high ends of the standard curve. All QCs samples used had a concentration near the mid-point (e.g., 10 ng/mL for the 200 mg study) of the standard curve.

DSI Comment - Deficiency 3

Based on the documentation we collected during the inspection at () horse serum was indeed used during method validation. According to information provided by () calibration standards and controls in horse serum were prepared on March 25, 1998. A validation experiment was conducted on March 26, 1998 using the controls prepared in horse serum on March 25, 1998. [Note: () was the primary person involved in the ibuprofen assay validation and the assay of subject plasma samples.]

Moreover, in the written response to the Form FDA-483 on March 3,

2000, () had acknowledged that horse serum was used initially during the assay development and validation process.

DSI Comment - Deficiencies 4 and 5

See comment in Deficiency 2.

DSI Comment - Deficiency 6

The written response from BASF is unsatisfactory.

Based on results of the standard curves used in the 200 mg (Curve_1) and 800 mg (Curve_100) ibuprofen studies, the lower limit of quantitation (LLOQ) should be () ng/mL and no () ng/mL (see data summarized below and in Attachment 3).

For Curve_1, the errors associated with calibration standards at 0.048, 0.098, 0.195, 0.39, 0.78, and 1.58 ng/mL were -1077%, -493%, -219%, -107%, -38.5%, and -7.8%. For Curve_100, the errors associated with calibration standards at 0.195, 0.39, 0.78, and 1.56 ng/mL were -321%, -146%, -63%, and -19%. Thus, the LLOQ of the assay should be 1.56 ng/mL because all calibration standards with concentrations lower than 1.56 ng/mL had errors > -38.5% in Curve_1 and > -63% in Curve_100.

DSI Comment - Deficiency 7

No comment is necessary for this deficiency

Conclusion:

BASF's written responses to deficiencies 1-6 are unsatisfactory. BASF should be informed that (1) failure to validate the assay near the high and low ends of the standard curve, and (2) failure to monitor the performance of each analytical run using high and low concentration QC samples are not acceptable. The assay performance near the mid concentration range of the standard curve is not representative of the performance near the high and low ends of the standard curve. The analytical work conducted by () failed to meet the minimum standards required to support Agency approval of generic drugs

Please append this transmittal memo to the original ANDA submission.

Martin K. Yau, Ph.D.

Attachment

cc:

HFD-45

HFD-48/Fujiwara/Yau/cf

HFD-650/Sanchez

HFD-650/Sathe

HFD-650/Nerurkar

Draft:MKY 5/9/01

File:5300 O:\BE\75661memo.ogd.doc

CC: ANDA 75-661
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)

J HFD-655/Reviewer (P.Sathe)
HFD-655/Bio Team Leader (SGNerurkar)
HFD-617/Project Manager
HFD-650/Dale Conner *for HFD 5/22/2001*

AW
AW 5/14/01

BIOEQUIVALENCY-DEFICIENCIES

1. STUDY AMENDMENT (STA) Strength: 200mg,
Submission Date: October, 31, 2000 Outcome: UN

Outcome Decisions:

UN - Unacceptable

WinBio Comments:

The amendment is unacceptable.

MAY 30 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-661

APPLICANT: BASF Corporation

DRUG PRODUCT: Ibuprofen 200mg film coated tablet

The Division of Bioequivalence has completed its review of your submission dated October 31, 2000. In this submission you have responded to the seven deficiencies communicated to you. The evaluation of your seven responses is given below. Based on this evaluation, your assay validation is still unacceptable. Because of this unacceptable assay validation and improperly submitted bioequivalence study data, the ANDA is not acceptable from the bioequivalence point of view. The following are the seven evaluations of your responses:

Evaluation 1:

The response is unsatisfactory because the DSI did not confirm it.

Evaluation 2:

You have not stated how many standard curves were used for analyzing samples from all subjects who participated in the bioequivalence study involving 200mg tablet (ANDA 75-661). Your response will be deemed unsatisfactory until you provide results of individual curves and the mean data (experimentally determined concentrations of calibration standards and QC samples).

