CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-682

Trade Name:	IBU Tablets
Generic Name:	Ibuprofen Tablets USP, 400 mg, 600 mg, and 800 mg
Sponsor:	BASF Corporation
Approval Date:	November 14, 2001

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APPLICATION NUMBER:
75-682

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APPLICATION NUMBER:

75-682

APPROVAL LETTER

ANDA 75-682

NOV 14 2001

BASF Corporation
Attention: Michael Gill
8800 Line Avenue
Shreveport, LA 71106

Dear Sir:

This is in reference to your abbreviated new drug application dated July 30, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for IBU Tablets (Ibuprofen Tablets USP, 400 mg, 600 mg, and 800 mg).

Reference is also made to your amendments dated May 5, August 2, and October 10, 2000; and September 10, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your IBU Tablets (Ibuprofen Tablets USP, 400 mg, 600 mg, and 800 mg) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Motrin Tablets® 400 mg, 600 mg, and 800 mg, respectively, of McNeil Consumer Products Company, Division of McNeilab Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/s/

Gary Buehler 11/14/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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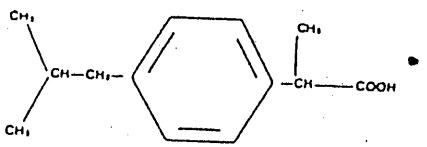
Final Printed Labeling

IBU® Tablets
Ibuprofen tablets, USP

DESCRIPTION

IBU Tablets contain the active ingredient ibuprofen, which is (±)-2-(p-isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74-77° C and is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone.

The structural formula is represented below:



IBU, a nonsteroidal anti-inflammatory agent, is available in 400 mg, 600 mg, and 800 mg tablets for oral administration. Inactive ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, FD&C Yellow No. 6 and 10, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, polysorbate, titanium dioxide.

CLINICAL PHARMACOLOGY

IBU Tablets contain ibuprofen which possesses analgesic and antipyretic activities. Its mode of action, like that of other non-steroidal anti-inflammatory agents, is not completely understood, but may be related to prostaglandin synthetase inhibition.

In clinical studies in patients with rheumatoid arthritis and osteoarthritis, ibuprofen has been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS). Ibuprofen may be well tolerated in some patients who have had gastrointestinal side effects with aspirin, but these patients when treated with ibuprofen should be carefully followed for signs and symptoms of gastrointestinal ulceration and bleeding. Although it is not definitely known whether ibuprofen causes less peptic ulceration than aspirin, in one study involving 885 patients with rheumatoid arthritis treated for up to one year, there were no reports of gastric ulceration with ibuprofen whereas frank ulceration was reported in 13 patients in the aspirin group (statistically significant $p<001$).

Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin. Studies using ^{51}Cr-tagged red cells indicate that fecal blood loss associated with Ibuprofen Tablets in doses up to 2400 mg daily did not exceed the normal range, and was significantly less than that seen in aspirin-treated patients.

In clinical studies in patients with rheumatoid arthritis, ibuprofen has been shown to be comparable to indomethacin in controlling the signs and symptoms of disease activity and to be associated with a statistically significant reduction of the milder gastrointestinal (see ADVERSE REACTIONS) and CNS side effects.

IBU may be used in combination with gold salts and/or corticosteroids.

Controlled studies have demonstrated that ibuprofen is a more effective analgesic than propoxyphene for the relief of episiotomy pain, pain following dental extraction procedures, and for the relief of the symptoms of primary dysmenorrhea.

In patients with primary dysmenorrhea, ibuprofen has been shown to reduce elevated levels of prostaglandin activity in the menstrual fluid and to reduce resting and active intrauterine pressure, as well as the frequency of uterine contractions. The probable mechanism of action is to inhibit prostaglandin synthesis rather than simply to provide analgesia.

The ibuprofen in IBU is rapidly absorbed. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and

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Ibuprofen tablets, USP

the integrated area under the serum drug concentration vs time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.

The administration of IBU Tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When IBU is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of the drug is minimally altered by the presence of food.

A bioavailability study has shown that there was no interference with the absorption of ibuprofen when ibuprofen was given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours.

Studies have shown that following ingestion of the drug, 45% to 79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-[*p*-(2hydroxymethyl-propyl) phenyl] propionic acid and metabolite B (37%), (+)-2[*p*-(2carboxypropyl)phenyl] propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

INDICATIONS AND USAGE

IBU Tablets are indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

IBU is indicated for relief of mild to moderate pain.

IBU is also indicated for the treatment of primary dysmenorrhea.

Since there have been no controlled clinical trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of ibuprofen in conjunction with aspirin, the combination cannot be recommended (see Drug Interactions).

Controlled clinical trials to establish the safety and effectiveness of ibuprofen in children have not been conducted.

CONTRAINDICATIONS

IBU Tablets should not be used in patients who have previously exhibited hypersensitivity to the drug, or in individuals with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS

Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal Anti-Inflammatory Therapy:

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with nonsteroidal anti-inflammatory drugs. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with nonsteroidal anti-inflammatory drugs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (eg age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory agents in causing such reactions. High doses of any such agents probably

IBU® Tablets
Ibuprofen tablets, USP

carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

General Precautions

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving IBU Tablets, the drug should be discontinued, and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen, therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on ibuprofen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious noninflammatory painful conditions.

Liver Effects: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 time the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with ibuprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg eosinophilia, rash, etc.), IBU should be discontinued.

Hemoglobin Levels: In cross-study comparisons with doses ranging from 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. This has been observed with other nonsteroidal anti-inflammatory drugs; the mechanism is unknown. With daily doses of 3200 mg the total decrease in hemoglobin may exceed 1 gram; if there are no signs of bleeding, it is probably not clinically important.

In two postmarketing clinical studies the incidence of a decreased hemoglobin level was greater than previously reported. Decrease in hemoglobin of 1 gram or more was observed in 17.1% of 193 patients on 1600 mg ibuprofen daily (osteoarthritis), and in 22.8% of 189 patients taking 2400 mg of ibuprofen daily (rheumatoid arthritis). Positive stool occult blood tests and elevated serum creatinine levels were also observed in these studies.

Aseptic Meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients

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with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Information for Patients

Ibuprofen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects., such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Nonsteroidal anti-inflammatory drugs are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of nonsteroidal anti-inflammatory drug treatment, particularly when the drugs are used for less serious conditions where treatment without such agents may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal Anti-inflammatory therapy).

Drug Interactions: *Coumarin-type anticoagulants.* Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, because bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on courmarin-type anticoagulants, the physician should be cautious when administering ibuprofen to patients on anticoagulants.

Aspirin: Animal studies show that aspirin given with nonsteroidal anti-inflammatory agents, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlative clinical studies have not been done.

Methotrexate: Ibuprofen, as well as other nonsteroidal anti-inflammatory drugs, probably reduces the tubular secretion of methotrexate based on *in-vitro* studies in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if ibuprofen is administered concomitantly with methotrexate.

H-2 Antagonists: In studies with human volunteers, co-administration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ibuprofen, the patient should be observed closely for signs of renal failure (see PRECAUTIONS, Renal Effects), as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration.

This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. (Read circulars for lithium preparation before use of such concurrent therapy.)

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of ibuprofen is not recommended during pregnancy.

Nursing Mothers: In limited studies, an assay capable of detecting 1 mcg/mL did not demonstrate ibuprofen in the milk of lactating mothers. However, because of the limited nature of the studies, and the possible adverse effects of prostaglandin-inhibiting drugs on neonates, ibuprofen is not recommended for use in nursing mothers.

ADVERSE REACTIONS

The most frequent type of adverse reaction occurring with Ibuprofen Tablets is gastrointestinal. In controlled clinical trials the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

In controlled studies when ibuprofen was compared to aspirin and indomethacin in equally effective doses, the overall incidence of gastrointestinal complaints was about half that seen in either the aspirin- or indomethacin-treated patients.

Adverse reactions observed during controlled clinical trials at an incidence greater than 1% are listed in the table. Those reactions listed in Column one encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Still other reactions occurring less frequently than 1 in 100 were reported in controlled clinical trials and from marketing experience. These reactions have been divided into two categories: Column two of the table lists reactions with therapy with ibuprofen where the probability of a causal relationship exists: for the reactions in Column three, a causal relationship with ibuprofen has not been established.

Reported side effects were higher at doses of 3200 mg/day than at doses of 2400 mg or less per day in clinical trials of patients with rheumatoid arthritis. The increases in incidence were slight and still within the ranges reported in the table.

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Ibuprofen tablets, USP

OVERDOSAGE

Approximately 1½ hours after the reported ingestion of from 7 to 10 Ibuprofen Tablets (400 mg), a 19-month old child weighing 12 kg was seen in the hospital emergency room, apneic and cyanotic, responding only to painful stimuli. This type of stimulus, however, was sufficient to induce respiration. Oxygen and parenteral fluids were given; a greenish-yellow fluid was aspirated from the stomach with no evidence to indicate the presence of ibuprofen. Two hours after ingestion the child's condition seemed stable; she still responded only to painful stimuli and continued to have periods of apnea lasting from 5 to 10 seconds. She was admitted to intensive care and sodium bicarbonate was administered as well as infusions of dextrose and normal saline. By four hours post-ingestion she could be aroused easily, sit by herself and respond to spoken commands. Blood level of ibuprofen was 102.9 µg/mL approximately 8½ hours after accidental ingestion. At 12 hours she appeared to be completely recovered.

In two other reported cases where children (each weighing approximately 10 kg) accidentally, acutely ingested approximately 120 mg/kg, there were no signs of acute intoxication or late sequelae. Blood level in one child 90 minutes after ingestion was 700 µg/mL – about 10 times the peak levels seen in absorption-excretion studies.

A 19-year old male who had taken 8,000 mg of ibuprofen over a period of a few hours complained of dizziness, and nystagmus was noted. After hospitalization, parenteral hydration and three days bed rest, he recovered with no reported sequelae.

Incidence Greater than 1% (but less than 3%) Probable Causal Relationship	Precise Incidence Unknown (but less than 1%) Probable Causal Relationship**	Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown**
GASTROINTESTINAL		
Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence)	Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; pancreatitis	
CENTRAL NERVOUS SYSTEM		
Dizziness*, headache, nervousness	Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma (See PRECAUTIONS)	Paresthesias, hallucinations, dream abnormalities, pseudo-tumor cerebri
DERMATOLOGIC		
Rash* (including maculopapular type), pruritus	Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia	Toxic epidermal necrolysis, photoallergic skin reactions
SPECIAL SENSES		
Tinnitus	Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS)	Conjunctivitis, diplopia, optic neuritis, cataracts
HEMATOLOGIC		
	Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS)	Bleeding episodes (eg epistaxis, menorrhagia)
METABOLIC/ENDOCRINE		
Decreased appetite		Gynecomastia, hypoglycemic reaction, acidosis
CARDIOVASCULAR		
Edema, fluid retention (generally responds promptly to drug discontinuation) (see PRECAUTIONS)	Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations	Arrhythmias (sinus tachycardia, sinus bradycardia)
ALLERGIC		
	Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS)	Serum sickness, lupus erythematosus syndrome. Henoch-Schonlein vasculitis, angioedema
RENAL		
	Acute renal failure (see PRECAUTIONS), decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria	Renal papillary necrosis
MISCELLANEOUS		
	Dry eyes and mouth, gingival ulcer, rhinitis	

* Reactions occurring in 3% to 9% of patients treated with ibuprofen. (Those reactions occurring in less than 3% of the patients are unmarked.)

** Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

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In cases of acute overdosage, the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen.

DOSAGE AND ADMINISTRATION

Do not exceed 3200 mg total daily dose. If gastrointestinal complaints occur, administer IBU Tablets with meals or milk.

Rheumatoid arthritis and osteoarthritis, including flareups of chronic disease:

Suggested Dosage: 1200 mg-3200 mg daily; 400, 600 mg or 800 mg tid or qid). Individual patients may show a better response to 3200 mg daily, as compared with 2400 mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy. Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk.

The dose should be tailored to each patient, and may be lowered or raised depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.

In general, patients with rheumatoid arthritis seem to require higher doses of ibuprofen than do patients with osteoarthritis.

The smallest dose of ibuprofen that yields acceptable control should be employed. A linear blood level dose-response relationship exists with single doses up to 800 mg (See CLINICAL PHARMACOLOGY for effects of food on rate of absorption).

The availability of three tablet strengths facilitates dosage adjustment.

In chronic conditions, a therapeutic response to therapy with ibuprofen is sometimes seen in a few days to a week but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

Mild to moderate pain: 400 mg every 4 to six hours as necessary for relief of pain.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than the 400 mg dose.

Dysmenorrhea: For the treatment of dysmenorrhea, beginning with the earliest onset of such pain, IBU should be given in a dose of 400 mg every 4 hours as necessary for the relief of pain.

HOW SUPPLIED

IBU Tablets are available in the following strengths, colors and sizes:

400 mg (brown, oval imprinted with IBU 400)	
Bottles of 100	NDC 10117-0400-1
Bottles of 500	NDC 10117-0400-5
Unit dose blister of 24	NDC 10117-0400-2
600 mg (brown, caplet, imprinted with IBU 600)	
Bottles of 100	NDC 10117-0600-1
Bottles of 500	NDC 10117-0600-5
Unit dose blister of 24	NDC 10117-0600-2
800 mg (brown, caplet, imprinted with IBU 800)	
Bottles of 100	NDC 10117-0800-1
Bottles of 500	NDC 10117-0800-5
Unit dose blister of 24	NDC 10117-0800-2

Store at room temperature. Avoid excessive heat 40°C (104°F).

BASF Corporation

Revised July 2001

IBU® (Ibuprofen Tablets, USP) 600 mg LOT 00000 EXP 00/0000 Mfg. by BASF Corporation Mount Olive, NJ 07828	IBU® (Ibuprofen Tablets, USP) 600 mg LOT 00000 EXP 00/0000 Mfg. by BASF Corporation Mount Olive, NJ 07828
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AP 11/14/01

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APPROVED

APPEARS THIS WAY
ON ORIGINAL

IBU® (Ibuprofen Tablets, USP) 800 mg LOT 00000 EXP 00/0000 Mfg. by BASF Corporation Mount Olive, NJ 07828	IBU® (Ibuprofen Tablets, USP) 800 mg LOT 00000 EXP 00/0000 Mfg. by BASF Corporation Mount Olive, NJ 07828
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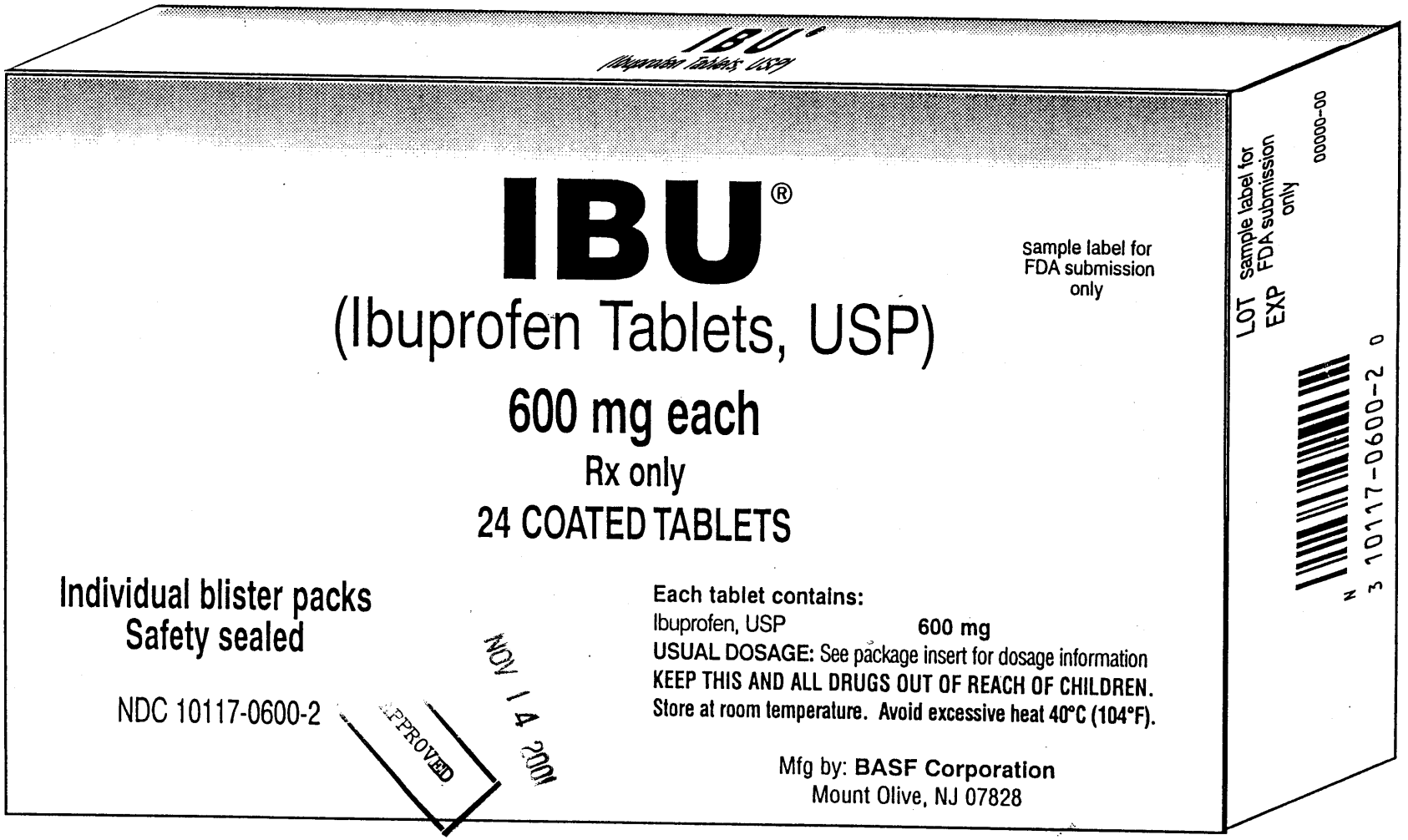
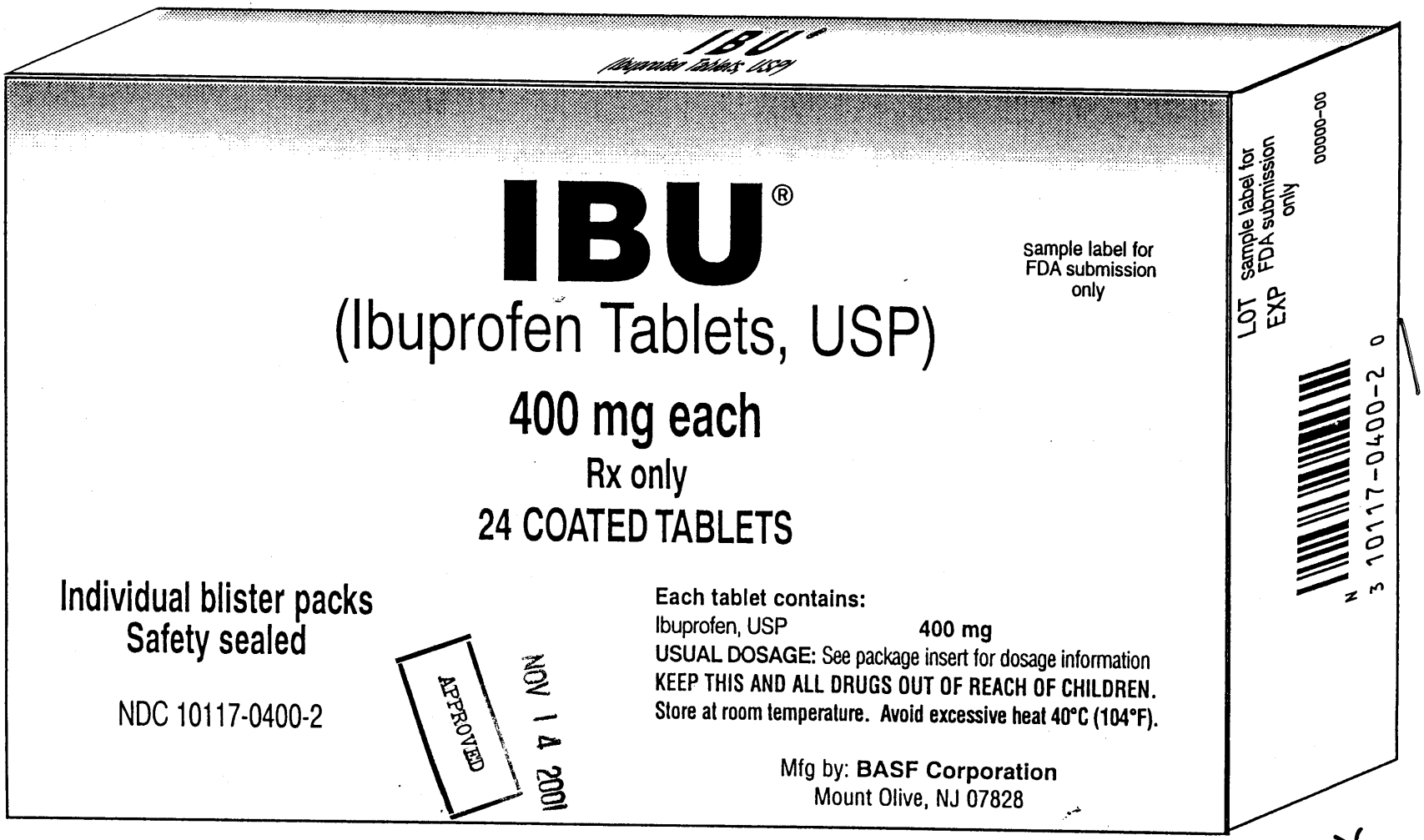

IBU®
(Ibuprofen Tablets, USP)
600 mg each
Rx only
24 COATED TABLETS
Sample label for FDA submission only
Individual blister packs
Safety sealed
NDC 10117-0600-2
APPROVED
NOV 14 2001
Each tablet contains:
Ibuprofen, USP 600 mg
USUAL DOSAGE: See package insert for dosage information
KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.
Store at room temperature. Avoid excessive heat 40°C (104°F).
Mfg by: BASF Corporation
Mount Olive, NJ 07828
LOT sample label for FDA submission only
EXP
00000-00
N 10117-0600-2 0



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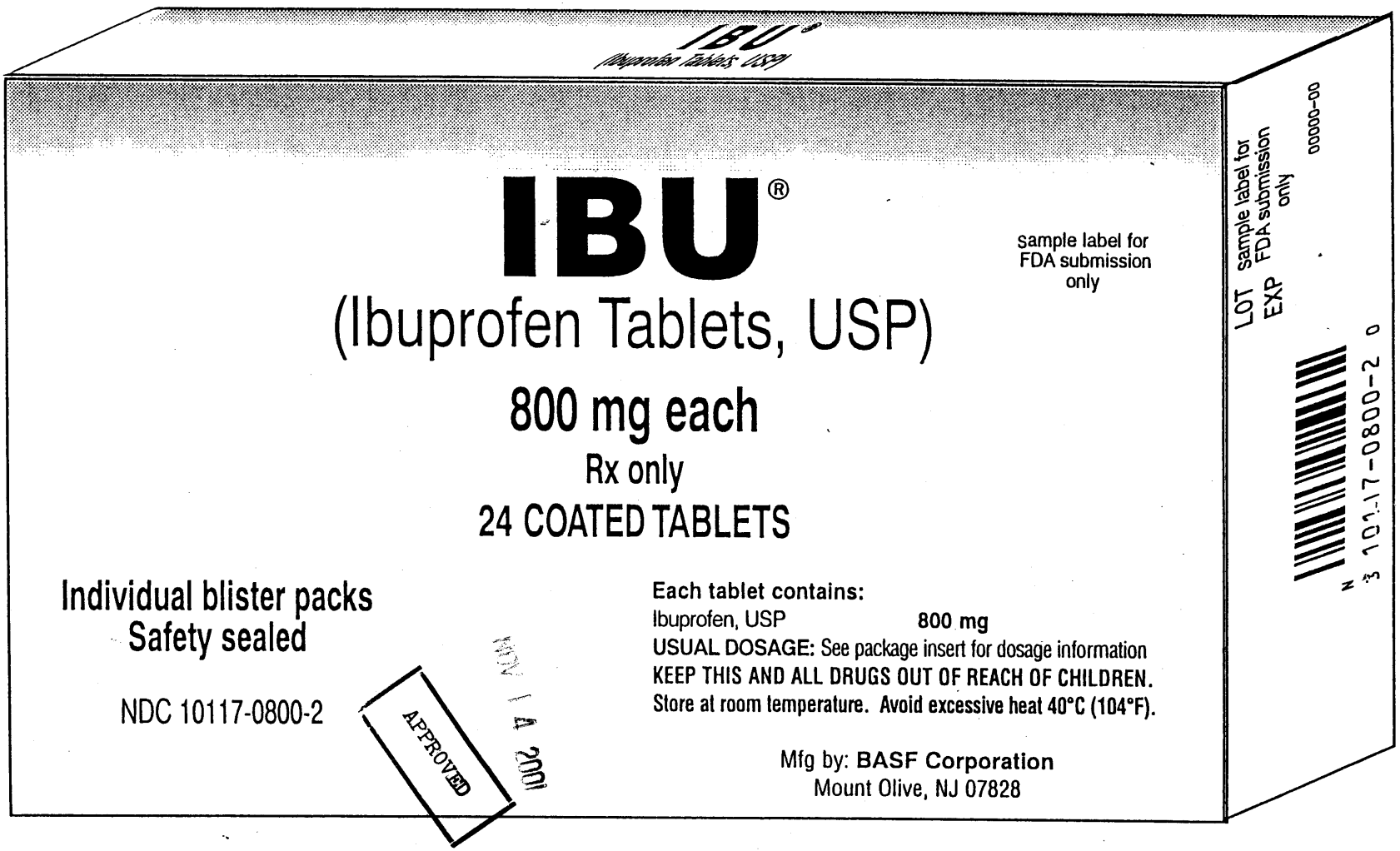
IBU®
(Ibuprofen Tablets, USP)
800 mg each
Rx only
24 COATED TABLETS
sample label for FDA submission only
Individual blister packs
Safety sealed
NDC 10117-0800-2
APPROVED
NOV 14 2001
Each tablet contains:
Ibuprofen, USP 800 mg
USUAL DOSAGE: See package insert for dosage information
KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.
Store at room temperature. Avoid excessive heat 40°C (104°F).
Mfg by: BASF Corporation
Mount Olive, NJ 07828
LOT Sample label for FDA submission only
EXP 00000-00
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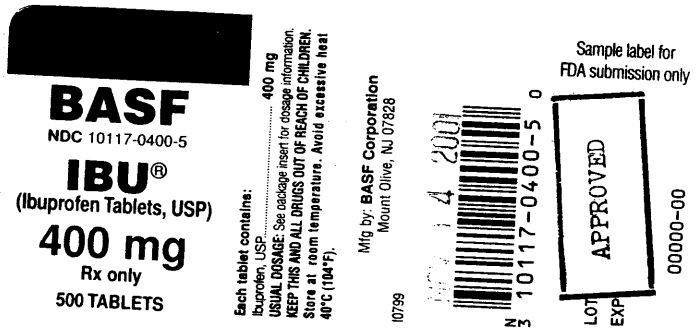

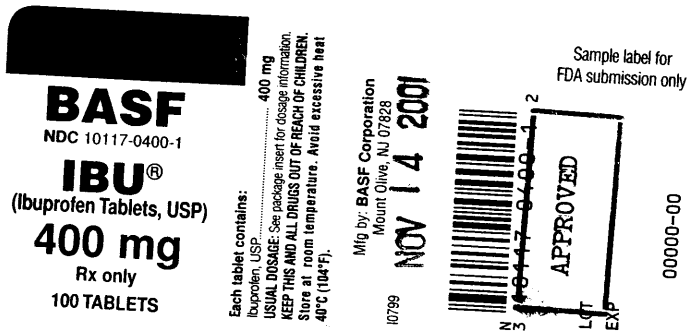

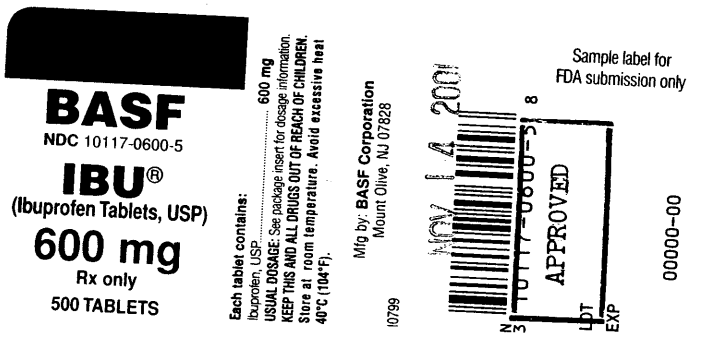

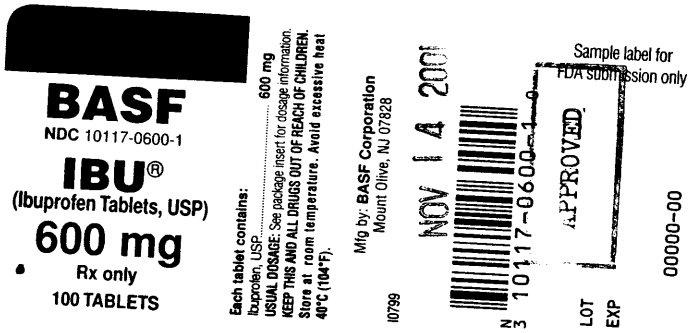

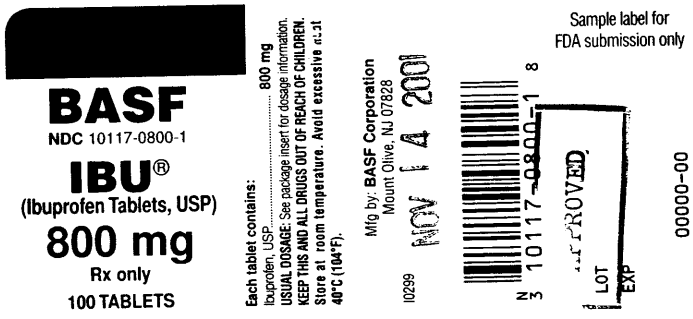

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Mfg. by BASF Corporation
Mount Olive, NJ 07828

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-682

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO**: No. 1

2. **ANDA**: 75-682

3. **NAME AND ADDRESS OF APPLICANT**:
BASF Corporation,
Attention: Michael Gill,
8800 Line Avenue,
Shreveport, LA 71106.

4. **LEGAL BASIS for ANDA SUBMISSION**: 505 (j), FFD & CA
Motrin® (NDA 17-463), McNeil Consumer Products Company, approved 05/22/85

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**: Ibuprofen Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
07/30/99 Submission of ANDA (Date of Application)
FDA:
08/02/99 Acknowledgment letter
08/16/99 Amendment letter

10. **PHARMACOLOGICAL CATEGORY**: Anti-inflammatory

11. **HOW DISPENSED**: Rx

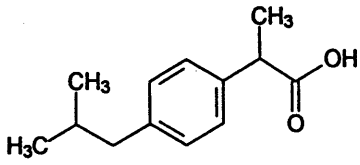
12. **RELATED IND/NDA/DMF(s)**:
Motrin® (NDA 17-463), McNeil Consumer Products Company, approved 05/22/85
See Item 37 for a complete list of DMFs.

13. **DOSAGE FORM**: Oral Tablets

14. **Strength**: 400mg 600mg and 800mg

15. **CHEMICAL NAMES AND STRUCTURE:**

Generic Name: Ibuprofen
Chemical Name: Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-
Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.29
CAS Registry Number: 15687-27-1, 58560-75-1
Anti-inflammatory.



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

EER was requested on 08/02/99. This does include the contract firms.

18. **CONCLUSIONS AND RECOMMENDATIONS: Not approvable**

19. **REVIEWER:** RD'Costa /S/ **DATE COMPLETED:** 01/27/99

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO**: No. 2

2. **ANDA**: 75-682

3. **NAME AND ADDRESS OF APPLICANT**:
BASF Corporation,
Attention: Michael Gill,
8800 Line Avenue,
Shreveport, LA 71106.

4. **LEGAL BASIS for ANDA SUBMISSION**: 505 (j), FFD & CA
Motrin® (NDA 17-463), McNeil Consumer Products Company, approved 05/22/85

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**: Ibuprofen Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
04/13/00 Major Amendment
07/30/99 Submission of ANDA (Date of Application)
FDA:
08/02/99 Acknowledgment letter
08/16/99 Amendment letter

10. **PHARMACOLOGICAL CATEGORY**: Anti-inflammatory

11. **HOW DISPENSED**: Rx

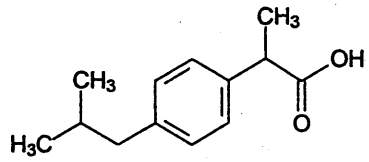
12. **RELATED IND/NDA/DMF(s)**:
Motrin® (NDA 17-463), McNeil Consumer Products Company, approved 05/22/85
See Item 37 for a complete list of DMFs.

13. **DOSAGE FORM**: Oral Tablets

14. **Strength**: 400mg 600mg and 800mg

15. **CHEMICAL NAMES AND STRUCTURE**:

Generic Name: Ibuprofen
Chemical Name: Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-
Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.29
CAS Registry Number: 15687-27-1, 58560-75-1
Anti-inflammatory.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**: N/A

18. **CONCLUSIONS AND RECOMMENDATIONS**: **Not approvable**

19. **REVIEWER**: RD'Costa

DATE COMPLETED: 10/18/00

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO**: No. 3

2. **ANDA**: 75-682

3. **NAME AND ADDRESS OF APPLICANT**:
BASF Corporation,
Attention: Michael Gill,
8800 Line Avenue,
Shreveport, LA 71106.

4. **LEGAL BASIS for ANDA SUBMISSION**: 505 (j), FFD & CA
Motrin® (NDA 17-463), McNeil Consumer Products Company, approved 05/22/85

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**: Ibuprofen Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
01/19/01 Minor Amendment
04/13/00 Major Amendment
07/30/99 Submission of ANDA (Date of Application)
FDA:
08/02/99 Acknowledgment letter
08/16/99 Amendment letter

10. **PHARMACOLOGICAL CATEGORY**: Anti-inflammatory

11. **HOW DISPENSED**: Rx

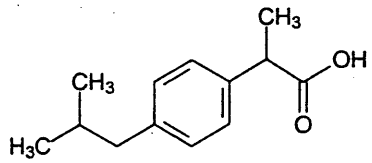
12. **RELATED IND/NDA/DMF(s)**:
Motrin® (NDA 17-463), McNeil Consumer Products Company, approved 05/22/85
See Item 37 for a complete list of DMFs.

13. **DOSAGE FORM**: Oral Tablets

14. **Strength**: 400mg 600mg and 800mg

15. **CHEMICAL NAMES AND STRUCTURE:**

Generic Name: Ibuprofen
Chemical Name: Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-
Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.29
CAS Registry Number: 15687-27-1, 58560-75-1
Anti-inflammatory.



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:** The Division of Chemistry has no further questions at this time. However, the bioequivalence of the drug product has not been established. Please refer to the comments provided to you via facsimile on March 19, 2001, from the division of Bioequivalence. You should address the issues in this communication prior to or concurrent with your response to this communication.

18. **CONCLUSIONS AND RECOMMENDATIONS:** Not Approvable - Minor

19. **REVIEWER:** RD'Costa /S/ **DATE COMPLETED:** 06/18/01

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMISTRY REVIEW NO**: No.4

2. **ANDA**: 75-682

3. **NAME AND ADDRESS OF APPLICANT**:
BASF Corporation,
Attention: Michael Gill,
8800 Line Avenue,
Shreveport, LA 71106.

4. **LEGAL BASIS for ANDA SUBMISSION**: 505 (j), FFD & CA
Motrin® (NDA 17-463), McNeil Consumer Products Company, approved 05/22/85

5. **SUPPLEMENT(s)**: N/A

6. **PROPRIETARY NAME**: N/A

7. **NONPROPRIETARY NAME**: Ibuprofen Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
09/10/01 Minor Amendment
01/19/01 Minor Amendment
04/13/00 Major Amendment
07/30/99 Submission of ANDA (Date of Application)
FDA:
08/02/99 Acknowledgment letter
08/16/99 Amendment letter

10. **PHARMACOLOGICAL CATEGORY**: Anti-inflammatory

11. **HOW DISPENSED**: Rx

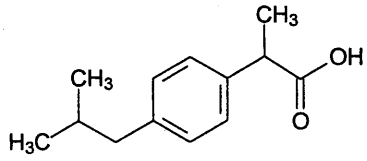
12. **RELATED IND/NDA/DMF(s)**:
Motrin® (NDA 17-463), McNeil Consumer Products Company, approved 05/22/85
See Item 37 for a complete list of DMFs.

13. **DOSAGE FORM**: Oral Tablets

14. **Strength**: 400mg 600mg and 800mg

15. **CHEMICAL NAMES AND STRUCTURE:**

Generic Name: Ibuprofen
Chemical Name: Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-
Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.29
CAS Registry Number: 15687-27-1, 58560-75-1
Anti-inflammatory.



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:** A Minor was issued to the firm, since the bioequivalence of the drug product has not been established. The Divisions of Chemistry and Labeling however, have no further questions at this time.

18. **CONCLUSIONS AND RECOMMENDATIONS: Approvable pending Bioequivalence.**

19. **REVIEWER:** RD'Costa

DATE COMPLETED: 10/15/01

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-682

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-682 SPONSOR : BASF
DRUG AND DOSAGE FORM : Ibuprofen Tablets
STRENGTH(S) : 800 mg , 600 mg, 400 mg
TYPES OF STUDIES : Fasting & Non-Fasting Studies (800 mg)
CINICAL STUDY SITE(S) :
ANALYTICAL SITE(S) :

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : ___ /S/ _____ DATE : 10/2/01

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : ___ /S/ _____ DATE : 10/2/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
for
INITIAL : /S/ DATE : 10/15/2001

4, 1 TM

Ibuprofen Film-Coated Tablets USP
ANDA #75-682: 800 mg, 600 mg & 400 mg
Reviewer: Hoainhon Nguyen
W #75682a.901

BASF Corp.
Shreveport, LA
Submission Date:
September 10, 2001

Review of a Study Amendment
(and Results of Two Bioequivalence Studies)

I. Background:

The firm has submitted the current amendment in response to the deficiency comments by the Division of Bioequivalence in the letter dated March 19, 2001. The deficiency comments were as follows: *"1.* [redacted] *2. However, you may reanalyze the entire set of samples for each study with all subjects included, using adequately validated analytical method. The reanalysis data then should be subject to bioequivalence demonstration using the confidence interval approach. It is important that the assay method validation includes long-term stability study which shows that the study samples are stable under the freezer storage condition from the time of sample collection to the time of sample reanalysis. The original assayed values of the original quality controls, calibration standards and study samples can not be used in the long-term stability study if these original values were not obtained based on an adequately validated assay method."* The single-dose fasting bioequivalence study and the single-dose non-fasting bioequivalence study were previously found unacceptable because the assay method was inadequately validated.

In the current amendment, the firm has reanalyzed the entire set of study samples from both studies using an analytical method fully validated in accordance with the DBE's current practice. The firm's reanalysis results are reviewed together with the information from the original submissions which were dated July 30, 1999 and May 2, 2000 and included the study designs of a fasting, single-dose bioequivalence study and a post-prandial bioequivalence study comparing its Ibuprofen Film-Coated Tablets USP, 800 mg, with McNeil's Motrin® 800 mg Ibuprofen Tablets, comparative dissolution data for the test and RLD products of 800 mg and for the 600 mg and 400 mg strengths of the test product, the formulations of all strengths and the waiver request for the 600 mg and 400 mg strengths. (Please note the

study designs and dissolution data were previously summarized in the review of the submission dated May 5, 2000.)

II. Bioequivalence Studies:

IIA. FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL #IBU800-Part I)

Study Objective: Bioequivalency of BASF's and McNeil's (Motrin®) 800 mg Ibuprofen Tablets under fasting conditions.