Evaluation 3:

The response is unsatisfactory because the DSI did not confirm it.

Evaluation 4:

Please see 'Evaluation 2'.

Evaluation 5:

Please see 'Evaluation 2'.

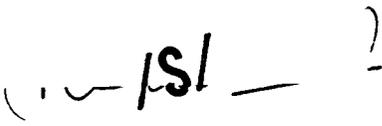
Evaluation 6:

The response is unsatisfactory because the DSI did not confirm it.

Evaluation 7:

Your response is acceptable.

Sincerely yours,

fw 

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

OCT 3 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-661

APPLICANT: BASF Corporation

DRUG PRODUCT: Ibuprofen 200 mg film coated tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The Division and Office of Generic Drugs deems the reported bioequivalence studies and results as unacceptable (towards demonstrating bioequivalence of the BASF 200 mg Ibuprofen tablet with the corresponding 200 mg reference Nuprin® or Motrin® tablet) because of the following:

1. You have not stated whether the validation information reported in response 1 refers to a pre or post study validation. In all likelihood it appears to be a post-study validation, which is not acceptable. This is a serious flaw.
2. You have given explanation for using only one standard curve. This explanation is not sufficient for the acceptance of the validation results. This is a serious flaw.
3. You have provided the information comparing the horse and human serums. The correlation between the animal (in this case horse) and the human data have never been accepted by the Division as a substituted for the adequate assay validation using only human plasma samples. This is a serious flaw.
4. Please refer to Comment 2 above.
5. You have not satisfactorily answered why only one QC sample with a concentration only near the mid-range of the standard curve was used in the original validation.
6. You have not satisfactorily answered why the original validation reported a standard curve lower limit of quantitation as mcg/ml instead of () mcg/ml.
7. You have accepted the responsibility of the deficiencies 8 through 16:
Even though not serious flaws, these refer to the inadequate and loose practices related to the assay conduct and data reporting.

The Division of Bioequivalence recommends the submission of a new study to support the approval of this product.

Sincerely yours,

JS/

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

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II

8/22/2000

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

Concur: /S/
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: 9/29/00

cc: ANDA 75-661 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

Ibuprofen
200 mg film coated Tablet
ANDA 75-661
Reviewer: Pradeep M. Sathe, Ph.D.

BASF Corporation
Shreveport, LA-77136
Submission Date:
June 23, 2000

REVIEW OF AN EIR REVIEW COVERING ANDA 75-661

BACKGROUND: The firm has approved 400 mg, 600 mg and 800 mg strengths on the market. These are prescription strengths. The Orange Book lists the 200mg tablet as an OTC product. The Orange Book recommended Innovator product is Nuprin^R 200 mg strength by McNeil Labs. In applications dated June 30 and August 16, 1999, the firm submitted ANDA application consisting of two bioequivalence studies (fasting and fed) and comparative dissolution involving the test product and the reference (200mg strength Motrin^{IB}) products. Though the dissolution information was considered barely acceptable, the bio-study information, data and results were found to be grossly inadequate and deficient in many areas. In a review dated Nov. 4, 1999, the firm was notified of the deficiencies. In addition, an inspection of the bioequivalence studies (conducted by () under the direction of () was requested from DSI.

As per DBE's request, DSI conducted an audit of the fasting and food challenge bioequivalence studies involving 200mg and 800mg strengths, between Jan 24-27, 2000. Following the inspection, FDA Form 483, was issued to (). The objectionable items and DSI's evaluation of the findings are given in Attachment I.