Study Facilities/Dates/Investigators:

Clinical: [redacted] between February 8 and 17, 1999; [redacted]

Analytical: [redacted]; between February 17 and April 2, 1999; [redacted] **The sample reanalysis was carried out between June 28, 2001 and July 25, 2001.**

The maximum sample storage duration between February 8 and April 2, 1999 is 53 days. The maximum sample storage duration between the first sample collection and the last sample reanalysis is 897 days.

Study Design: 2-treatment, 2-period, randomized crossover

Demographics: 24 normal, healthy male and female volunteers: 3 blacks and 21 caucasians; 4 males and 20 females; average age of 32.3 yrs (20 subjects between age range of 18-40 and 4 subjects between age range of 41-64); average height of 165.9 cm (152-192 cm) and average weight of 65.9 kg (51-91 kg); selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Pages 136-137, Vol. 1.2.

Restrictions:

No prescription and OTC medications for at least 2 weeks and 1 week, respectively, prior to the study and no concomitant medications during the study sessions.

No alcoholic beverages and no xanthine-containing beverages or food for 48 hours prior to and during the study period.

No food for 10 hours overnight prior to and for 4 hours postdose.

Washout: 36 hours (between the last sampling time of Period I and dosing time of Period II).

Confinement: approximately 1-2 hours pre-dose until 12 hours post-dose. The fasting restrictions were described in the Subject Consent Form and reviewed with each subject prior to dosing.

NOTES:

1. Twelve of the 24 subjects who participated in the Food Effect Study were also entered in the Fasting Study 60 hours after the Food Effect Study was completed.

2. The 24 subjects were dosed for the Fasting Study in different groups: Group 1 (12 subjects, dosed on 2/8/99 for Period I and 2/10/99 for Period II), Group 2 (11 subjects, dosed on 2/9/99 for Period I and 2/11/99 for Period II) and Group 3 (1 subject, dosed on 2/9/99 for Period I and 2/17/99 for Period II).

3. Although the Fasting Study was labeled as Phase One Study and the Food Effect as Phase Two Study, the Fasting Study was conducted after the Food Effect study.

Treatments and Sampling:

Treatment IBU-fa(Test Product): One of BASF's Ibuprofen 800 mg tablets, lot # WO11433 (Batch size of ——— units, potency of 99.8%); manuf. date: 11/98.

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AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Method: Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Since the subjects were dosed in different dates (see NOTES on page 3 of this review), the reviewer re-analyzed the PK parameters using the ANOVA model which was recommended by Don Schuirmann*: CLASS SEQ SUBJ PER TRT GRP; MODEL Y=SEQ SUBJ(SEQ) PER (GRP) TRT;. The assumptions used for this model are: 1) The groups were studied at the same site, 2) the groups were not widely separated in time, and 3) the subjects in the 2 groups were recruited from the same population. The assumptions were considered appropriate for this study. In the reanalysis, the groups were as follows: Group I: Subjects # 501, 504, 505, 506, 510, 511, 513-518, dosed on 2/8/99 (Period I) and 2/10/99 (Period II); Group II: Subjects # 502, 503, 507, 508, 509, 512, 519, 521-524, dosed on 2/9/99 (Period I) and 2/11/99 (Period II); and Group III: Subject # 520 dosed on 2/9/99(Period I) and 2/17/99 (Period II).

The results of the reanalysis are given in italics in the PK parameter summary table.

**NOTE: For reference concerning Schuirmann's model, see the example review of ANDA 65-065 (Biochemie; Amoxicillin & Clavulanate Potassium Tablets; 2/11/00; under Single-Dose Fasting Bioequivalence Study No. 99050)*

Results:

According to the reviewer's models, there was statistically significant difference

(alpha=0.05) between treatment for LCMAX (P=0.0264).

All 24 enrolled volunteers completed the clinical portion of the study. There was no drop-out. The statistical analysis was performed using 24 data sets. The results are summarized in the tables below:

Table I
Fasting Study
Ibuprofen Comparative Pharmacokinetic Parameters
Dose=800 mg; n=24

Parameters	BASF's Mean (CV%)	Motrin® Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) µg.hr/ml	208.0*	213.4*	[0.91;1.02] *[0.92; 1.02]***	0.96 *0.97***
AUC (0-Inf) µg.hr/ml	218.4*	220.8*	[0.93;1.03] *[0.94; 1.04]***	0.98 *0.99***
CMAX(µg/ml)	58.1*	62.8*	[0.87;0.97] *[0.87; 0.98]***	0.92 *0.92***
TMAX (hrs)	1.9(18)	1.6(43)		
KEL (1/hrs)	0.39(17)	0.39(18)		
T1/2 (hrs)	1.8(18)	1.6(20)		

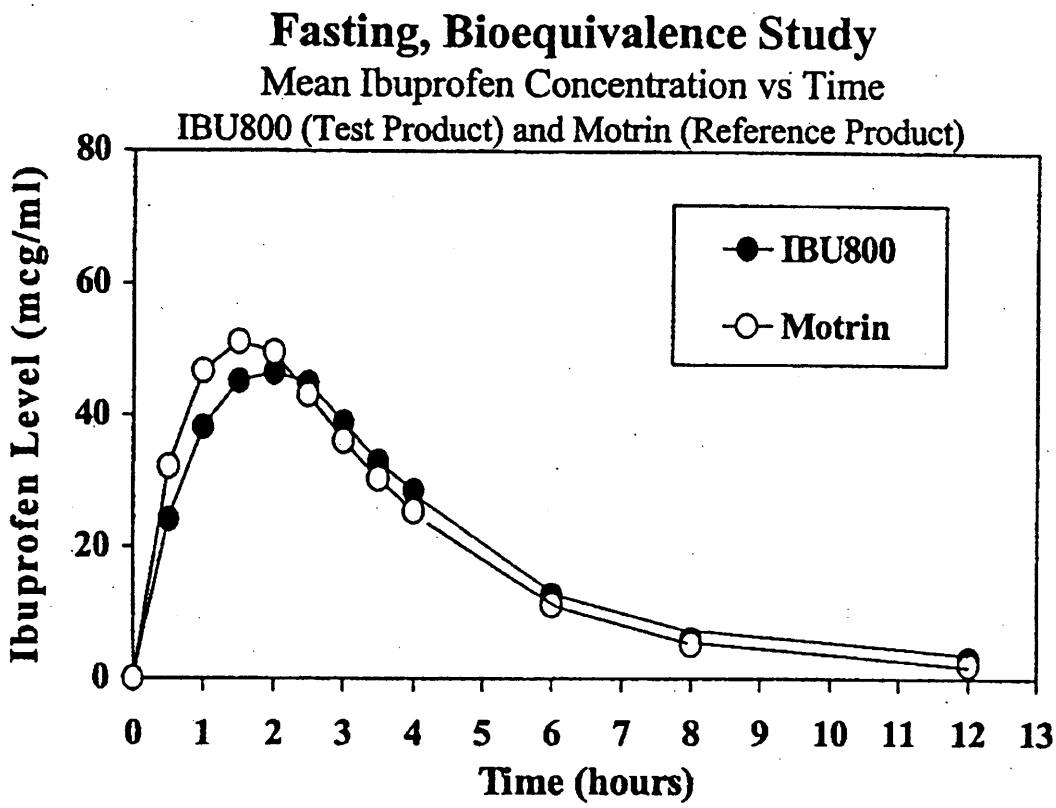
*Geometric LSMeans
**Reviewer's reanalysis using Schuirmann's model

Table II
Fasting Study
Comparative Mean Plasma Levels of Ibuprofen
Dose=800 mg; n=24

Plasma Sampling Time	IBU800 (Test)				Motrin (Reference)			Ratio of Means (Test:Ref)
	n	Mean	%CV		n	Mean	%CV	
pre-dose	24	0			24	0		
0.5 hour	22	24.2	78.3		24	32.1	62.5	0.75
1.0 hour	24	38.1	57.1		24	46.7	42.0	0.82
1.5 hour	23	45.2	38.2		24	51.1	30.9	0.88
2.0 hour	24	46.4	23.8		24	49.7	22.5	0.93
2.5 hour	24	44.9	26.8		24	43.2	27.1	1.04
3.0 hour	24	38.9	35.3		24	36.2	32.0	1.07
3.5 hour	24	33.0	41.4		24	30.4	39.2	1.09
4.0 hour	24	28.5	51.2		24	25.5	43.4	1.12
6.0 hour	24	12.6	54.5		24	11.1	49.0	1.14
8.0 hour	23	5.9	49.8		23	5.3	48.9	1.11
12 hour	7	3.2	53.2		12	2.2	31.5	1.45

Adverse Events: There was no serious adverse event reported. No drug-related adverse reactions were reported during the Test and Reference treatments.

APPEARS THIS WAY
ON ORIGINAL



IIB. FED/FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL #IBU800-Part II)

Study Objective: Bioequivalency of BASF's 800 mg Ibuprofen Tablets and McNeil's Motrin® 800 mg tablets under fed and fasting conditions following a 800 mg dose.

Study Facilities/Dates/Investigators:

Clinical: [redacted], between February 1 and 5, 1999 (with one subject (#601) dosed between February 3 and 9, 1999) ; [redacted]

Analytical: [redacted], between April 6 and May 6, 1999; [redacted]

The maximum sample storage duration between February 1 and May 6, 1999 is 95

days. The maxium sample storage duration between the first sample collection and the last sample reanalysis is 904 days.

Study Design: 3-treatment, 3-period, 6-sequence randomized crossover

Demographics:

12 normal, healthy male and female volunteers: 1 black and 11 caucasians; 2 males and 10 females; average age of 32.8 yrs (9 subjects between age range of 18-40 and 3 subjects between age range of 41-64); average height of 169.0 cm (153-191 cm) and average weight of 65.6 kg (51-85 kg); selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Same as in Fasting Study above.

Restrictions/Washout/Confinement: See the fasting study above.

Fasted Conditions: No food for 10 hours overnight prior to and for 4 hours postdose.

Fed Conditions: The subjects fasted for overnight until 30minutes prior to their scheduled dosing times, when they were given a standard breakfast. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American processed cheese, 1 slice of Canadian bacon, 2 oz of hashbrown potatoes, 6 fluid oz of orange juice and 8 fluid oz of whole milk.

Treatments and Sampling:

Treatment IBU-fe(Test Product, Fed): Same as **Treatment IBU-fa** of the fasting study except given under fed conditions.

Treatment MOT-feB(Reference Product, Fed): Same as **Treatment MOT-fa** of the fasting study except given under fed conditions.

Treatment IBU-fa(Test Product, Fasted): Same as **Treatment IBU-fa** of the fasting study.

Blood samples collected: Same as in the fasting study above.

Reanalysis Assay Methodology: by [redacted]

Assay procedure: assay procedure of ibuprofen consisted of [redacted]

NOTE: The samples from the fasting and non-fasting studies were reanalyzed at the same time and the reanalysis assay validation data were pooled and summarized under the Reanalysis Assay Methodology of the Fasting Study above.

Pharmacokinetic Method:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Method: Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for LACU(0-T) and LCMAX.

Results:

There was statistically significant difference (alpha=0.05) between treatment for LAUC(0-T) (P=0.0033).

All 12 enrolled volunteers completed the clinical portion of the study. There was no drop-out. The statistical analysis was performed using 12 data sets. The results are summarized in the tables below:

Table III
Non-Fasting Study
Ibuprofen Comparative Pharmacokinetic Parameters
Dose=800 mg; n=12

Parameters	BASF's(fasted) Mean (CV%)	BASF's (fed) Mean (CV%)	Motrin®(fed) Mean (CV%)	Ratio T_{fed}/R_{fed}
AUC (0-T) µg.hr/ml	233.7*	213.1*	208.2	1.02
AUC (0-Inf) µg.hr/ml	244.6*	235.8*	216.8	1.09
CMAX(µg/ml)	58.2*	46.7*	50.1	0.93
TMAX (hrs)	1.7(41)	2.1(78)	2.0(51)	
KEL (1/hrs)	0.38(21)	0.25(36)	0.31(13)	
T1/2 (hrs)	1.9(27)	3.3(54)	2.3(13)	

*Geometric LSMeans

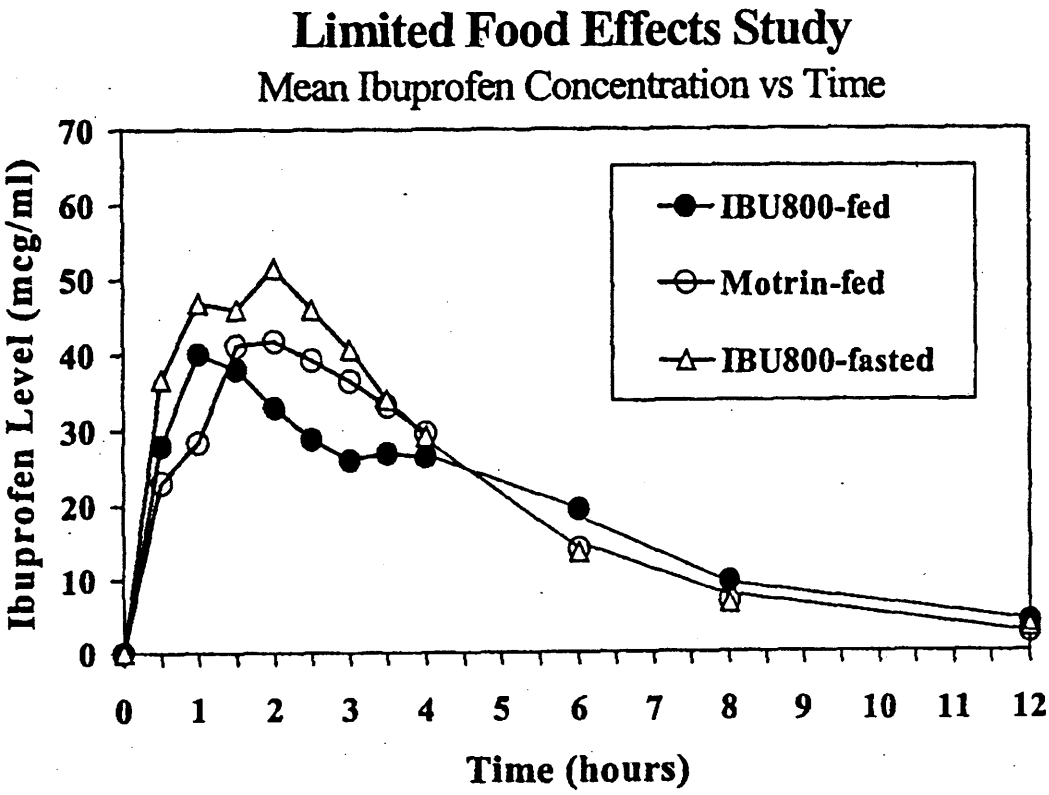
APPEARS THIS WAY
ON ORIGINAL

Table IV
Non-Fasting Study
Comparative Mean Plasma Levels of Ibuprofen
Dose=800 mg; n=12

Plasma Sampling Time	IBU800 - fasted (mcg/ml)			IBU800 - fed (mcg/ml)			Motrin - fed (mcg/ml)			Ratio of Means: IBU-fed to Motrin-fed
	n	Mean	%CV	n	Mean	%CV	n	Mean	%CV	
pre-dose	12	0	...	12	0	...	0	0	...	
0.5 hour	12	36.8	42.8	9	27.8	94.0	6	23.0	106.9	1.21
1.0 hour	12	46.9	35.5	12	37.0	62.1	12	28.2	81.7	1.31
1.5 hour	12	46.1	37.0	12	38.0	42.8	12	41.1	34.5	0.92
2.0 hour	11	51.6	25.2	12	32.9	38.8	12	41.8	33.7	0.78
2.5 hour	12	46.0	31.7	12	28.6	36.1	12	39.2	33.3	0.73
3.0 hour	12	40.8	32.4	12	25.8	29.7	12	36.4	29.0	0.71
3.5 hour	12	33.9	32.6	12	26.8	30.7	12	33.0	33.9	0.81
4.0 hour	12	29.1	32.8	12	26.2	27.3	12	29.5	40.0	0.89
6.0 hour	12	13.5	44.2	12	19.4	70.2	12	14.1	42.9	1.38
8.0 hour	12	6.6	51.2	12	9.6	68.7	12	6.8	38.2	1.41
12 hour	6	3.3	64.8	11	4.0	53.4	12	2.5	38.2	1.60

Adverse Events: There was no adverse event reported.

APPEARS THIS WAY
ON ORIGINAL



III. Dissolution Testing: USP24's method

Drug (Generic Name): Ibuprofen Tablets Firm: BASF Corp.
Dose Strength: 800 mg, 600 mg & 400 mg ANDA# 75-682
Submission Date: May 5, 2000

Table - In-Vitro Dissolution Testing

A. Conditions for Dissolution Testing:
USP XXIV Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: pH 7.2 phosphate buffer Volume: 900 ml
Reference Drug: (Manuf.) Motrin Tablets (McNeil)
Assay Methodology: Not given
Specifications: NLT [illegible]% in 60 minutes

B. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # WO11433 Strength (mg) 800 Mean % Dissolved(CV%)	Range	Reference Product Lot # 95BUB Strength (mg) 800 Mean % Dissolved(CV%)	Range
15	95(2.7)		98(0.9)	
30	96(2.5)		98(0.9)	
45	97(2.1)		98(0.9)	
60	98(1.8)		98(0.9)	

Sampling Times (Min.)	Test Product Lot # WO11429 Strength (mg) 600 Mean % Dissolved(CV%)	Range	Reference Product Lot # 63BSP Strength (mg) 600 Mean % Dissolved(CV%)	Range
15	97(1.7)		99(0.9)	
30	98(1.5)		100(0.9)	
45	98(1.6)		101(1.0)	
60	99(1.6)		101(0.9)	

Sampling Times (Min.)	Test Product Lot # WO11426 Strength (mg) 400 Mean % Dissolved(CV%)	Range	Reference Product Lot # 91BSU Strength (mg) 400 Mean % Dissolved(CV%)	Range
15	98(1.6)		100(1.4)	
30	99(1.6)		101(1.0)	
45	99(1.6)		100(0.9)	
60	99(1.6)		101(1.0)	

The dissolution data for the 800 mg, 600 mg and 400 mg strengths of the test and reference product are acceptable.

IV. Formulations:

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ON ORIGINAL

Quantitative Composition Summary By Tablet Strength

Ingredients	Ibuprofen Compressed Tablet Composition		
	400 mg/Tablet	600 mg/Tablet	800 mg/Tablet
Ibuprofen, USP	400.0	600.0	800.0
Microcrystalline Cellulose, NF			
Croscarmellose Sodium, NF			
Polysorbate			
Colloidal Silicon Dioxide, NF			
Magnesium Stearate, NF			
	[2]	[2]	[2]
	[2]	[2]	[2]
Polydextrose			
Hydroxypropyl Methylcellulose			
Hydroxypropyl Methylcellulose			
Hydroxypropyl Methylcellulose			
Polyethylene Glycol, NF			
Carnauba Wax, NF			
Titanium Dioxide, USP			
Iron Oxide			
FD&C Yellow No. 10			
FD&C Yellow No. 6			
Final Weight of Film Coated Tablet (g)	454.0	678.5	903.1

[1]

[2]

V. 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.

3. The formulations of the 400 mg and 600 mg strengths are proportionally similar to that of the 800 mg strength which underwent acceptable *in vivo* bioequivalence testing. The biowaiver requests for the 400 mg and 600 mg strengths are granted.

VI. 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, 800 mg, lot # WO11433, comparing it with the reference product, McNeil's Motrin® 800 mg Tablets, lot # 95BUB, have been found **acceptable** by the Division of Bioequivalence. The test product, BASF's Ibuprofen Tablets, 800 mg, is deemed bioequivalent to the reference product, McNeil's Motrin 800 mg Tablets under fasting and non-fasting conditions.

2. The in-vitro dissolution testing conducted by BASF on its Ibuprofen Tablets, 800 mg, 600 mg and 400 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.

3. The waiver request for the 600 mg and 400 mg strengths of the test product is granted. The test product, BASF's Ibuprofen Tablets, 600 mg and 400 mg, are deemed bioequivalent to the reference product, McNeil's Motrin Tablets, 600 mg and 400 mg, respectively.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 10/2/2001
FT INITIALED YHUANG

Concur: /S/ Date: 10/15/2001

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

cc: ANDA # 75-682 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/09-27-01/W #75682a.901
Also as V:\firmsam\BASF\ltrs&rev\75682a.901
Attachment: None

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Film-Coated Tablets USP, 800 mg, 600 mg & 400 mg

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.