In a review of 'EIR review' dated April 13 and April 20, 2000, the Division evaluated the DSI and Firm's responses. Due to the fatal flaws, such as incomplete/inadequate () assay validation, use of a single standard curve in the assay validation, use of horse serum instead of human blank plasma for calibration/control standards for assay validation, the Division decided that the study results, data and reports are of dubious nature and cannot be relied upon for approval. The reported bio-equivalence studies and results were therefore declared unacceptable towards demonstrating bioequivalence of the BASF 200mg Ibuprofen tablet with the corresponding 200mg reference Nuprin^R or Motrin^{IB} tablet.

CURRENT AMENDMENT: The amendment consists of firm's response (Attachment II) to the DSI cited deficiencies.

COMMENTS:

The comments pertain to the DSI cited deficiencies and firm's subsequent responses to the cited deficiencies. The comments are delineated in the same order (please refer to Attachments I and II):

1. The firm has not stated whether the validation information reported in response 1 refers to a pre or post study validation. In all likelihood it appears to be a post-study validation, which is not acceptable. This is a serious flaw.
2. The firm has given explanation for using only one standard curve. This explanation is not sufficient for the acceptance of the validation results. This is a serious flaw.
3. The firm has provided the information comparing the horse and human serums. The correlation between the animal (in this case horse) and the human data have never been accepted by the Division as a substitute for the adequate assay validation using only human plasma samples. This is a serious flaw.
4. Please refer to Comment 2 above.
5. The firm has not satisfactorily answered why only one QC sample with a concentration only near the mid-range of the standard curve was used in the original validation.
6. The firm has not satisfactorily answered why the original validation reported a standard curve lower limit of quantitation as () mcg/ml instead of () mcg/ml.
7. The firm has accepted the responsibility of the deficiency.
- 8 through 16: Even though not the serious flaws, they refer to the inadequate and loose practices related to the assay conduct and data reporting. The firm has accepted the responsibility and stated that these practices would be avoided in the future studies.

RECOMMENDATION:

Following the review of information given in Attachments I and II, the Division still feels that conduct of the bio-equivalence study and its assay have many serious flaws, making the study results unacceptable in supporting the approval of the application. The DBE recommends the submission of a new study to support the approval of this product.

The Comments should be forwarded to the firm.

CC: ANDA 75-661
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)

HFD-655/Reviewer (P.Sathe) *PS* 8/22/00

HFD-655/Bio Team Leader (SGNerurkar)

HFD-617/Project Manager

for HFD-650/Dale Conner *BCD* 9/29/00

CON 8/22/00

BIOEQUIVALENCY-DEFICIENCIES

1. **STUDY AMENDMENT**

Submission Date: June 23, 2000

Strength: 200mg.

Outcome: UN

Outcome Decisions:

UN - Unacceptable

WinBio Comments:

Ibuprofen
200 mg film coated Tablet
ANDA 75-661
Reviewer: Pradeep M. Sathe, Ph.D.

BASF Corporation
Shreveport, LA-77136
Submission Dates:
April 13, April 20, 2000

REVIEW OF AN EIR REVIEW COVERING ANDA 75-661

BACKGROUND: The firm has approved 400 mg, 600 mg and 800 mg strengths on the market. These are prescription strengths. The Orange Book lists the 200mg tablet as an OTC product. The Orange Book recommended Innovator product is Nuprin^R 200 mg strength by McNeil Labs. In applications dated June 30 and August 16, 1999, the firm submitted ANDA application consisting of two bioequivalence studies (fasting and fed) and comparative dissolution involving the test product and the reference (200mg strength Motrin^{IB}) products. Though the dissolution information was considered barely acceptable, the bio-study information, data and results were found to be grossly inadequate and deficient in many areas. In a review dated Nov. 4, 1999, the firm was notified of the deficiencies. In addition, an inspection of the bioequivalence studies (conducted by _____) under the direction of _____ was requested from DSI.

CURRENT EIR REVIEW:

As per DBE's request, DSI conducted an audit of the fasting and food challenge bio-equivalence studies involving 200mg and 800mg strengths, between Jan 24-27, 2000. Following the inspection, FDA Form 483, was issued to _____. The objectionable items and DSI's evaluation of the findings are given in Attachment I.