We acknowledge that the dissolution testing has been 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/

for

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

APPEARS THIS WAY
ON ORIGINAL

CC:ANDA 75-682
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen /S/
HFD-652/ YHuang "/S/ 10/5/2001
HFD-617/ K. Scarnina /S/ 10/16/01
HFD-650/ D. Conner for /S/ 10/15/2001

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 09-10-01

1. STUDY AMENDMENT (STA) 01C Strength: 800 MG
Clinical: Outcome: AC
Analytical:

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-682 SPONSOR : BASF
DRUG AND DOSAGE FORM : Ibuprofen Tablets
STRENGTH(S) : 800 mg , 600 mg, 400 mg
TYPES OF STUDIES : Fasting & Non-Fasting Studies (800 mg)
CINICAL STUDY SITE(S) : _____
ANALYTICAL SITE(S) : _____

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : ___ /S/ _____ DATE : 10/2/01

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : ___ /S/ _____ DATE : 10/2/2001

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

for

INITIAL : _ /S/ _____ DATE : 10/15/2001

BIOEQUIVALENCY AMENDMENT

ANDA 75-682

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

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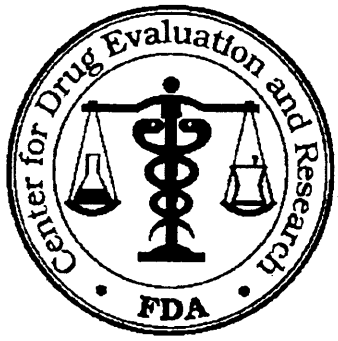

TO: APPLICANT: BASF Corporation TEL: 318-861-8103

ATTN: Michael Gill FAX: 318-861-8297

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Mr. Gill:

This facsimile is in reference to the bioequivalency data submitted on January 19, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Tablets USP, 800 mg, 600 mg, and 400 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

(V8)

Btvg 3/19/01

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pages of

trade secret and/or

confidential

commercial

information

Ibuprofen Film-Coated Tablets USP
ANDA #75-682: 800 mg, 600 mg & 400 mg
Reviewer: Hoainhon Nguyen
W #75682a.101

BASF Corp.
Shreveport, LA
Submission Date:
January 19, 2001

Review of a Study Amendment
(Expedited Review)

The firm has sent the current amendment in response to the deficiency comments by the Division of Bioequivalence in the letter dated November 20, 2000. (A copy of the deficiency letter is attached)

1. Submission History:

July 30, 1999: The firm submitted the results of a single-dose, fasting bio study and a single-dose, non-fasting bio study for the 800 mg strength of the test product, dissolution data for all strengths and waiver requests for the 600 mg and 400 mg strengths. The studies were found **incomplete** because the clinical report, the analytical report and the statistical report were lacking much of essential information and the dissolution data were inadequate (See a copy of this deficiency letter attached).

May 5, 2000: The firm submitted the requested information. The studies and dissolution data were reviewed. The studies were found **unacceptable** because the assay method was inadequately validated. *"(i) There was only one calibration curve (labeled Curve_100, calibrated 2/15/99) used for all study samples, which were assayed in 24 separate runs in the Fasting Study (runs dated February 17 through April 2, 1999), and in 13 separate runs in the Food Effect Study (runs dated April 6 through May 6, 1999). A calibration curve should have been generated for each analyte in each analytical run and used to calculate the concentration of the analyte in the unknown samples in the run. (ii) The QC samples used in each run were at only one concentration, [redacted] The QC samples for each run should have been in duplicate at three different concentrations (one near LOQ (i.e., [redacted], one in midrange, and one close to the high end of the range)."* In addition, the long-term stability data did not cover the entire sample storage period.

August 2, 2000: The firm submitted justifications for their assay method validation practices which were primarily based on the guidelines for certification of

a clinical laboratory by the [redacted] The validation practices were found inadequate in assuring and validating the quality of assays used in bioequivalence studies. In addition, the long-term stability data deficiency was not adequately addressed. (See a copy of this deficiency letter attached)

October 10, 2000: The firm submitted further justification for their assay method validation practices: the use of the state-of-the-art equipment and citing of Dr. Shah's publication, "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies (Conference Report), *Pharmaceutical Research* 1992; 9:588-592. In addition, the firm has extracted and assayed stored calibration standards that were prepared at the same time as the bio study standards, as well as assayed freshly prepared calibration standards. The firm compared response results of the old standards from the bio study with the freshly assayed old standards and the freshly assayed new standards. The firm also submitted the additional long-term stability data.

The firm was informed that according to the agency's current practices, even for the most state-of-the-art [redacted] equipment, adequate use of **in-study** standard curves and quality controls is requested for demonstration of the analytical method validity. Dr. Shah's publication was misquoted and misinterpreted by the firm. The data resulted from the firm's reanalysis of the original standards and quality controls were found inadequate in demonstrating the in-study analytical method performance and thus the validity of the original study sample results. The long-term stability data were found acceptable.

[redacted]

original and reassayed sample results. A protocol for the reanalysis is submitted for review.

2. Discussion of the Firm's Current Proposal & the Reanalysis Protocol:

The division statistician, Helen Hauxiang, is consulted for a possible statistical method and criteria which could be used to compare the proposed reanalyzed data with the original data and to test the "sameness" between the two sets of data. Helen has suggested the followings (See her consult responses attached):

1. The statistical criteria should be that *"the ratio of the new mean (reanalysis) and the old mean for the blood* (i.e., plasma) *concentration at each time point should be within (0.80;1.25) under alpha=0.05 and power=0.80."*

2. The statistician has reviewed the original plasma concentration data from the fasting study, the mean, standard deviation and coefficient of variance (CV) for each treatment at all 11 time points. Based on these data, she recommended that the reanalysis of samples should be done for all subjects of the study instead of only 6 subjects as the firm has proposed. *"The coefficient of variance ranges from ..... The sample size, ..., per reanalysis is required to attain a power of 0.80 in the case of an equivalence range (0.80, 1.25) with alpha=0.05 when CV=..... The required sample size will increase when the coefficient of variance increases. Therefore, the total of subjects in the fasting study needs to be reanalyzed for the new results."* The reanalyzed data should be compared with the original data using the above criteria.

3. Similarly, for the non-fasting study, based on the original plasma concentration data provided, the statistician recommended that all subjects of the study, instead of only ... as proposed, should be reanalyzed. *"The coefficient of variance (CV) for the old blood* (i.e., plasma) *concentration data from the food study ranges from ..... The sample size, ..., per reanalysis is required to attain a power of 0.80 in the case of an equivalence range (0.80,1.25) with alpha=0.05 when CV=..... Consequently, the total of subjects in the food study needs to be reanalyzed for the new results."* The reanalyzed data should be compared with the original data using the above criteria.

[redacted]

The Division of Bioequivalence therefore has the following recommendations for the firm's current proposal of reanalysis of study samples.

3. Recommendations:

[redacted]

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 2/28/2001
FT INITIALED YHUANG

Concur /S/ Date: 2/28/01

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

cc: ANDA # 75682a.101 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/01-31-01/W #75682a.101/Revised 02-27-01
Also as V:\firmsam\basf\ltrs&rev\75682a.101
Attachment: 6 pages

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CC:ANDA 75-682
ANDA DUPLICATE
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HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen /S/
HFD-652/ YHuang /S/ 3/28/2001
HFD-617/ K. Scardina /S/ 3/5/01
HFD-650/ D. Conner /S/ 3/2/01

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Printed in final on / /

BIOEQUIVALENCY - INCOMPLETE Submission date: 01-19-01

1. STUDY AMENDMENT (STA) Strength: 800 MG, 600 MG & 400 MG
Outcome: IC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

W# 75682 a.101 Attachment (1 of 6)

BIOEQUIVALENCY DEFICIENCIES (submission 10/10/00)

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Tablets, 400 mg, 600 mg & 800 mg

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

As stated in earlier deficiency comments, the in-study assay quality assurance activities as listed by you are not considered adequate by the Division of Bioequivalence. The precision and accuracy of the assay method used for the bio study should be demonstrated fully by use of in-study calibration curves and QC samples that represent the actual study concentration range, for each individual analytical run.

According to the publication of Shah (1992) cited by you, the statement *"A confidence interval approach yielding comparable accuracy and precision is an acceptable alternative."* (page 591) was referred to the statistical method of presenting QC data. The confidence interval approach was suggested as an alternative method to "number-of-QC approach" which dictated that *"At least four of the six QC samples must be within 20% of their respective nominal values; two of the six QC samples (not both at the same concentration) may be outside the ±20% respective nominal value."* The referred publication also recommended that *"A standard curve should be generated for each analytical run for each analyte and should be used for calculating the concentration of analyte in the unknown samples assayed with that run."*(page 590) and for QC samples, *"At a minimum, three concentrations representing the entire range of the calibration curve should be studied: one near the lower limit of quantitation (LOQ), one near the center, and one near the upper boundary of the standard curve."* (page 590)

The additional submitted data of the re-extracted standard curve and the fresh standard curve in comparison with the bio study standard curve, as well as the data of the ___ ___, QC samples quantitated based on these standard curves, can not be considered adequate in demonstrating and validating the in-study analytical method performance. At best, the newly generated standard curves and QC samples illustrated the stability of the stored standards and

W# 75682a. 101 Attachment (2 of 6)

controls as well as the variability of the assay particular to that assay date of the curves and the controls of that particular concentration.

The Division acknowledges that the long-term stability data as submitted in the current amendment are acceptable for the concentrations of ——— The drug ibuprofen at this concentration has been shown to be stable in plasma at -70°F for 570 days. However, in the future, you should also include QC samples of at least another higher concentration in the stability studies.

In summary, according to the agency's current practices, even for the most state-of-the-art chromatography equipment, adequate use of **in-study** standard curves and quality controls is requested for demonstration of the analytical method validity. For adequate assay validation, you are referred to the draft bioanalytical method guidance (which was the Reference #1 in your current correspondence) and also to the Division deficiency comments #1 and 2, dated July 26, 2000. The fasting bio study and the non-fasting bio study as submitted by you are therefore considered **unacceptable** due to inadequate assay validation. You are requested to conduct new bioequivalence studies for the test product.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

CC:ANDA 75-682
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen /S/
HFD-652/ YHuang /S/ 10/25/2000
HFD-617/ K. Scardina / /
HFD-650/ D. Conner /S/ 10/31/00

V:\FIRMSAM\BASF\ltrs&rev\75682a.o00
Printed in final on / /

BIOEQUIVALENCY - UNACCEPTABLE Submission date: 10-10-00

1. STUDY AMENDMENT (STA) 01C Strengths: 800 mg
   Clinical: ____________ Outcome: **UN**
   Analytical: ____________

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

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ON ORIGINAL

W# 75682a.101 Attachment (3 of 6)

BIOEQUIVALENCY DEFICIENCIES (Submission 7/30/99)

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Tablets, 400 mg, 600 mg & 800 mg

(Please also refer to the deficiency comments for ANDA #75-661 (Submission dated June 30 and August 16, 1999) which are conveyed to you in a separate letter.)

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

For both fasting and non-fasting studies:

1. The study clinical report is incomplete. It should provide the following information: dates of starting and completing the study and dates of each dosing period, length of confinement period for study subjects, any protocol deviation and sampling deviation.

3. The analytical report is incomplete. It should provide the following information, specifically for the submitted study of the 800 mg strength: dates of analyses, all raw numerical data for each run(including peak heights or areas, peak height or area ratios, calculated concentrations) of all standards, controls, samples, summary results of all standard curves for each run(including each standard concentration), summary results for each of low, medium and high quality controls. Long-term stability study should cover the length of time equivalent to the longest freezer storage period of the actual samples. Any relevant analytical Standard Operating Procedures should be submitted for review.

3. The statistical report is incomplete. It should provide mean plasma concentrations versus time (including CV%), individual and mean plots of plasma concentration versus time.

4. For dissolution data: The dissolution profiles for the 600 mg and 400 mg strengths of the reference product, Motrin tablets, should be provided side-by-side with the dissolution profiles for the respective strengths of the test product for comparison.

W# 75682a.101 Attachment (4 of 6)

BIOEQUIVALENCY DEFICIENCIES (Submission 8/2/00)

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Tablets, 400 mg, 600 mg & 800 mg

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 Division of Bioequivalence acknowledges that the analytical method was validated prior to the bio studies. However, an analytical method is not considered adequately and fully validated for a bio study unless it is also validated ***during the study.***

2. The guidelines for certification of a clinical laboratory by the CAP concerning the use of fresh calibration curves, as stated in the CAP's "Inspection Checklist" document and given by you, are not considered adequate by the FDA for bioequivalence studies. A draft guidance of "Bioanalytical Methods Validation for Human Studies"(Issued 12/1998, Posted 1/5/1999) outlines the generally accepted validation practices for a bio study.

   You had listed specific efforts by the analytical laboratory to minimize the variation and assure the accuracy of the assay during the study sample analysis, such as using internal standard, blinding the technician and using a single ——— for all study samples. However, only in-study validation data from calibration curves and quality controls obtained for each assay run are accepted as the quality assurance for each assay run, according to the agency's current practices.

3. As stated in Comment 1 above, ***pre-study*** validation results alone, even when obtained "***under a variety of analytical conditions and under different concentrations of ibuprofen***", are not considered adequate. The reproducibility of the assay method has to be demonstrated also ***during the study sample analysis*** by using quality controls, for each assay run, of at least three different concentrations which cover the range of the plasma concentrations of the actual study samples.

4. Stability data obtained at only two time points, Day 0 and Day 80, are not sufficient to establish the trend or linearity of the sample degradation. Therefore, the

W# 75-682a.101 Attachment (5 of 6)

extrapolated stability data for Day 95 are not considered valid. Stability data at Day 95 or longer must be directly measured from control samples that are actually stored in the freezer for this exact amount of time or longer.

Sincerely yours,

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

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W# 75682a.101 Attachment (6 of 6)

1/30/01

Hoainhon,

My purpose is that the ratio of the new mean (reanalysis) and the old mean for the blood concentration at each time point should be within (.80, 1.25) under alpha = .05 and power=.80.

The old blood concentration data from the fasting study provide mean, standard deviation, and coefficient of variance (CV) for each treatment at 11 time points. The coefficient of variance ranges from ~~~~~ The sample size, ~, per reanalysis is required to attain a power of 0.80 in the case of an equivalence range (0.80, 1.25) with alpha = .05 when CV= ~ The required sample size will increase when the coefficient of variance increases. Therefore, the total of subjects in the fasting study needs to be reanalyzed for the new results.

The coefficient of variance (CV) for the old blood concentration data from the food study ranges from ~~~~~ The sample size ~ per reanalysis is required to attain a power of 0.80 in the case of an equivalence range (0.80, 1.25) with alpha = .05 when CV= ~Consequence, the total of subjects in the food study needs to be reanalyzed for the new results.

Helen

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21

Ibuprofen Film-Coated Tablets USP
ANDA #75-682: 800 mg, 600 mg & 400 mg
Reviewer: Hoainhon Nguyen
W #75682a.o00

BASF Corp.
Shreveport, LA
Submission Date:
October 10, 2000

Review of a Study Amendment

1. Background:

The firm has submitted the current amendment in response to the deficiency comments by the Division of Bioequivalence in the letter dated August 29, 2000.

DBE deficiency comments (August 29, 2000):

"1. The Division of Bioequivalence acknowledges that the analytical method was validated prior to the bio studies. However, an analytical method is not considered adequately and fully validated for a bio study unless it is also validated during the study.

2. The guidelines for certification of a clinical laboratory by the CAP concerning the use of fresh calibration curves, as stated in the CAP's "Inspection Checklist" document and given by you, are not considered adequate by the FDA for bioequivalence studies. A draft guidance of "Bioanalytical Methods Validation for Human Studies"(Issued 12/1998, Posted 1/5/1999) outlines the generally accepted validation practices for a bio study.

You had listed specific efforts by the analytical laboratory to minimize the variation and assure the accuracy of the assay during the study sample analysis, such as using internal standard, blinding the technician and using a single ——— for all study samples. However, only in-study validation data from calibration curves and quality controls obtained for each assay run are accepted as the quality assurance for each assay run, according to the agency's current practices.

3. As stated in Comment 1 above, pre-study validation results alone,

even when obtained "under a variety of analytical conditions and under different concentrations of ibuprofen", are not considered adequate. The reproducibility of the assay method has to be demonstrated also during the study sample analysis by using quality controls, for each assay run, of at least three different concentrations which cover the range of the plasma concentrations of the actual study samples.

4. Stability data obtained at only two time points, Day 0 and Day 80,

[redacted]

Current Amendment: The firm's responses are summarized in two parts. In the first part, the firm addressed together the first three deficiency comments which concern the issue of in-study validation. In the second part, the firm addressed the the fourth deficiency comment which concern the long-term stability issue.

1. According to the firm, the in-study validation was assured through the

[redacted]

study, supports our approach used for the calibration curves and QC controls." (NOTE: The analytical assays were performed in a period of 43 days for the fasting study and 30 days for the non-fasting study)

The firm cited Dr. Shah's publication, "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies (Conference Report), Pharmaceutical Research 1992; 9:588-592, for *"a confidence interval approach yielding comparable accuracy and precision"* as *"an acceptable alternative"* to using *"three concentration levels described for QC samples utilizing duplicate injections per concentration"* which *"are used to provide analytical run statistical assessment for analytical methods that have potential for drift of lack of control throughout the run."*

In addition, the firm has extracted and assayed stored calibration standards that were prepared at the same time as the bio study standards, as well as assayed freshly prepared calibration standards. The firm compared response results of the old standards from the bio study with the freshly assayed old

2. Comments:

1. As stated in earlier deficiency comments, the in-study assay quality assurance activities as listed by the firm are not considered adequate by the Division of Bioequivalence. The precision and accuracy of the assay method used for the bio study should be demonstrated by use of in-study calibration curves and QC samples that represent the actual study concentration range, for each individual analytical run.

According to the publication of Shah (1992) cited by the firm, the statement *"A confidence interval approach yielding comparable accuracy and precision is an acceptable alternative."* (page 591) was referred to the statistical method of presenting QC data. The confidence interval approach was suggested as an alternative method to "number-of-QC approach" which dictated that *"At least four of the six QC samples must be within 20% of their respective nominal values; two of the six QC samples (not both at the same concentration) may be outside the ±20% respective nominal value."* The referred publication also recommended that *"A standard curve should be generated for each analytical run for each analyte and should be used for calculating the concentration of analyte in the unknown samples assayed with that run."*(page 590) and for QC samples, *"At a minimum, three concentrations representing the entire range of the calibration curve should be studied: one near the lower limit of quantitation (LOQ), one near the center, and one near the upper boundary of the standard curve."* (page 590)

The additional submitted data of the re-extracted standard curve and the fresh standard curve in comparison with the bio study curve, as well as the data of the [redacted] QC samples quantitated based on these standard curves, can not be considered adequate in demonstrating and validating the in-study analytical method performance. At best, the newly generated standard curves and QC samples illustrated the stability of the stored standards and controls as well as the variability of the assay particular to that assay date of the curves and the controls of that particular concentration.

2. The long-term stability data as submitted in the current amendment are considered acceptable for the concentrations of [redacted]. The drug ibuprofen at this concentration has been shown to be stable in plasma at -

70°F for 570 days. However, in the future, the firm should also include QC samples of at least another higher concentration in the stability studies.

3. **Recommendation:**

According to the agency's current practices, even for the most state-of-the-art [redacted] equipment, adequate use of in-study standard curves and quality controls, as outlined in the draft bioanalytical method guidance and in the deficiency comments #1 and 2 dated July 26, 2000, is requested for demonstration of the analytical method validity. The fasting bio study and the non-fasting bio study as submitted by the firm are therefore considered **unacceptable** due to inadequate assay validation. The firm is requested to conduct new bioequivalence studies for the test product.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 10/25/2000

Concur: /S/ Date: 10/31/00
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 75-682 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/10-19-00/W #75682a.o00
Also as V:\firmsam\BASF\ltrs&rev\75682a.o00
Attachment: 0 page

Ibuprofen Film-Coated Tablets USP
ANDA #75-682: 800 mg, 600 mg & 400 mg
Reviewer: Hoainhon Nguyen
W #75682a.800

BASF Corp.
Shreveport, LA
Submission Date:
August 2, 2000

Review of a Study Amendment

I. Background:

The firm has submitted the current amendment in response to the deficiency comments by the Division of Bioequivalence in the letter dated July 26, 2000. The DBE deficiency comments were as follows:

"For both fasting and non-fasting studies, the assay method was not adequately validated.

(i) There was only one calibration curve (labeled Curve_100, calibrated 2/15/99) used for all study samples, which were assayed in 24 separate runs in the Fasting Study (runs dated February 17 through April 2, 1999), and in 13 separate runs in the Food Effect Study (runs dated April 6 through May 6, 1999). A calibration curve should have been generated for each analyte in each analytical run and used to calculate the concentration of the analyte in the unknown samples in the run.

(ii) The QC samples used in each run were at only one concentration, The QC samples for each run should have been in duplicate at three different concentrations (one near LOQ (i.e., ≤ , one in midrange, and one close to the high end of the range).

(iii) Stability study covered 80-day storage period but the maximum freezer storage duration for the actual samples was 95 days (This comment is applied to the Food Effect Study)."

The firm's responses are summarized below.

1. The analytical method was validated well *prior to the study*. The results

of the pre-study validation were given to illustrate the validity of the method (Page 2 of the amendment letter).

2. *"The laboratory analysis for this study was performed according to the guidelines for certification of a clinical laboratory by the College of American Pathologists (CAP). The CAP's document used was the "Commission on Laboratory Accreditation: Inspection Checklist, Section 3B, Toxicology, 1998.1 edition." The interval for calibration (defined as the relationship between a drug concentration and the measured response) is determined by the criteria outlined in the following table."* The table specifies that a new calibration standard curve should only be used for the following reasons: (a) a complete change of reagents; (b) quality control fails to meet established criteria; (c) after major maintenance or service; (d) at least once every six months; and (e) when recommended by the manufacturer. Since none of these reasons was applicable to the assay used for the study, only one calibration curve was used for the entire study. (The CAP guideline table was given on Page 3 of the amendment letter.)

3. *"A single mid range concentration was used for the QC samples because this was a highly reproducible study under a variety of analytical conditions and at different concentrations of ibuprofen. The coefficient of variation was determined for low, mid and high range concentrations (, respectively) on the standard curves used during different phases of assay development and obtained under a variety of conditions (different stock solutions, and 2 different s over a 10 month period) prior to study sample analysis...Thus, this was a highly reproducible study and this reproducibility did not change during the course of the study."*

4. *"We acknowledge that some of the study samples exceeded the freezer storage period of the stability samples for the Food Effect Study...The stability data generated for the long term storage period indicates no significant degradation throughout the storage period and we would project acceptable stability to well beyond 120 days at –70F. The slope is presented in the chart below* (The chart was given on Page 5 of the amendment letter.). *Predictive stability to the 95 day storage period for the final sample run for the Food Effects Study would suggest no impact*

on this study..."

II. Comments:

1. The Division of Bioequivalence acknowledges that the analytical method was validated prior to the bio studies. However, an analytical method is not considered adequately and fully validated for a bio study unless it is also validated ***during the study.***

2. The guidelines for certification of a clinical laboratory by the CAP concerning the use of fresh calibration curves, as stated in the CAP's "Inspection Checklist" document and given by the firm, are not considered adequate by the FDA for bioequivalence studies. A draft guidance of "Bioanalytical Methods Validation for Human Studies"(Issued 12/1998, Posted 1/5/1999) outlines the generally accepted validation practices for a bio study.

The firm had listed specific efforts by the analytical laboratory to minimize the variation and assure the accuracy of the assay, such as using internal standard, blinding the technician and using a single [redacted] for all study samples. However, only in-study validation data from calibration curves and quality controls obtained for each assay run are accepted as the quality assurance for each assay run, according to the agency's current practices.

3. As stated in Comment 1 above, pre-study validation results alone are not considered adequate. The reproducibility of the assay method has to be demonstrated also during the study sample analysis by using quality controls of at least three different concentrations which are in the range of the plasma concentrations of the actual study samples.

4. Stability data obtained at only two time points, Day 0 and Day 80, are not sufficient to establish the trend or linearity of the sample degradation. Therefore, the extrapolated stability data for Day 95 are not considered valid. Stability data at Day 95 or longer must be directly measured from control samples that are actually stored in the freezer for this exact amount of time or longer.

In summary, additional information submitted by the firm in the current amendment has not changed the previous review recommendations for the bio studies.

III. 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, 800 mg, lot # WO11433, comparing it with the reference product, McNeil's Motrin® 800 mg Tablets, lot # 95BUB, have been found **unacceptable** by the Division of Bioequivalence due to the deficiencies cited in the Comments above and in the previous review of the submission dated May 5, 2000.

2. The in-vitro dissolution testing conducted by BASF on its Ibuprofen Tablets, 800 mg, 600 mg and 400 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 [redacted] of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

3. The waiver request for the 600 mg and 400 mg strengths of the test product can not be granted due to the unacceptability of the *in vivo* studies.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 8/8/2000
FT INITIALED YHUANG

/S/

Concu _____ Date: 8/21/00

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

cc: ANDA # 75-682 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/08-07-00/W #75682a.800
Also as V:\firmsam\BASF\ltrs&rev\75682a.800
Attachment: 0 page

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

AUG 29 2000

ANDA 75-682

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: BASF Corporation PHONE: 318-861-8103

ATTN: Michael Gill FAX: 318-861-8297

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on 02 August 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Film-Coated Tablets USP, 800mg, 600mg, and 400mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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Ibuprofen Film-Coated Tablets USP
ANDA #75-682: 800 mg, 600 mg & 400 mg
Reviewer: Hoainhon Nguyen
W #75682sdw.799

BASF Corp.
Shreveport, LA
Submission Date:
July 30, 1999

Review of Two Bioequivalence Studies, Dissolution Data and a Waiver Request

I. Background:

The firm has submitted the results of a fasting, single-dose bioequivalence study and a post-prandial bioequivalence study comparing its Ibuprofen Film-Coated Tablets USP, 800 mg, with McNeil's Motrin® 800 mg Ibuprofen Tablets. Comparative dissolution data for the test and RLD products of 800 mg and for the 600 mg and 400 mg strengths of the test product are also submitted. The firm has requested a waiver of *in vivo* bioequivalence requirements for the 600 mg and 400 mg based on the formulation proportionality between the strengths.

II. Bioequivalence Studies:

IIA. FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL #IBU800-Part I)

Study Objective: Bioequivalency of BASF's and McNeil's (Motrin®) 800 mg Ibuprofen Tablets under fasting conditions.

Study Facilities/Dates/Investigators:

Clinical: [redacted] dates not given; [redacted]

Analytical: [redacted] dates not given; [redacted]

Study Design: 2-treatment, 2-period, randomized crossover

Demographics: 24 normal, healthy male and female volunteers; 22-48 years of age; height ranged 152-192 cm; weight 51-91 kg; selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Pages 136-137, Vol. 1.2.

Restrictions:

No prescription and OTC medications for at least 2 weeks and 1 week, respectively, prior to the study and no concomitant medications during the study sessions.

No alcoholic beverages and no xanthine-containing beverages or food for 48 hours prior to and during the study period.

No food for 10 hours overnight prior to and for 4 hours postdose.

Washout: 36 hours.

Confinement: not given.

Treatments and Sampling:

Treatment IBU-fa(Test Product): One of BASF's Ibuprofen 800 mg tablets, lot # WO11433 (Batch size of ——— units, potency of 99.8%); manuf. date: 11/98.

Treatment MOT-fa(Reference Product): One of McNeil's Motrin® 800 mg ibuprofen tablets, lot # 95BUB (Potency: 102.5%); exp. 11/02.

Blood samples collected: predose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0 and 12 hours postdose. Plasma samples were stored at -70^{0}C pending assay.

Deficiencies:

1. The study clinical report is incomplete. The report should provide the following information: dates of starting and completing the study and dates of each dosing period, length of confinement period for study subjects, any protocol deviation and sampling deviation.

2. The analytical report should provide the following information, specifically for the submitted study of the 800 mg strength: dates of analyses, all raw numerical data for each run(including peak heights or areas, peak height or area ratios, calculated concentrations) of all standards, controls, samples, summary results of all standard curves for each run(including each standard concentration), summary results for each of low, medium and high quality controls. Long-term stability study should cover the length of time equivalent to the longest freezer storage period of the actual samples. Any relevant analytical Standard Operating Procedures should also be submitted for review.

3. The statistical report should provide mean plasma concentration versus time (including CV%), individual and mean plots of plasma concentration versus time.

IIB. FED/FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL #IBU800-Part II)

Study Objective: Bioequivalency of BASF's 800 mg Ibuprofen Tablets and McNeil's Motrin® 800 mg tablets under fed and fasting conditions following a 800 mg dose.

Study Facilities/Dates/Investigators: Same as in Fasting Study above.

Study Design: 3-treatment, 3-period, randomized crossover

Demographics:

12 normal, healthy male and female volunteers; 25-48 years of age; height ranged 153-191 cm; weight ranged 51-85 kg; selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Same as in Fasting Study above.

Restrictions/Washout/Confinement: See the fasting study above.

Fasted Conditions: No food for 10 hours overnight prior to and for 4 hours postdose.

Fed Conditions: The subjects fasted for overnight until 30minutes prior to their scheduled dosing times, when they were given a standard breakfast. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American processed cheese, 1 slice of Canadian bacon, 2 oz of hashbrown potatoes, 6 fluid oz of orange juice and 8 fluid oz of whole milk.

Treatments and Sampling:

Treatment IBU-fe(Test Product, Fed): Same as **Treatment IBU-fa** of the fasting study except given under fed conditions.

Treatment MOT-feB(Reference Product, Fed): Same as **Treatment MOT-fa** of the fasting study except given under fed conditions.

Treatment IBU-fa(Test Product, Fasted): Same as **Treatment IBU-fa** of the fasting study.

Blood samples collected: Same as in the fasting study above.

Deficiencies: similar report format deficiencies as in the Fasting Study above.

III. Dissolution Testing: USP's method

Drug (Generic Name): Ibuprofen Tablets Firm: BASF Corp.
Dose Strength: 400 mg, 600 mg & 800 mg ANDA# 75-682
Submission Date: July 30, 1999

A. Conditions for Dissolution Testing:
USP XXIII Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: pH 7.2 buffer Volume: 900 ml
Reference Drug: (Manuf.) Motrin Tablets (McNeil)
Assay Methodology: Not given
Specifications: NLT —% in 60 minutes

B. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # WO11433 Strength (mg) 800 Mean % Dissolved(CV%)	Range	Reference Product Lot # 95BUB Strength (mg) 800 Mean % Dissolved(CV%)	Range
15	95(2.7)	—	98(0.9)	—
30	96(2.5)	—	98(0.9)	—
45	97(2.1)	—	98(0.9)	—
60	98(1.8)	—	98(0.9)	—

Sampling Times (Min.)	Test Product Lot # WO11429 Strength (mg) 600 Mean % Dissolved(CV%)	Range	Reference Product Lot # Not Submitted Strength (mg) 600 Mean % Dissolved(CV%)	Range
15	97(1.7)	—	____	____
30	98(1.5)	—	____	____
45	98(1.6)	—	____	____
60	99(1.6)	—	____	____

Sampling Times (Min.)	Test Product Lot # WO11426 Strength (mg) 400		Reference Product Lot # Not Submitted Strength (mg) 400	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	98(1.6)			
30	99(1.6)			
45	99(1.6)			
60	99(1.6)			

IV. Formulation Comparison: See comparative formulations of all strengths of the test product attached.

V. Comment:

The formulations of the 800 mg, 600 mg and 400 mg are proportionally similar.

VI. Deficiencies:

The first 3 following deficiencies are for both fasting and non-fasting studies:

1. The study clinical report is incomplete. The report should provide the following information: dates of starting and completing the study and dates of each dosing period, length of confinement period for study subjects, any protocol deviation and sampling deviation.

2. The analytical report should provide the following information, specifically for the submitted study of the 800 mg strength: dates of analyses, all raw numerical data for each run(including peak heights or areas, peak height or area ratios, calculated concentrations) of all standards, controls, samples, summary results of all standard curves for each run(including each standard concentration), summary results for each of low, medium and high quality controls. Long-term stability study should cover the length of time equivalent to the longest freezer storage period of the actual samples. Any relevant analytical Standard Operating Procedures should also submitted for review.

3. The statistical report should provide mean plasma concentrations versus time (including CV%), individual and mean plots of plasma concentration versus time.

4. Dissolution data are deficient in that the dissolution profiles for the 600 mg and 400 mg strengths of the reference product, Motrin tablets, were not provided.

VII. 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, 800 mg, lot # WO11433, comparing it with the reference product, McNeil's Motrin® 800 mg Tablets, lot # 95BUB, have been found **incomplete** by the Division of Bioequivalence due to the deficiencies #1-3 cited above.

2. The in-vitro dissolution testing conducted by BASF on its Ibuprofen Tablets, 800 mg, 600 mg and 400 mg, has been found **incomplete** due to the dissolution deficiency #4 listed above.

3. The waiver request for the 600 mg and 400 mg strengths of the test product can not be considered until the review of the bio studies and dissolution data is completed.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 9/27/99
FT INITIALED YHUANG

Concur /S/ Date: 9/29/99
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 75-682 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/09-23-99/W #75682sdw.799
Also as V:\firmsam\BASF\ltrs&rev\75682sdw.799
Attachment: 1 page

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CC:ANDA 75-682
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Finals with Dates)
HFD-652/ HNguyen /S/
HFD-652/ YHuang /S/ 9/7/99
HFD-617/ E. Hu /S/ 10/12/99
HFD-650/ D. Conner /S/ 9/29/99

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BIOEQUIVALENCY - INCOMPLETE Submission date: 07-30-99

1. FASTING STUDY (STF) o/c Strengths: 800 mg
   Clinical: ~~~~~ **Outcome:** **IC**
   Analytical: ~~~~~

2. NON-FASTING STUDY (STP) o/c Strengths: 800 MG
   Clinical: ~~~~~ **Outcome:** **IC**
   Analytical: ~~~~~

3. DISSOLUTION WAIVER (DIW) Strength: 600 mg & 400 mg
   o/c **Outcome:** **IC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Tablets, 400 mg, 600 mg & 800 mg

(Please also refer to the deficiency comments for ANDA #75-661 (Submission dated June 30 and August 16, 1999) which are conveyed to you in a separate letter.)

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

For both fasting and non-fasting studies:

1. The study clinical report is incomplete. It should provide the following information: dates of starting and completing the study and dates of each dosing period, length of confinement period for study subjects, any protocol deviation and sampling deviation.

3. The analytical report is incomplete. It should provide the following information, specifically for the submitted study of the 800 mg strength: dates of analyses, all raw numerical data for each run(including peak heights or areas, peak height or area ratios, calculated concentrations) of all standards, controls, samples, summary results of all standard curves for each run(including each standard concentration), summary results for each of low, medium and high quality controls. Long-term stability study should cover the length of time equivalent to the longest freezer storage period of the actual samples. Any relevant analytical Standard Operating Procedures should be submitted for review.

3. The statistical report is incomplete. It should provide mean plasma concentrations versus time (including CV%), individual and mean plots of plasma concentration versus time.

4. For dissolution data: The dissolution profiles for the 600 mg and 400 mg strengths of the reference product, Motrin tablets, should be provided side-by-side with the

dissolution profiles for the respective strengths of the test product for comparison.

Sincerely yours,

/S/

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

W# 75682 sdw. 799 Attachment I

Quantitative Composition Summary By Tablet Strength

Ingredients	Ibuprofen Compressed Tablet Composition		
	400 mg/Tablet	600 mg/Tablet	800 mg/Tablet
Ibuprofen, USP	400.0	600.0	800.0
Microcrystalline Cellulose, NF			
Croscarmellose Sodium, NF			
Polysorbate			
Colloidal Silicon Dioxide, NF			
Magnesium Stearate, NF			
	2	2	2
	2	2	2
Polydextrose			
Hydroxypropyl Methylcellulose			
Hydroxypropyl Methylcellulose			
Hydroxypropyl Methylcellulose			
Polyethylene Glycol, NF			
Carnauba Wax, NF			
Titanium Dioxide, USP			
Iron Oxide			
FD&C Yellow No. 10			
FD&C Yellow No. 6			
	454.0	678.5	903.1
	3	3	3
	2,3	2,3	2,3

1

2

BIOEQUIVALENCY AMENDMENT

NOV 23

ANDA 75-682

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: BASF Corporation PHONE: (318) 861-8103

ATTN: Michael Gill FAX: (318) 861-8297

FROM: Elaine Hu PROJECT MANAGER (301) 827-5847

Dear Mr. Gill:

This facsimile is in reference to the bioequivalency data submitted on July 30, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Film-Coated Tablets, 800, 600, and 400 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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B. Mc
11/22/99

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Tablets, 400 mg, 600 mg & 800 mg

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

For both fasting and non-fasting studies, the assay method was not adequately validated.

(i) There was only one calibration curve (labeled Curve_100, calibrated 2/15/99) used for all study samples, which were assayed in 24 separate runs in the Fasting Study (runs dated February 17 through April 2, 1999), and in 13 separate runs in the Food Effect Study (runs dated April 6 through May 6, 1999). A calibration curve should have been generated for each analyte **in each analytical run** and used to calculate the concentration of the analyte in the unknown samples in the run.

(ii) The QC samples used in each run were at only one concentration, ——— The QC samples for each run should have been in duplicate **at three different concentrations** (one near LOQ (i.e., ——— one in midrange, and one close to the high end of the range).

(iii) Stability study covered 80-day storage period but the maximum freezer storage duration for the actual samples was 95 days (This comment is applied to the Food Effect Study).

The results of both the Fasting and Food Effect Studies, therefore, can not be considered valid and acceptable due to the above deficiencies.

Sincerely yours,

/S/

fw

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

CC:ANDA 75-682
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen /S/
HFD-652/ YHuang /S/ 5/[illegible]/2000 6/6/2000
HFD-617/ P. Nguyen /S/ 7/15/00
HFD-650/ D. Conner for DW 7/14/2000

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BIOEQUIVALENCY - UNACCEPTABLE Submission date: 05-05-00

1. STUDY AMENDMENT (STA) O/C Strengths: 800 mg
Clinical: Outcome: UN
Analytical:

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT JUL 26 2000

ANDA 75-682

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: BASF Corporation PHONE: 318-861-8103

ATTN: Michael Gill FAX: 318-861-8297

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on 05 May 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Film-Coated Tablets, 400, 600, and 800mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Tablets, 400 mg, 600 mg & 800 mg

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 Division of Bioequivalence acknowledges that the analytical method was validated prior to the bio studies. However, an analytical method is not considered adequately and fully validated for a bio study unless it is also validated ***during the study.***

2. The guidelines for certification of a clinical laboratory by the CAP concerning the use of fresh calibration curves, as stated in the CAP's "Inspection Checklist" document and given by you, are not considered adequate by the FDA for bioequivalence studies. A draft guidance of "Bioanalytical Methods Validation for Human Studies" (Issued 12/1998, Posted 1/5/1999) outlines the generally accepted validation practices for a bio study.

   You had listed specific efforts by the analytical laboratory to minimize the variation and assure the accuracy of the assay during the study sample analysis, such as using internal standard, blinding the technician and using a single ———— for all study samples. However, only in-study validation data from calibration curves and quality controls obtained for each assay run are accepted as the quality assurance for each assay run, according to the agency's current practices.

3. As stated in Comment 1 above, ***pre-study*** validation results alone, even when obtained ***"under a variety of analytical conditions and under different concentrations of ibuprofen"***, are not considered adequate. The reproducibility of the assay method has to be demonstrated also ***during the study sample analysis*** by using quality controls, for each assay run, of at least three different concentrations which cover the range of

the plasma concentrations of the actual study samples.

4. Stability data obtained at only two time points, Day 0 and Day 80, are not sufficient to establish the trend or linearity of the sample degradation. Therefore, the extrapolated stability data for Day 95 are not considered valid. Stability data at Day 95 or longer must be directly measured from control samples that are actually stored in the freezer for this exact amount of time or longer.