DIVISION COMMENTS:

1. In the submission, the firm has responded to the deficiencies communicated to the firm on 11/04/99. Firm's response is not evaluated here because of the DSI cited deficiencies, which made the study results unacceptable.
2. The DSI 'Review of the EIR', lists many serious flaws in the study conduct, assay and data analysis. Due to these inadequacies, the study results, data and reports are of dubious nature and cannot be relied upon. The reported bio-equivalence studies and results are therefore unacceptable towards demonstrating bioequivalence of the BASF 200mg Ibuprofen tablet with the corresponding 200mg reference Nuprin^R or Motrin^{IB} tablet.

3. In light of the DSI's review and recommendations, the earlier acceptable recommendations by DBE regarding this ANDA, if any, should be considered rescinded.

/S/
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II.

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

Concur:

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

Date: *5/31/00*

cc: ANDA 75-661 EIR (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

U 2 Document

OTHER (DSI inspection)

UN (unacceptable)

JUN 20 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-661

APPLICANT: BASF Corporation

DRUG PRODUCT: Ibuprofen 200mg film coated tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The Division and Office of Generic Drugs deems the reported bio-equivalence studies and results as unacceptable (towards demonstrating bioequivalence of the BASF 200mg Ibuprofen tablet with the corresponding 200mg reference Nuprin^R or Motrin^{IB} tablet) because of the following deficiencies (identified by Division of Scientific Investigations):

1. The () assay was not fully validated.
2. The assay validation data provided in the ANDA submissions were generated using a single standard curve.
3. Horse serum instead of blank human plasma was used to prepare calibration and control standards during assay validation.
4. A standard curve was not generated with each analytical run.
5. Quality control (QC) samples with a concentration only near the mid-range (e.g. 10 mcg/ml) of the standard curve was used.
6. The standard curve used for the study has a lower limit of quantitation () mcg/ml and not () mcg/ml as was reported.
7. The identity of persons recording all data in case report forms including dosing of test and reference formulations is missing.
8. The thermometer in the -20°C freezer used to store plasma samples would not read below -10°C.
9. The thermometers in both -20°C freezer and in the -70°C freezer used to store plasma samples were not traceable to a reference standard.

10. Subject #307 was not within 10% of the ideal body weight for his height and was not excluded from the study.
11. Measurements were not taken to determine study subjects frame size even though the height and weight table used specified ideal heights and weights for small, medium and large frames.
12. The case report forms indicated that corrections to the data were not routinely initialed and dated.
13. Subject #402's Case Report Form showed that the subject received treatment 2:3 (reference fed) on 12/14/98 when subject #402 actually received the treatment on 12/18/98.
14. No record of randomization was seen for the 200mg and 800mg studies.
15. There was no documentation to show that the SAS subroutines used to calculate pharmacokinetic parameters (e.g. AUC, Cmax) and 90% confidence interval limits were validated.
16. There was no SOP for data handling and for conduct of pharmacokinetic data analysis.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Dale P. Conner", enclosed in a large, hand-drawn circle.

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

CC: ANDA 75-661
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer (P.Sathe) *PS 6/11/00*
HFD-655/Bio Team Leader (SGNerurkar)
HFD-617/Project Manager
HFD-650/Dale Conner *DC 6/7/00*

AW 6/4/00

BIOEQUIVALENCY-DEFICIENCIES

1. **OTHER (OTH) Review of an EIR review** Strength: 200mg.
Submission Date: April 13, 2000 Outcome: UN
* Please enter as a U2 document.
2. **STUDY AMENDMENT (STA)** Strength: 200mg.
Submission Date: April 20, 2000 Outcome: UN

Outcome Decisions:

UN - Unacceptable

WinBio Comments:

Ibuprofen
200 mg film coated Tablet
ANDA 75-661
Reviewer: Pradeep M. Sathe, Ph.D.