Sincerely yours,

/S/

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

CC:ANDA 75-682
ANDA DUPLICATE
DIVISION FILE
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HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen 8/21/00
HFD-652/ YHuang 8/21/00
HFD-617/ K. Scardina 8/23/00
HFD-650/ D. Conner 8/21/00

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BIOEQUIVALENCY - UNACCEPTABLE Submission date: 08-02-00

1. STUDY AMENDMENT (STA) 01C Strengths: 800 mg, 400 mg, 600 mg
   Clinical: ~~_____~~ **Outcome:** **UN**
   Analytical: _____

OUTCOME DECISIONS: **IC** - Incomplete (fatal flaw) **UN** - Unacceptable
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

Ibuprofen Film-Coated Tablets USP
ANDA #75-682: 800 mg, 600 mg & 400 mg
Reviewer: Hoainhon Nguyen
W #75682a.500

BASF Corp.
Shreveport, LA
Submission Date:
May 5, 2000

Review of a Study Amendment
(and Results of Two Bioequivalence Studies)

I. Background:

The firm has submitted the current amendment in response to the deficiency comments by the Division of Bioequivalence in the letter dated November 23, 1999. The deficiency comments are attached.

The firm's responses are reviewed together with the original submission which included the results of a fasting, single-dose bioequivalence study and a post-prandial bioequivalence study comparing its Ibuprofen Film-Coated Tablets USP, 800 mg, with McNeil's Motrin® 800 mg Ibuprofen Tablets, comparative dissolution data for the test and RLD products of 800 mg and for the 600 mg and 400 mg strengths of the test product, and the waiver request for the 600 mg and 400 mg strengths.

II. Bioequivalence Studies:

IIA. FASTING IN-VIVO BIOEQUIVALENCE STUDY
(PROTOCOL #IBU800-Part I)

Study Objective: Bioequivalency of BASF's and McNeil's (Motrin®) 800 mg Ibuprofen Tablets under fasting conditions.

Study Facilities/Dates/Investigators:

Clinical: [redacted]; between February 8 and 17, 1999; [redacted]

Analytical: [redacted]

; between February 17 and April 2, 1999;

The maximum sample storage duration between February 8 and April 2, 1999 is 53 days.

Study Design: 2-treatment, 2-period, randomized crossover

Demographics: 24 normal, healthy male and female volunteers; 22-48 years of age; height ranged 152-192 cm; weight 51-91 kg; selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Pages 136-137, Vol. 1.2.

Restrictions:

No prescription and OTC medications for at least 2 weeks and 1 week, respectively, prior to the study and no concomitant medications during the study sessions.

No alcoholic beverages and no xanthine-containing beverages or food for 48 hours prior to and during the study period.

No food for 10 hours overnight prior to and for 4 hours postdose.

Washout: 36 hours (between the last sampling time of Period I and dosing time of Period II).

Confinement: approximately 1-2 hours pre-dose until 12 hours post-dose. The fasting restrictions were described in the Subject Consent Form and reviewed with each subject prior to dosing.

NOTES:

1. Twelve of the 24 subjects who participated in the Food Effect Study were also entered in the Fasting Study 60 hours after the Food Effect Study was

completed.

2. The 24 subjects were dosed for the Fasting Study in different groups: Group 1 (12 subjects, dosed on 2/8/99 for Period I and 2/10/99 for Period II), Group 2 (11 subjects, dosed on 2/9/99 for Period I and 2/11/99 for Period II) and Group 3 (1 subject, dosed on 2/9/99 for Period I and 2/17/99 for Period II).

3. Although the Fasting Study was labeled as Phase One Study and the Food Effect as Phase Two Study, the Fasting Study was conducted after the Food Effect study.

Treatments and Sampling:

Treatment IBU-fa(Test Product): One of BASF's Ibuprofen 800 mg tablets, lot # WO11433 (Batch size of [redacted] units, potency of 99.8%); manuf. date: 11/98.

Treatment MOT-fa(Reference Product): One of McNeil's Motrin® 800 mg ibuprofen tablets, lot # 95BUB (Potency: 102.5%); exp. 11/02.

Blood samples collected: predose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0 and 12 hours postdose. Plasma samples were stored at -70^{0}C pending assay.

Assay Methodology: by [redacted]

Redacted 1

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trade secret and/or

confidential

commercial

information

IIB. FED/FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL #IBU800-Part II)

Study Objective: Bioequivalency of BASF's 800 mg Ibuprofen Tablets and McNeil's Motrin® 800 mg tablets under fed and fasting conditions following a 800 mg dose.

Study Facilities/Dates/Investigators:

Clinical: [redacted] between February 1 and 5, 1999 (with one subject (#601) dosed between February 3 and 9, 1999) ; [redacted]

Analytical: [redacted] between April 6 and May 6, 1999; [redacted]

The maximum sample storage duration between February 1 and May 6, 1999 is 95 days.

Study Design: 3-treatment, 3-period, randomized crossover

Demographics:

12 normal, healthy male and female volunteers; 25-48 years of age; height ranged 153-191 cm; weight ranged 51-85 kg; selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Same as in Fasting Study above.

Restrictions/Washout/Confinement: See the fasting study above.

Fasted Conditions: No food for 10 hours overnight prior to and for 4 hours postdose.

Fed Conditions: The subjects fasted for overnight until 30minutes prior to their scheduled dosing times, when they were given a standard breakfast. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American processed cheese, 1 slice of Canadian bacon, 2 oz of hashbrown potatoes, 6 fluid oz of orange juice and 8 fluid oz of whole milk.

Treatments and Sampling:

Treatment IBU-fe(Test Product, Fed): Same as **Treatment IBU-fa** of the fasting study except given under fed conditions.

Treatment MOT-feB(Reference Product, Fed): Same as **Treatment MOT-fa** of the fasting study except given under fed conditions.

Treatment IBU-fa(Test Product, Fasted): Same as **Treatment IBU-fa** of the fasting study.

Blood samples collected: Same as in the fasting study above.

Assay Methodology: by [redacted]

The study results, therefore, can not be considered valid and acceptable due to the above deficiencies.

III. Dissolution Testing: USP24's method

Drug (Generic Name): Ibuprofen Tablets Firm: BASF Corp.
Dose Strength: 800 mg, 600 mg & 400 mg ANDA# 75-682
Submission Date: May 5, 2000

Table - In-Vitro Dissolution Testing

A. Conditions for Dissolution Testing:
USP XXIV Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: pH 7.2 phosphate buffer Volume: 900 ml
Reference Drug: (Manuf.) Motrin Tablets (McNeil)
Assay Methodology: Not given
Specifications: NLT ~o in 60 minutes

B. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # WO11433 Strength (mg) 800 Mean % Dissolved(CV%)	Range	Reference Product Lot # 95BUB Strength (mg) 800 Mean % Dissolved(CV%)	Range
15	95(2.7)		98(0.9)	
30	96(2.5)		98(0.9)	
45	97(2.1)		98(0.9)	
60	98(1.8)		98(0.9)	

Sampling Times (Min.)	Test Product Lot # WO11429 Strength (mg) 600 Mean % Dissolved(CV%)	Range	Reference Product Lot # 63BSP Strength (mg) 600 Mean % Dissolved(CV%)	Range
15	97(1.7)		99(0.9)	
30	98(1.5)		100(0.9)	
45	98(1.6)		101(1.0)	
60	99(1.6)		101(0.9)	

Sampling Times (Min.)	Test Product Lot # WO11426 Strength (mg) 400 Mean % Dissolved(CV%)	Range	Reference Product Lot # 91BSU Strength (mg) 400 Mean % Dissolved(CV%)	Range
15	98(1.6)		100(1.4)	
30	99(1.6)		101(1.0)	
45	99(1.6)		100(0.9)	
60	99(1.6)		101(1.0)	

IV. Deficiencies: For *in vivo* bio studies, see Deficiencies under Assay Methodology for both the Fasting and Food Effect Studies.

V. Comments: The dissolution data for the 800 mg, 600 mg and 400 mg strengths of the test and reference product are acceptable.

VI. 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, 800 mg, lot # WO11433, comparing it with the reference product, McNeil's Motrin® 800 mg Tablets, lot # 95BUB, have been found **unacceptable** by the Division of Bioequivalence due to the deficiencies cited above.

2. The in-vitro dissolution testing conducted by BASF on its Ibuprofen Tablets, 800 mg, 600 mg and 400 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.

3. The waiver request for the 600 mg and 400 mg strengths of the test product can not be granted due to the unacceptability of the *in vivo* studies and incompleteness of the *in vitro* testing.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 6/6/2000
FT INITIALED YHUANG

Concur: /S/ Date: 7/14/2000
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 75-682 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/05-16-00/W #75682a.500
Also as V:\firmsam\BASF\ltrs&rev\75682a.500
Attachment: 2 pages

APPEARS THIS WAY
ON ORIGINAL

Ibuprofen Film-Coated Tablets USP
ANDA #75-682: 800 mg, 600 mg & 400 mg
Reviewer: Hoainhon Nguyen
W #75682sdw.799

BASF Corp.
Shreveport, LA
Submission Date:
July 30, 1999

Review of Two Bioequivalence Studies, Dissolution Data and a Waiver Request

I. Background:

The firm has submitted the results of a fasting, single-dose bioequivalence study and a post-prandial bioequivalence study comparing its Ibuprofen Film-Coated Tablets USP, 800 mg, with McNeil's Motrin® 800 mg Ibuprofen Tablets. Comparative dissolution data for the test and RLD products of 800 mg and for the 600 mg and 400 mg strengths of the test product are also submitted. The firm has requested a waiver of *in vivo* bioequivalence requirements for the 600 mg and 400 mg based on the formulation proportionality between the strengths.

II. Bioequivalence Studies:

IIA. FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL #IBU800-Part I)

Study Objective: Bioequivalency of BASF's and McNeil's (Motrin®) 800 mg Ibuprofen Tablets under fasting conditions.

Study Facilities/Dates/Investigators:

Clinical: [redacted] dates not given; [redacted]

Analytical: [redacted] dates not given; [redacted]

Study Design: 2-treatment, 2-period, randomized crossover

Demographics: 24 normal, healthy male and female volunteers; 22-48 years of age; height ranged 152-192 cm; weight 51-91 kg; selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Pages 136-137, Vol. 1.2.

Restrictions:

No prescription and OTC medications for at least 2 weeks and 1 week, respectively, prior to the study and no concomitant medications during the study sessions.

No alcoholic beverages and no xanthine-containing beverages or food for 48 hours prior to and during the study period.

No food for 10 hours overnight prior to and for 4 hours postdose.

Washout: 36 hours.

Confinement: not given.

Treatments and Sampling:

Treatment IBU-fa(Test Product): One of BASF's Ibuprofen 800 mg tablets, lot # WO11433 (Batch size of ——— units, potency of 99.8%); manuf. date: 11/98.

Treatment MOT-fa(Reference Product): One of McNeil's Motrin® 800 mg ibuprofen tablets, lot # 95BUB (Potency: 102.5%); exp. 11/02.

Blood samples collected: predose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0 and 12 hours postdose. Plasma samples were stored at -70^{0}C pending assay.

Deficiencies:

1. The study clinical report is incomplete. The report should provide the following information: dates of starting and completing the study and dates of each dosing period, length of confinement period for study subjects, any protocol deviation and sampling deviation.

2. The analytical report should provide the following information, specifically for the submitted study of the 800 mg strength: dates of analyses, all raw numerical data for each run(including peak heights or areas, peak height or area ratios, calculated concentrations) of all standards, controls, samples, summary results of all standard curves for each run(including each standard concentration), summary results for each of low, medium and high quality controls. Long-term stability study should cover the length of time equivalent to the longest freezer storage period of the actual samples. Any relevant analytical Standard Operating Procedures should also be submitted for review.

3. The statistical report should provide mean plasma concentration versus time (including CV%), individual and mean plots of plasma concentration versus time.

IIB. FED/FASTING IN-VIVO BIOEQUIVALENCE STUDY (PROTOCOL #IBU800-Part II)

Study Objective: Bioequivalency of BASF's 800 mg Ibuprofen Tablets and McNeil's Motrin® 800 mg tablets under fed and fasting conditions following a 800 mg dose.

Study Facilities/Dates/Investigators: Same as in Fasting Study above.

Study Design: 3-treatment, 3-period, randomized crossover

Demographics:

12 normal, healthy male and female volunteers; 25-48 years of age; height ranged 153-191 cm; weight ranged 51-85 kg; selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests.

Inclusion/exclusion criteria: Same as in Fasting Study above.

Restrictions/Washout/Confinement: See the fasting study above.

Fasted Conditions: No food for 10 hours overnight prior to and for 4 hours postdose.

Fed Conditions: The subjects fasted for overnight until 30minutes prior to their scheduled dosing times, when they were given a standard breakfast. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American processed cheese, 1 slice of Canadian bacon, 2 oz of hashbrown potatoes, 6 fluid oz of orange juice and 8 fluid oz of whole milk.

Treatments and Sampling:

Treatment IBU-fe(Test Product, Fed): Same as **Treatment IBU-fa** of the fasting study except given under fed conditions.

Treatment MOT-feB(Reference Product, Fed): Same as **Treatment MOT-fa** of the fasting study except given under fed conditions.

Treatment IBU-fa(Test Product, Fasted): Same as **Treatment IBU-fa** of the fasting study.

Blood samples collected: Same as in the fasting study above.

Deficiencies: similar report format deficiencies as in the Fasting Study above.

III. Dissolution Testing: **USP's method**

Drug (Generic Name): Ibuprofen Tablets Firm: BASF Corp.
Dose Strength: 400 mg, 600 mg & 800 mg ANDA# 75-682
Submission Date: July 30, 1999

A. Conditions for Dissolution Testing:
USP XXIII Basket__ Paddle X RPM 50 rpm Units Tested: 12
Medium: pH 7.2 buffer Volume: 900 ml
Reference Drug: (Manuf.) Motrin Tablets (McNeil)
Assay Methodology: Not given
Specifications: NLT —% in 60 minutes

B. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # WO11433 Strength (mg) 800		Reference Product Lot # 95BUB Strength (mg) 800	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	95(2.7)	[illegible]	98(0.9)	[illegible]
30	96(2.5)	[illegible]	98(0.9)	[illegible]
45	97(2.1)	[illegible]	98(0.9)	[illegible]
60	98(1.8)	[illegible]	98(0.9)	[illegible]

Sampling Times (Min.)	Test Product Lot # WO11429 Strength (mg) 600		Reference Product Lot # Not Submitted Strength (mg) 600	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	97(1.7)	[illegible]	____	____
30	98(1.5)	[illegible]	____	____
45	98(1.6)	[illegible]	____	____
60	99(1.6)	[illegible]	____	____

Sampling Times (Min.)	Test Product Lot # WO11426 Strength (mg) 400		Reference Product Lot # Not Submitted Strength (mg) 400	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	98(1.6)		___	___
30	99(1.6)		___	___
45	99(1.6)		___	___
60	99(1.6)		___	___

IV. Formulation Comparison: See comparative formulations of all strengths of the test product attached.

V. Comment:

The formulations of the 800 mg, 600 mg and 400 mg are proportionally similar.

VI. Deficiencies:

The first 3 following deficiencies are for both fasting and non-fasting studies:

1. The study clinical report is incomplete. The report should provide the following information: dates of starting and completing the study and dates of each dosing period, length of confinement period for study subjects, any protocol deviation and sampling deviation.

2. The analytical report should provide the following information, specifically for the submitted study of the 800 mg strength: dates of analyses, all raw numerical data for each run(including peak heights or areas, peak height or area ratios, calculated concentrations) of all standards, controls, samples, summary results of all standard curves for each run(including each standard concentration), summary results for each of low, medium and high quality controls. Long-term stability study should cover the length of time equivalent to the longest freezer storage period of the actual samples. Any relevant analytical Standard Operating Procedures should also submitted for review.

3. The statistical report should provide mean plasma concentrations versus time (including CV%), individual and mean plots of plasma concentration versus time.

4. Dissolution data are deficient in that the dissolution profiles for the 600 mg and 400 mg strengths of the reference product, Motrin tablets, were not provided.

VII. 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, 800 mg, lot # WO11433, comparing it with the reference product, McNeil's Motrin® 800 mg Tablets, lot # 95BUB, have been found **incomplete** by the Division of Bioequivalence due to the deficiencies #1-3 cited above.

2. The in-vitro dissolution testing conducted by BASF on its Ibuprofen Tablets, 800 mg, 600 mg and 400 mg, has been found **incomplete** due to the dissolution deficiency #4 listed above.

3. The waiver request for the 600 mg and 400 mg strengths of the test product can not be considered until the review of the bio studies and dissolution data is completed.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 9/27/99
FT INITIALED YHUANG

Concur: /S/ Date: 9/29/99
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 75-682 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/09-23-99/W #75682sdw.799
Also as V:\firmsam\BASF\ltrs&rev\75682sdw.799
Attachment: 1 page

CC:ANDA 75-682
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen /S/
HFD-652/ YHuang /S/ 9/27/99
HFD-617/ E. Hu /S/ 10/12/99
HFD-650/ D. Conner /S/ 9/29/99

V:\FIRMSAM\BASF\ltrs&rev\75682sdw.799
Printed in final on / /

BIOEQUIVALENCY - INCOMPLETE Submission date: 07-30-99

1. FASTING STUDY (STF) o/c Strengths: 800 mg
   Clinical: **Outcome:** IC
   Analytical:

2. NON-FASTING STUDY (STP) o/c Strengths: 800 MG
   Clinical: **Outcome:** IC
   Analytical:

3. DISSOLUTION WAIVER (DIW) Strength: 600 mg & 400 mg
   o/c **Outcome:** IC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

W# 75682 sdw. 799 Attachment I

Quantitative Composition Summary By Tablet Strength

Ingredients	Ibuprofen Compressed Tablet Composition		
	400 mg/Tablet	600 mg/Tablet	800 mg/Tablet
Ibuprofen, USP	400.0	600.0	800.0
Microcrystalline Cellulose, NF			
Croscarmellose Sodium, NF			
Polysorbate			
Colloidal Silicon Dioxide, NF			
Magnesium Stearate, NF			
Compressed Tablet Weight			
	2	2	2
	2	2	2
Polydextrose			
Hydroxypropyl Methylcellulose			
Hydroxypropyl Methylcellulose			
Hydroxypropyl Methylcellulose			
Polyethylene Glycol, NF			
Carnauba Wax, NF			
Titanium Dioxide, USP			
Iron Oxide			
FD&C Yellow No. 10			
FD&C Yellow No. 6			
Final Weight of Film Coated Tablet (g)	454.0	678.5	903.1
	3	3	3
	2,3	2,3	2,3

1

2

BIOEQUIVALENCY AMENDMENT

NOV 23 1999

ANDA 75-682

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: BASF Corporation PHONE: (318) 861-8103

ATTN: Michael Gill FAX: (318) 861-8297

FROM: Elaine Hu PROJECT MANAGER (301) 827-5847

Dear Mr. Gill:

This facsimile is in reference to the bioequivalency data submitted on July 30, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Film-Coated Tablets, 800, 600, and 400 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\glossary\biofax.frm

ic!
11/22/99

NOV 23

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Tablets, 400 mg, 600 mg & 800 mg

(Please also refer to the deficiency comments for ANDA #75-661 (Submission dated June 30 and August 16, 1999) which are conveyed to you in a separate letter.)

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

For both fasting and non-fasting studies:

1. The study clinical report is incomplete. It should provide the following information: dates of starting and completing the study and dates of each dosing period, length of confinement period for study subjects, any protocol deviation and sampling deviation.

3. The analytical report is incomplete. It should provide the following information, specifically for the submitted study of the 800 mg strength: dates of analyses, all raw numerical data for each run(including peak heights or areas, peak height or area ratios, calculated concentrations) of all standards, controls, samples, summary results of all standard curves for each run(including each standard concentration), summary results for each of low, medium and high quality controls. Long-term stability study should cover the length of time equivalent to the longest freezer storage period of the actual samples. Any relevant analytical Standard Operating Procedures should be submitted for review.

3. The statistical report is incomplete. It should provide mean plasma concentrations versus time (including CV%), individual and mean plots of plasma concentration versus time.

4. For dissolution data: The dissolution profiles for the 600 mg and 400 mg strengths of the reference product, Motrin tablets, should be provided side-by-side with the

dissolution profiles for the respective strengths of the test product for comparison.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-682 APPLICANT: BASF Corp.