BASF Corporation
Shreveport, LA-77136
Submission Dates:
April 13, April 20, 2000

REVIEW OF AN EIR REVIEW COVERING ANDA 75-661

BACKGROUND: The firm has approved 400 mg, 600 mg and 800 mg strengths on the market. These are prescription strengths. The Orange Book lists the 200mg tablet as an OTC product. The Orange Book recommended Innovator product is Nuprin^R 200 mg strength by McNeil Labs. In applications dated June 30 and August 16, 1999, the firm submitted ANDA application consisting of two bioequivalence studies (fasting and fed) and comparative dissolution involving the test product and the reference (200mg strength Motrin^{IB}) products. Though the dissolution information was considered barely acceptable, the bio-study information, data and results were found to be grossly inadequate and deficient in many areas. In a review dated Nov. 4, 1999, the firm was notified of the deficiencies. In addition, an inspection of the bioequivalence studies (conducted by () under the direction of () was requested from DSI.

CURRENT EIR REVIEW:

As per DBE's request, DSI conducted an audit of the fasting and food challenge bio-equivalence studies involving 200mg and 800mg strengths, between Jan 24-27, 2000. Following the inspection, FDA Form 483, was issued to () The objectionable items and DSI's evaluation of the findings are given in Attachment I.

DIVISION COMMENTS:

1. In the submission, the firm has responded to the deficiencies communicated to the firm on 11/04/99. Firm's response is not evaluated here because of the DSI cited deficiencies, which made the study results unacceptable.
2. The DSI 'Review of the EIR', lists many serious flaws in the study conduct, assay and data analysis. Due to these inadequacies, the study results, data and reports are of dubious nature and cannot be relied upon. The reported bio-equivalence studies and results are therefore unacceptable towards demonstrating bioequivalence of the BASF 200mg Ibuprofen tablet with the corresponding 200mg reference Nuprin^R or Motrin^{IB} tablet.

3. In light of the DSI's review and recommendations, the earlier acceptable recommendations by DBE regarding this ANDA, if any, should be considered rescinded.

/S/
Pradeep M. Sathe 5/8/00
Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II. *5/8/2000*
/S/

RD INITIALED BY SNERURKAR
FT INITIALED BY SNERURKAR

Concur */S/*
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: 5/31/00

cc: ANDA 75-661 EIR (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

U 2 Document

OTHER (DSI inspection)

UN
(unacceptable)

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-661 APPLICANT: BASF Corporation

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

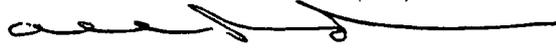
1. We acknowledge your statement that tablet weight is used as an in-process control parameter instead of tablet thickness and that the testing of hardness and disintegration of tablet core eliminates the need to measure tablet friability. Please provide test data to demonstrate the correlation between tablet weight and tablet thickness and correlation between tablet hardness/disintegration and tablet friability. We recommend that the testing of tablet thickness and friability be part of your tablet manufacturing in-process controls. Please revise your drug product manufacturing in-process control specifications accordingly.
2. You have established your drug product stability chromatographic impurity specifications as NMT % individual and NMT % total. Please provide stability data to justify these impurity specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

You were advised by the Division of Bioequivalence (DOB) in a communication dated October 3, 2000 that the bioequivalence studies and results you submitted were reviewed and were deemed as unacceptable. Based on this review you were recommended by DOB to submit a new bioequivalence study to support the approval of this

drug product. Please do not respond to this letter until all the bioequivalence deficiencies have been satisfactorily addressed or resolved. Due to this recommendation your responses to this letter will be considered as a MAJOR amendment and should be so designated in your cover letter.

Sincerely yours,



✓ Rashmikant M. Patel, Ph.D.
Director,
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-661

APPLICANT: BASF Labs.