DRUG PRODUCT: Ibuprofen Tablets, 400 mg, 600 mg & 800 mg

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

As stated in earlier deficiency comments, the in-study assay quality assurance activities as listed by you are not considered adequate by the Division of Bioequivalence. The precision and accuracy of the assay method used for the bio study should be demonstrated fully by use of in-study calibration curves and QC samples that represent the actual study concentration range, for each individual analytical run.

According to the publication of Shah (1992) cited by you, the statement *"A confidence interval approach yielding comparable accuracy and precision is an acceptable alternative."* (page 591) was referred to the statistical method of presenting QC data. The confidence interval approach was suggested as an alternative method to "number-of-QC approach" which dictated that *"At least four of the six QC samples must be within 20% of their respective nominal values; two of the six QC samples (not both at the same concentration) may be outside the ±20% respective nominal value."* The referred publication also recommended that *"A standard curve should be generated for each analytical run for each analyte and should be used for calculating the concentration of analyte in the unknown samples assayed with that run."*(page 590) and for QC samples, *"At a minimum, three concentrations representing the entire range of the calibration curve should be studied: one near the lower limit of quantitation (LOQ), one near the center, and one near the upper boundary of the standard curve."* (page 590)

The additional submitted data of the re-extracted standard curve and the fresh standard curve in comparison with the bio study standard curve, as well as the data of the

——— QC samples quantitated based on these standard curves, can not be considered adequate in demonstrating and validating the in-study analytical method performance. At best, the newly generated standard curves and QC samples illustrated the stability of the stored standards and controls as well as the variability of the assay particular to that assay date of the curves and the controls of that particular concentration.

The Division acknowledges that the long-term stability data as submitted in the current amendment are acceptable for the concentrations of ——— The drug ibuprofen at this concentration has been shown to be stable in plasma at -70°F for 570 days. However, in the future, you should also include QC samples of at least another higher concentration in the stability studies.

In summary, according to the agency's current practices, even for the most state-of-the-art chromatography equipment, adequate use of **in-study** standard curves and quality controls is requested for demonstration of the analytical method validity. For adequate assay validation, you are referred to the draft bioanalytical method guidance (which was the Reference #1 in your current correspondence) and also to the Division deficiency comments #1 and 2, dated July 26, 2000. The fasting bio study and the non-fasting bio study as submitted by you are therefore considered **unacceptable** due to inadequate assay validation. You are requested to conduct new bioequivalence studies for the test product.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-682

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-682
Date of Submission: April 13, 2000
Applicant's Name: BASF Corporation
Established Name: Ibuprofen Tablets USP, 400 mg, 600 mg & 800 mg

---

Labeling Deficiencies:

1. **CONTAINER** – bottles of 100 & 500 tablets.
   Satisfactory in **draft** as of the July 30, 1999 submission.

2. **UNIT DOSE BLISTERS**
   Satisfactory as of the July 30, 1999 submission.

3. **UNIT DOSE CARTON** – 24 count
   Satisfactory in **draft** as of the April 13, 2000 submission

4. **INSERT**
   a. PRECAUTIONS; Renal Effects – Second paragraph, second sentence:
      ...patients administration of a nonsteroidal ...[add a space between "a" and "nonsteroidal"]

   b. Chart; revise the following heading to read as follows: [add asterisks]

      Precise Incidence Unknown
      (but less than 1%)
      Probable Causal Relationship**

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-682

FIRM: BASF Corporation,
Attention: Michael Gill,
8800 Line Avenue,
Shreveport, LA 71106.

DOSAGE FORM: Oral Tablets

STRENGTH: 400mg, 600mg and 800mg

DRUG: Ibuprofen Tablets, USP

CGMP STATEMENT/EIR UPDATED STATUS:
The Establishment Evaluation Request is acceptable as of June 12, 2000.

BIO STUDY: DSI inspection requested by DBE (10/19/01); inspection request cancelled (11/5/01).

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
The drug substance and the drug product are both listed in the USP 24/NF 19 monograph. Therefore, FDA methods validation is not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Containers used in the stability studies are identical to those listed in container section.

LABELING:
Acceptable as of October 02, 2001.

STERILIZATION VALIDATION (IF APPLICABLE):
Non sterile drug product.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
The exhibit batch sizes were as follows:

Potency	Batch #	Theoretical Yield (tablets)
400mg	WO 11426	[redacted]
600mg	WO 11429	[redacted]
800mg	WO 11433	[redacted]

The 800mg dosage form of the drug product was used for bio-study.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?):

The stability batches are identical to the executed batches.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch will be produced in a similar manner as the executed batch. The proposed post-approval batch size for each dosage form is as follows:

Potency	Proposed Batch Size (tablets)
400mg	[redacted]
600mg	[redacted]
800mg	[redacted]

CHEMIST: RD'Costa, Ph.D. /S/ 11/07/01 DATE: October 15, 2001

SUPERVISOR: AMueller, Ph.D. /S/ 11-7-01 DATE: October 15, 2001

File: V:\firmsam\basf\ltrs&rev\75682aps.r01.doc
Date: October 15, 2001

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-682 **Date of Submission**: July 30, 1999

Applicant's Name: BASF Corporation

Established Name: Ibuprofen Tablets USP, 400 mg, 600 mg & 800 mg

Labeling Deficiencies:

1. **GENERAL COMMENTS** - bottles of [redacted]

   The Agency does not approve bulk labeling, however, your container labels are satisfactory in **draft** as of the July 30, 1999 submission.

2. **CONTAINER** – bottles of 100 & 500 tablets.

   Satisfactory in **draft** as of July 30, 1999 submission.

3. **UNIT DOSE BLISTERS**

   Satisfactory as of July 30, 1999 submission.

4. **UNIT DOSE CARTON** – 24 count

   Revise to include "Rx only".

5. **INSERT**

   a. INDICATIONS AND USAGE
   Fourth paragraph, last sentence –

   ...be recommended (see **Drug Interactions**).[use bold lettering as does the RLD]

   b. CONTRAINDICATIONS
   First sentence –

   ...other non-steroidal anti-inflammatory agents. [spelling "anti"]

   c. PRECAUTIONS
   Nursing Mothers; first sentence –

   In limited studies, an assay capable...[spelling "an assay"]

   e. ADVERSE REACTIONS

   Chart; Incidence Greater than 1% (but less than 3%) Probable Causal Relationship column; CARDIOVASCULAR –

   ...to drug discontinuation) (see... [add a parenthesis following "discontinuation"]

   f. HOW SUPPLIED
   Delete the ' [redacted] ..." statement from the text.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-682

CORRESPONDENCE

ANDA 75-682

NOV 14 2001

BASF Corporation
Attention: Michael Gill
8800 Line Avenue
Shreveport, LA 71106

Dear Sir:

This is in reference to your abbreviated new drug application dated July 30, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for IBU Tablets (Ibuprofen Tablets USP, 400 mg, 600 mg, and 800 mg).

Reference is also made to your amendments dated May 5, August 2, and October 10, 2000; and September 10, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your IBU Tablets (Ibuprofen Tablets USP, 400 mg, 600 mg, and 800 mg) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Motrin Tablets® 400 mg, 600 mg, and 800 mg, respectively, of McNeil Consumer Products Company, Division of McNeilab Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 11/14/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

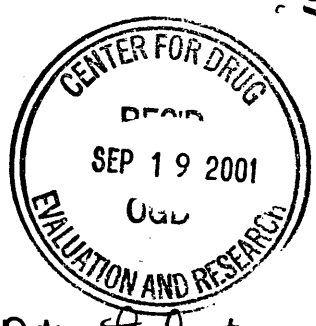
APPEARS THIS WAY
ON ORIGINAL

BASF Corporation

BASF

BIOAVAILABILITY
ORIG AMENDMENT
N/AM

September 10, 2001



Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
(301-594-0320)

AM noted, to:
1) CMC Review then
2) Labeling reviewer.
Bio to receive dup.

RE: ANDA 75-682
Ibuprofen Tablets, USP, 400 mg, 600 mg and 800 mg

Bioequivalency Amendment
Minor Amendment – Submission of Final Printed Labeling

Dear Sir or Madam:

Pursuant to 21 CFR 314.96, we are providing our response to the March 19, 2001 facsimile received from Project Manager Krista M. Scardina. Our Bioequivalency Amendment is provided in hard copy format and responds to all deficiencies listed in your facsimile. A copy of the facsimile communication is provided in this submission immediately following the Form FDA 356h.

In addition, pursuant to 21 CFR 314.120, we are amending our application, ANDA 75-682, in response to your June 26, 2001 facsimile received from Project Manager Timothy Ames, 301-827-5798. A copy of the facsimile communication is provided in this submission immediately following the March 19, 2001 facsimile. This minor amendment contains twelve (12) copies of Final Printed Labeling which have been revised, as instructed in your June 26, 2001 facsimile. In accordance with 21 CFR 314.94 (a)(8)(iv), we are providing a side-by-side comparison of our proposed insert labeling with that of our last submission with all differences annotated and explained.

This amendment addresses all deficiencies listed from the March 19, 2001 and June 26, 2001 facsimiles, respectively. If you have any questions or comments regarding this communication, please contact me at phone number 318-861-8103 or via facsimile at 318-861-8297.

Sincerely,

Michael Gill
Manager Regulatory Compliance

BASF Corporation

BASF

January 19, 2001

NDA ORIG AMENDMENT
N/Ac

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
(301-594-0320)

RE: ANDA 75-682
Ibuprofen Tablets, USP, 400 mg, 600 mg, and 800 mg
Major Amendment
Request for Reclassification of Amendment to Minor Amendment
Request for Expedited Review
Request for Teleconference with the Division of Bioequivalence to Discuss the Attached Protocol

Dear Sir or Madam:

Pursuant to 21 CFR 314.120 we are amending our application, ANDA 75-682, in response to your November 20, 2000 facsimile received from Project Manager Timothy Ames, (301) 827-5798. A copy of the facsimile communication is provided in this submission immediately following the Form FDA 356h. We are requesting a reclassification of this amendment from Major to Minor status, along with a request for an expedited review based upon economic hardship which will occur should the review and response time continue to be prolonged. We are including in this submission a response to the chemistry deficiencies as well as an analytical protocol to address the outstanding bioequivalence deficiencies.

document.

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pages of

trade secret and/or

confidential

commercial

information

The following information is added to Section XII: In-Process Controls.

Tablet Friability: perform according to USP
Specification: target value [redacted] of sample
Tablet Thickness: measure the width of the tablet
Specification:

400 mg	600 mg	800 mg
[redacted]	[redacted]	[redacted]

Data Summary:

Strength	Lot Number	Friability [redacted]	Thickness
400 mg	WO11411	[redacted]	5.6mm – 6.1mm
600 mg	WO11414	[redacted]	5.6mm – 6.1mm
800 mg	WO11418	[redacted]	6.9mm – 7.4mm

The tablet master formula has been updated to include these specifications. Please see the example pages in Attachment 4.

Please contact me via telephone at 318-861-8103 or via facsimile at 318-861-8297 to discuss any issues or questions related to chemistry, labeling or bioequivalence information contained in this submission.

Sincerely,

BASF CORPORATION

Michael A. Gill
Regulatory Compliance Manager

APPEARS THIS WAY
ON ORIGINAL

BASF Corporation

BASF

October 10, 2000

DRUG AMENDMENT
N/A B

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
(301-594-0320)

RE: ANDA 75-682
Ibuprofen Tablets, USP, 400 mg, 600 mg and 800 mg
Bioequivalency Amendment

Dear Sir or Madam:

Pursuant to 21 CFR 314.96, we are providing our response to the August 29, 2000 facsimile received from Project Manager Krista M. Scardina. Our Bioequivalency Amendment is provided in hard copy format and responds to all deficiencies listed in your facsimile. A copy of the facsimile communication is provided in this submission immediately following the Form FDA 356h. For ease of review, we have provided in bold italics the specific deficiencies listed in the August 29, 2000 facsimile followed by our response.

Deficiencies numbered one (1), two (2), and three (3) each address the issue of in-study validation. In the interest of providing a degree of coherence to our response to these observations, we have grouped the first three deficiencies together followed by our response.

1. ***The Division of Bioequivalence acknowledges that the analytical method was validated prior to the bio studies. However, an analytical method is not considered adequately and fully validated for a bio study unless it is also validated during the study.***

2. ***The guidelines for certification of a clinical laboratory by the CAP concerning the use of fresh calibration curves, as stated in the CAP's "Inspection Checklist" document and given by you, are not considered adequate by the FDA for bioequivalence studies. A draft guidance of "Bioanalytical Methods Validation for Human Studies" (Issued 12/1998, Posted 1/5/1999) outlines the generally accepted validation practices for a bio study.***

   You had listed specific efforts by the analytical laboratory to minimize the variation and assure the accuracy of the assay during the study sample analysis, such as using internal standard, blinding the technician and using a single ——— for all study samples. However, only in-study validation data from calibration curves and quality controls obtained for each assay run are accepted as the quality assurance for each assay run, according to the agency's current practices.

CENTER FOR DRUG
REC'D
OCT 11 2000
OGD
EVALUATION AND RESEARCH

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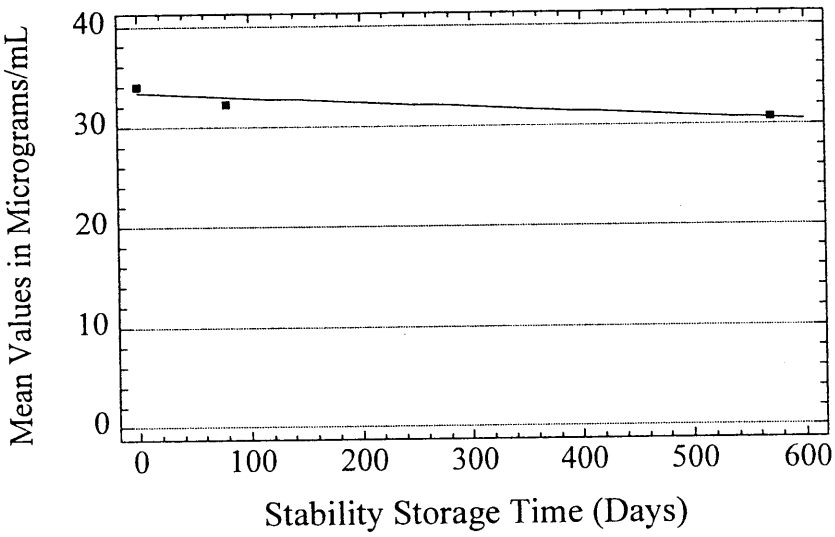
pages of

trade secret and/or

confidential

commercial

information



This amendment addresses all deficiencies listed. If you have any questions or comments regarding this communication, please contact me at phone number (318) 861-8103 or via facsimile at (318) 861-8297.

Sincerely,

BASF CORPORATION

Michael Gill
Regulatory Compliance Manager

APPEARS THIS WAY
ON ORIGINAL

BASF Corporation

BASF

August 2, 2000

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
(301-594-0320)

NDA ORIG AMENDMENT
AB

RE: ANDA 75-682
Ibuprofen Tablets, USP, 400 mg, 600 mg and 800 mg
Bioequivalency Amendment

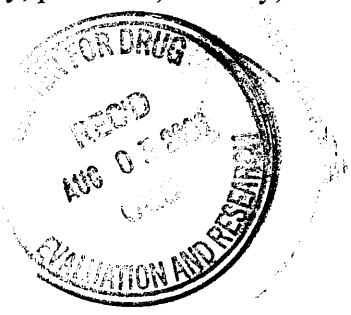
Dear Sir or Madam:

Pursuant to 21 CFR 314.96, we are providing our response to the July 26, 2000 facsimile received from Project Manager Krista M. Scardina. Our Bioequivalency Amendment is provided in hard copy format and responds to all deficiencies listed in your facsimile. A copy of the facsimile communication is provided in this submission immediately following the Form FDA 356h. For ease of review, we have provided in bold italics the specific deficiencies listed in the July 26, 2000 facsimile followed by our response.

For both fasting and non-fasting studies, the assay method was not adequately validated.

The ibuprofen assay used in this study incorporated methods developed by [redacted] as described in the assay validation report submitted with the original submission and with the deficiency response dated May 5, 2000. The recovery for the extraction method reported by [redacted] at ibuprofen concentrations of [redacted] and [redacted] was [redacted] and [redacted] respectively with precision at these concentrations of [redacted] and [redacted] The precision of this [redacted] method reported by [redacted] for concentrations ranging from [redacted] varied between [redacted] with an accuracy reported across this range of concentrations of [redacted]. The findings at this laboratory are consistent with the findings for validation of these methods at other laboratories.

This assay was fully validated in this laboratory with respect to accuracy, precision, stability, specificity and recovery. These results are summarized below.



(i) **There was only one calibration curve (labeled Curve_100, calibrated 2/15/99 used for all study samples, which were assayed in 24 separate runs in the Fasting Study (runs dated February 17 through April 2, 1999), and in 13 separate runs in the Food Effect Study (runs dated April 6 through May 6, 1999). A calibration curve should have been generated for each analyte in each analytical run and used to calculate the concentration of the analyte in the unknown samples in the run.**

The laboratory analysis for this study was performed according to the guidelines for certification of a clinical laboratory by the College of American Pathologists (CAP). The CAP's document used was the "Commission on Laboratory Accreditation: Inspection Checklist, Section 3B, Toxicology, 1998.1 edition." The interval for calibration (defined as the relationship between a drug concentration and the measured response) is determined by the criteria outlined in the following table.

In this table, the first column lists the specific indications described in the CAP's Inspection Checklist. For each specific guideline, the second column describes how these guidelines for the use of standard curves were met in this study.

CAP's guideline	IBU Bioequivalence Study
A complete change of reagents that affect the range used to report patient results or quality control values	There were no changes in the reagents during method validation or sample analysis.
Quality control fails to meet established criteria	Quality control samples throughout all studies consistently met established criteria for validity. The coefficient of variation for all controls in the 800 mg studies was 6.7%. In both the 200 and 800 mg studies, the percent variation was consistently within 15% for 98.1% of all QC samples. Exceptions to the 15% variation were rarely noted. There were a total of 6 QC samples in both 800mg studies (2.5% of 238 QC samples) with a greater than 15% variation from the control, 4 with the variation being 17-20% and 2 being greater than 20%. In all cases, subsequent QC samples returned to within 15% and no consistent patterns were noted in variation.
After major maintenance or service	There were no major repairs or service to the — during either the 200mg or 800mg studies. Also, a single — and column were used for analyses of samples from these studies throughout each of these studies.
At least once every six months	The total duration of the laboratory analysis for both of the 800 mg studies was 10 weeks.
When recommended by the manufacturer	There are no specific recommendations by the manufacturer.

Additionally, several of the aspects of the laboratory analysis were specifically done to minimize variation and assure the accuracy of these results. There was a single analyte tested for in each analytical run. An internal standard, naproxen, was used to assure the quality of each injection. All samples were run in duplicate to assure the accuracy of the measurements obtained in this study. The technician was blinded to the drug the subject had received. Samples were run consecutively according to the subject number. All samples for a single study subject were extracted and run without interruption to minimize any variability between treatments in a subject. Finally, for this study there was a dedicated technician using a dedicated —— . The study was run with no intervening samples or studies being done during this time by this technician or on this —— . A single column was used for this study. This further reduces the chances of variability affecting the results of the study.

(ii) The QC samples used in each run were at only one concentration, 30 mcg/mL. The QC samples for each run should have been in duplicate at three different concentrations (one near LOQ (i.e., $\leq$ 3xLOQ), one in midrange, and one close to the high end of the range.

A single mid range concentration was used for the QC samples because this was a highly reproducible study under a variety of analytical conditions and at different concentrations of ibuprofen. The coefficient of variation was determined for low, mid and high range concentrations (1.56, 12.5, and 50 mg/mL, respectively) on the standard curves used during different phases of assay development and obtained under a variety of conditions (different stock solutions, [redacted] columns and 2 different [redacted] over a 10 month period) prior to study sample analysis. Under these highly variable conditions, the coefficients of variation were 11.1%, 10.9% and 7.6% for low, mid and high concentrations, respectively. When the standard curves used in the analysis of the study samples are included, the coefficients of variation are 10.8%, 9.1% and 7.5% for these same concentrations. Thus, this was a highly reproducible study and this reproducibility did not change during the course of the study.