DRUG PRODUCT: Ibuprofen, 200 mg tablet

The Division of Bioequivalence considers the submission incomplete. In the present form it lacks organization and is difficult to review. The following deficiency has been identified:

1. To avoid confusion, the two bio-studies (fasting and 'food challenge', should be preferably presented separately in two volumes. Each study should be addressed through the following focal points:

STUDY NUMBER AND CATEGORY e.g. SINGLE DOSE FASTING STUDY:A. TITLE:B. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

1. Principal Investigator:
2. Bio-Study Site:
3. Analytical Investigator:
4. Analysis Site:
5. Study Dates: Period I: Period II:
6. Analysis Dates:

C. STUDY OBJECTIVE:D. STUDY DESIGN AND NUMBER OF SUBJECTS:E. SUBJECT SELECTION/EXCLUSION CRITERIA:F. SUBJECT RESTRICTIONS:G. TREATMENTS:

1. TEST: ***** Tablet, **** mg (firm name), Lot # *****, Assay Potency= ****%, Batch Size=***** tablets
2. REFERENCE: ***** Tablet, **** mg (Innovator), Lot # *****, Potency= ****%, Expiry date: *****

H. STUDY SCHEDULES:

1. Methods:
2. Randomization Scheme:

Treatments

Period I Period II

Volunteer Number

Sequence	A	B	*****
	B	A	*****

3. **Blood Sampling:** Number of samples drawn, total volume of blood collected, samples scheme, collection and storage.

I. **ASSAY:** Type of assay, detection mode.

1. **Extraction:**

2. **Run Conditions:**

Analytical Column:

Mobile Phase:

Flow rate:

Injection Volume:

Detector:

Integrator:

Internal Standard:

Approximate Retention Times:

3. **Calibration:** equation:

4. **Analytical Validation:**

Specificity:

Recovery:

Limit of Quantitation:

Intra-assay variability:

Inter-assay variability:

Linear Dynamic Range:

Freeze Thaw Cycles:

Room Temperature Stability:

In-Process Stability:

Long-Term Stability: Must cover at least the duration of the study.

J. **PHARMACOKINETICS AND STATISTICS:** Methods should be provided. The statistical data should be arranged with respect to each treatment. The mean standard deviation and coefficient of variation of the data should be provided. If a General Linear Model is used for the statistical analysis; it should have the following classes and structure: Response Parameter= Sequence Sequence(Subject) Period

Treatment

K. ADVERSE EVENTS: Please provide a table with probable possible or definite relationship of the adverse events to the administered drug product.

L. RESULTS:

- i) A Table with time, Mean (n=24, say) Plasma levels with %CV's and the ratio of the means
- ii) A Table of Mean Pharmacokinetic Parameters with 90% confidence intervals
- iii) Plasma profiles of the two treatments (in case of 'food challenge' study three treatments) with respect to each subject and mean profiles (plots).
- iv) The plasma levels of each treatment should be tabulated and presented with their mean, standard deviation and coefficient of variation information. The pharmacokinetic parameters should be submitted in an ASCII format (on a 3.5" diskette) with the following variables. Please provide a separate file for each study.

Subject	Sequence	Period	Treatment	AUCt	AUCinf	Cmax	Tmax	Tl/2
1	***	***	***	***	***	**	***	***
2	***	***	***	**	***	**	***	***

A similar format should be used to present the results of the 'food challenge' study.

2. It is not clear why the firm has used the MIXED EFFECTS model instead of the GENERAL LINEAR model for the statistical analysis of the fasting study data. Please explain.
3. It is not understood why the 'food challenge' study was conducted using only 12 subjects leading to only 2 subjects per sequence. Please clarify.
4. The firm should complete the "How Supplied" section of the labelling. It is pointed out that the firm **may not** make changes

such as 'scoring' to the test product, unless it is also seen with the innovator product.

Sincerely yours,

A handwritten signature in black ink, appearing to be "Dale P. Conner", with a large, stylized initial "S" written over it.

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