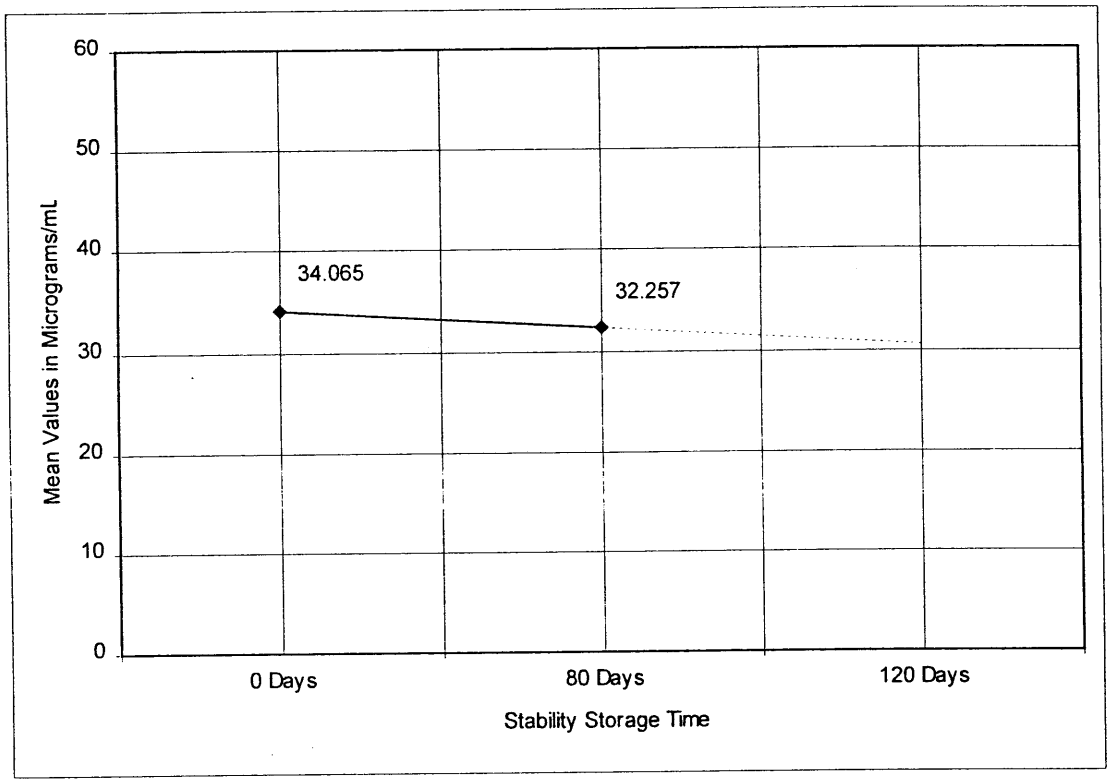
The use of a single concentration for QC samples is also supported by the consistent performance of this study during sample analysis. There was minimal variation in the coefficient of variation for the controls in this study (6.7% for all studies) and very few samples falling outside of the desired 15% variation from the control (1.9% of 474 QC samples). Additionally, an internal standard was used in this assay to assure the consistency and quality of each analysis.

(iii) Stability study covered 80-day storage period but the maximum freezer storage duration for the actual samples was 95 days (This comment is applied to the Food Effect Study).

We acknowledge that some of the study samples exceeded the freezer storage period of the stability samples for the Food Effect Study. A chart of the total storage periods for each of the patients samples is provided below:

PATIENT #	DATE OF INITIAL STORAGE	DATE OF COMPLETION OF ANALYTICAL	TOTAL STORAGE TIME
601	2-1-99	4-7-99	66 days
602	2-1-99	4-9-99	68 days
603	2-1-99	4-13-99	72 days
604	2-1-99	4-14-99	73 days
605	2-1-99	4-16-99	75 days
606	2-1-99	4-20-99	79 days
607	2-1-99	4-21-99	80 days
608	2-1-99	4-23-99	82 days
609	2-1-99	4-27-99	86 days
610	2-1-99	4-28-99	87 days
611	2-1-99	4-29-99	88 days
612	2-1-99	5-3-99	92 days

The stability data generated for the long term storage period indicates no significant degradation throughout the storage period and we would project acceptable stability to well beyond 120 days at -70°F. The slope is presented in the chart below. Predictive stability to the 95 day storage period for the final sample run for the Food Effects Study would suggest no impact on this study, nor on the overall results of the study, which clearly support comparability of the Reference and Test samples in the Fasting and Food Effects Studies.



The determination criteria for demonstration of *in vivo* bioequivalence of the test article (ibuprofen drug product) versus the reference listed drug is based on the ratios of averages of log transformed data for AUC and Cmax meeting the 80% to 125% range. The ibuprofen fasting study data demonstrates values for log transformed data well within the acceptable range for *in vivo* bioequivalence determination. The Limited Food Effects Study demonstrates a comparable food effect between our test product and the reference listed drug. Therefore, we consider the Fasting and Food Effects Studies valid and acceptable.

This amendment addresses all deficiencies listed. If you have any questions or comments regarding this communication, please contact me at phone number (318) 861-8103 or via facsimile at (318) 861-8297.

Sincerely,

BASF CORPORATION

Michael Gill
Regulatory Compliance Manager

APPEARS THIS WAY
ON ORIGINAL

BASF Corporation

BASF

May 5, 2000

NDA ORIG AMENDMENT
N/AB

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
(301-594-0320)

RE: ANDA 75-682
Ibuprofen Tablets, USP, 400 mg, 600 mg and 800 mg
Bioequivalency Amendment

Dear Sir or Madam:

Pursuant to 21 CFR 314.96, we are providing our response to the November 23, 1999 facsimile received from Project Manager Elaine Hu, (301) 827-5847. Our Bioequivalency Amendment is provided in hard copy format with two (2) diskettes, each containing the data files for their respectively labeled study. A copy of the facsimile communication is provided in this submission immediately following the Form FDA 356h. For ease of review, we have provided in bold Italics the specific deficiencies listed in the November 23, 1999 facsimile followed by our response.

1. ***The study clinical report is incomplete. It should provide the following information: dates of starting and completing the study and dates of each dosing period, length of confinement period for study subjects, any protocol deviation and sampling deviation.***

   The clinical study report provided in the original submission dated July 30, 1999 has been rewritten into two (2) separate reports: Report 1 is the 800 mg, Single Dose, Fasting, Bioequivalence Study and Report 2 is the 800 mg, Limited Food Effects Study. Both of these reports have the information requested in deficiency #1 listed above.

2. ***The analytical report is incomplete. It should provide the following information, specifically for the submitted study of the 800 mg strength: dates of analyses, all raw numerical data for each run (including peak heights or areas, peak height or area ratios, calculated concentrations) of all standards, controls, samples, summary results of all standard curves for each run (including each standard concentration), summary results for each of low, medium and high quality controls. Long-term***

stability study should cover the length of time equivalent to the longest freezer storage period of the actual samples. Any relevant analytical Standard Operating Procedures should be submitted for review.

The analytical reports for both the Ibuprofen 800 mg Fasting Study and the Ibuprofen 800 mg Limited Food Effects Study are provided in this Bioequivalency Amendment. Each of the reports addresses the above-described deficiencies.

3. ***The statistical report is incomplete. It should provide mean plasma concentrations versus time (including CV%), individual and mean plots of plasma concentration versus time.***

   The statistical reports have been rewritten to provide all of the items described in the deficiency letter listed above for each of the Ibuprofen 800 mg studies (Fasting and Limited Food Effects) and are provided in this Bioequivalency Amendment.

4. ***For dissolution data: The dissolution profiles for the 600 mg and 400 mg strengths of the reference product, Motrin tablets, should be provided side-by-side with the dissolution profiles for the respective strengths of the test product for comparison.***

   The in-vitro dissolution data and summary report (page 1578) included comparative dissolution profiles of the test products (IBU® 800 mg, IBU 600 mg and IBU 400 mg) and the Referenced Label Drug (RLD) Motrin® 800 mg. The requested additional comparative profiles of the 600 mg and 400 mg strengths of the test products, using the equivalent strengths of the Motrin products, are provided in the tabbed section on pages 006-021 following the facsimile communication. The tabbed section is organized as follows:

   <u>IBU 600 mg vs. Motrin 600 mg</u>

   Page 007: Narrative Summary - Comparative Dissolution Profiles
   Page 009: Tabular Summary - Comparative Dissolution Profiles
   Page 011: Dissolution Data: 15 minute time intervals
   Page 013: Dissolution Data: 10 minute time intervals

   <u>IBU 400 mg vs. Motrin 400 mg</u>

   Page 015: Narrative Summary – Comparative Dissolution Profiles
   Page 017: Tabular Summary – Comparative Dissolution Profiles
   Page 019: Dissolution Data: 15 minute time intervals
   Page 021: Dissolution Data: 10 minute time intervals

Additional tabular summary tables of the application dissolution data, comparing Ibuprofen strengths (800 mg, 600 mg and 400 mg) to the referenced listed drug, Motrin® 800 mg, are provided in the tabbed section on pages 022-027. The tabbed section is organized as follows:

Tabular Summary of Comparative Dissolution Data

Page 023: IBU® 800 mg vs. Motrin 800 mg
Page 025: IBU 600 mg vs. Motrin 800 mg
Page 027: IBU 400 mg vs. Motrin 800 mg

This amendment addresses all deficiencies listed. If you have any questions or comments regarding this communication, please contact me at phone number (318) 861-8103 or via facsimile at (318) 861-8297.

Sincerely,

BASF CORPORATION

Michael Gill

Michael Gill
Manager, Regulatory Services & Compliance

APPEARS THIS WAY
ON ORIGINAL

BASF Corporation

BASF

April 13, 2000

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
(301-594-0320)

DR. Label
NDA ORIG AMENDMENT
AC

RE: ANDA 75-682
Ibuprofen Tablets, USP, 400 mg, 600 mg, and 800 mg
Major Amendment

Dear Sir or Madam:

Pursuant to 21 CFR 314.120 we are amending our application, ANDA 75-682, in response to your February 7, 2000 facsimile received from Project Manager Bonnie McNeal, (301) 827-5848, transmitting deficiencies from both the chemistry and labeling review of the ANDA. A copy of the facsimile communication is provided in this submission immediately following the Form FDA 356h. For ease of review, we have provided in bold Italics the specific deficiencies listed in the February 7, 2000 facsimile followed by our response.

A. The deficiencies presented below represent MAJOR deficiencies.

1. The calculated total iron per day in each dosage form exceeds the daily iron intake as required per 21 CFR 73.1200. Please reduce the amount of iron intake per day in the dosage form so as not to exceed 5 mg.

As noted on page 1587, the quantity of [redacted] Iron Oxide in the [redacted] formula will be [redacted] This results in the following daily intake of iron:

Strength	Iron Oxide		Fe^{+}	Maximum Daily Tablets	Total Iron (mg) per Day
	[redacted]	[redacted]			
400 mg	[redacted]	[redacted]	[redacted]	8	[redacted]
600 mg	[redacted]	[redacted]	[redacted]	5	[redacted]
800 mg	[redacted]	[redacted]	[redacted]	4	[redacted]

The following application pages are revised to reflect this change and are included in Tab C: pages 1585, 1586, 1587, 1685, 1749, 1751, 1752, and 1820.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 14 2000
OGD

2. ***Please re-submit your certification (page 1599) for Organic Volatile Impurities using the new USP 24 monograph limit values.***

   The re-certification for the USP 24 monograph is included in Tab D.

3. ***Your drug substance supplier (page 1598) has identified and supplied analytical data for known impurities. Please incorporate this information into your Certificate of Analysis for future lots of drug substance.***

   This information is currently captured as part of the [redacted] specification in our drug substance Certificate of Analysis. The individual values listed on page 1598 are from historic trends, providing an understanding of the types of impurities that typically would contribute to the [redacted] results. [The Ibuprofen USP monograph test [redacted] is used for analysis of the individual impurities listed on page 1598 of the original application (see example [redacted] in original application pages 2293 and 2294).]

   The historic trends listed are comparable to the drug substance stability data included in the drug substance DMF # [redacted] The analysis of the drug product stability showed a similar level of impurities in the product exposed to accelerated conditions.

   The comparability of the historic drug substance data, the data from drug substance used for the application batches, and the application batch stability data supports the use of USP [redacted] Purity results for the drug substance to monitor for impurity level acceptance.

4. ***Please list the [redacted] test in the [redacted] testing protocol and report the result.***

   [redacted]

Redacted 3

pages of

trade secret and/or

confidential

commercial

information

Labeling Deficiencies:

1. *GENERAL COMMENTS – bottles of* [redacted]

   The Agency does not approve bulk labeling, however, your container labels are satisfactory in draft as of July 30, 1999 submission.

2. *CONTAINER – bottles of 100 & 500 tablets.*

   Satisfactory in draft as of July 30, 1999 submission.

3. *UNIT DOSE Blisters*

   Satisfactory as of July 30, 1999 submission.

4. *UNIT DOSE CARTON – 24 count*

   Revise to include "Rx only".

5. *INSERT*

   a. *INDICATIONS AND USAGE*
   Fourth paragraph, last sentence –

   ...be recommended (see Drug Interactions).[use bold lettering as does the RLD]

   b. *CONTRAINDICATIONS*
   First sentence –

   ...other non-steroidal anti-inflammatory agents. [spelling "anti"]

   c. *PRECAUTIONS*
   Nursing Mothers; first sentence –

   In limited studies, an assay capable...[spelling "an assay"]

   e. *ADVERSE REACTIONS*

   Chart; Incidence Greater than 1% (but less than 3%) Probable Causal Relationship column; CARDIOVASCULAR –

   ...to drug discontinuation) (see...[add a parenthesis following "discontinuation"]

f. HOW SUPPLIED
Delete the ' ——————— " statement from the text.

Please revise your labels and labeling, as instructed above, and submit in draft print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rid/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

We have revised our unit dose carton labeling as instructed and are providing draft prints for your review. The corrected side-by-side comparison with annotations is also included. (Refer to Tab J) We will monitor the website as suggested and will update our draft labeling to incorporate any changes that may occur for the reference listed drug.

The reviewer or project manager should feel free to contact me by telephone (318/861-8103) or e-mail (gillma@basf.com) if there are any questions or clarifications that we may provide.

Sincerely,

BASF CORPORATION

Michael Gill
Regulatory Specialist

APPEARS THIS WAY
ON ORIGINAL

BASF Corporation

BASF

NEW CORRESP
NC

February 18, 2000

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Bonnie McNeal, Project Manager (301) 827-5848

RE: ANDA 75-682
Intent to Amend the Application

Dear Ms. McNeal:

Pursuant to 21 CFR 314.120, we do intend to amend ANDA 75-682 to address the major deficiencies listed in your facsimile dated February 7, 2000.

If you have questions regarding this submission, please contact me at (318) 861-8103.

Sincerely,

Michael Gill
Regulatory Specialist

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG
FEB 22 2000
EVALUATION AND RESEARCH

8800 Line Avenue, Shreveport, Louisiana 71106, Post Office Box 6750, Shreveport, Louisiana 71136-6750 (318) 861-8200

ANDA 75-682

BASF Corporation
Attention: Michael Gill
8800 Line Avenue
Shreveport, LA 71106

SEP 16 1999

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your amendment dated August 16, 1999.

NAME OF DRUG: Ibuprofen Tablets USP, 400 mg, 600 mg, and 800 mg

DATE OF APPLICATION: July 30, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 2, 1999

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Bonnie McNeal
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASF Corporation

BASF

August 16, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

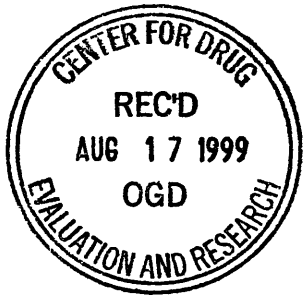
RE: ANDA 75-682, Ibuprofen 800 mg Tablets
Information Amendment requested by FDA Reviewer Nasser Mahmud

Dear Mr. Sporn:

This information amendment was requested in a telephone conversation with FDA Reviewer Nasser Mahmud on August 11, 1999. Mr. Mahmud requested that we clarify our commitment to withdraw our existing ibuprofen ANDAs upon the approval of this current application.

I explained to Mr. Mahmud that BASF Corporation does own the currently approved ANDAs 70-745, 70-099, 70-083, 70-088, and NDA # 18-197 for ibuprofen tablets. These were the original ibuprofen applications that were submitted by Boots Pharmaceuticals, Inc. and approved by the FDA. BASF Corporation acquired these applications from Boots Pharmaceuticals through the corporate acquisition of the Boots Pharmaceuticals, Inc. business in 1995. These are separate applications for each strength of ibuprofen tablet and are separate formulations for each strength as well.

We have developed a new common formulation for all of our strengths of ibuprofen tablets (200 mg, 400 mg, 600 mg, and 800 mg). The development of a common formulation to use for all of our different ibuprofen tablet strengths provides us with a much better manufacturing process from a quality point of view as well as a much more economical product for the consumer.



8800 Line Avenue, Shreveport, Louisiana 71106, Post Office Box 6750, Shreveport, Louisiana 71136-6750 (318) 861-8200

We have submitted the 400 mg, 600 mg, and 800 mg ibuprofen tablet application as a single ANDA. We intend to withdraw all of the other separate ANDAs upon approval of this single new ANDA (once the distributed market supply under the current ANDAs is exhausted). The 200 mg ANDA was submitted as a separate application on June 30, 1999 (ANDA # 75-661).

Thank you for the prompt handling of this amendment.

Should you have additional questions, please contact me at 318-861-8103.

Sincerely,

BASF CORPORATION

Michael Gill
Regulatory Specialist

APPEARS THIS WAY
ON ORIGINAL

BASF Corporation

BASF

July 30, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA for Ibuprofen, USP (400 mg, 600 mg and 800 mg)

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, BASF Corporation submits today an original abbreviated new drug application (ANDA), seeking approval to market Ibuprofen Tablets, USP, (400 mg, 600 mg and 800 mg) that are bioequivalent to the reference listed drug manufactured by McNeil Consumer Products Company, pursuant to NDA #017463. The submission includes an in vivo bioequivalence study comparing our Ibuprofen Tablets, USP, 800 mg strength to the reference listed drug. Also included in this submission is data supporting the approval of both a 400 mg and 600 mg Ibuprofen Tablet that are quantitatively proportional to our 800 mg Ibuprofen Tablet formulation. We are requesting a waiver for demonstration of in vivo bioequivalence for the 400 mg and 600 mg tablet formulations.

The contact person for this submission is Michael Gill
Regulatory Specialist

Written correspondence can be mailed to BASF Corporation
8800 Line Avenue
Shreveport, LA 71106

Or faxed to 318/861-8297

Phone calls to address any questions or issues are welcome. My phone number is 318/861-8103.

The proprietary name, IBU®, is used in the submission to denote our Ibuprofen Tablets, USP.

This ANDA consists of six volumes. BASF is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA; and a technical review copy (in red folders) which contains all the information in the archival copy, with the exception of the Bioequivalence Section (VI). A separate copy of the Bioequivalence Section is provided in an orange folder. The ANDA is being submitted in hard copy format with a single diskette containing the data file for the in vivo bioequivalence studies (fed and fasting for the ibuprofen 800mg tablets).

For more detailed information about the organization of this ANDA, please refer to Page 001 of the ANDA, "Executive Summary-Organization of the ANDA."

In the event post approval methods validation process issues arise, BASF commits to full resolution of all issues as a basis of approval.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the Form FDA 356h and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to the New Orleans, Louisiana District Office. This "field copy" was contained in a burgundy folder. A copy of our cover letter to the New Orleans, Louisiana District Office is attached.

Thank you for your prompt handling of this submission.

Sincerely,

BASF CORPORATION

Michael Gill
Regulatory Specialist

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-682

BASF Corporation
Attention: Michael Gill
8800 Line Avenue
Shreveport, LA 71106

SEP 16 1999

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your amendment dated August 16, 1999.

NAME OF DRUG: Ibuprofen Tablets USP, 400 mg, 600 mg, and 800 mg

DATE OF APPLICATION: July 30, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 2, 1999

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Bonnie McNeal
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research