CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75661

CORRESPONDENCE

ANDA 75-661

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

AUG 2 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 the telephone conversation dated July 21, 1999 and your amendment dated July 27, 1999.

NAME OF DRUG: Ibuprofen Tablets USP, 200 mg

DATE OF APPLICATION: June 30, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 1, 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

ack for [illegible]
S. Middleton
30 SEP 99

BASF

July 27, 1999

NEW CORRES

NC

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

Attention: Ms. Sandra Middleton

RE: Correspondence Amendment to ANDA #75-661
Requested in telephone conversation with Ms. Sandra Middleton

Dear Mr. Sporn:

In response to our telephone conversation with Ms. Sandra Middleton, we are submitting original signed documents that were inadvertently omitted from the archival copy of our recent ANDA submission (ANDA #75-661).

The original documents being provided as replacement pages to the copies originally submitted are listed below:

Form FDA 356h	Pages 003, 004, 005
Field Copy Certification	
Patent Certification	Page 012
Financial Disclosure/Certification Form FDA 3454	Page 071
Certification of GMP Compliance	Pages 1576a and 1635
Certification of Organic Volatile Impurities	Page 1579a
Generic Drug Enforcement Act	Pages 2109 and 2110
Environmental Impact Analysis Statement	Page 2108

Also included in this amendment are replacement pages for the annotated side-by-side comparison of actual labeling for the reference listed drug (RLD) and our IBU® 200 mg Tablet and actual bottle and box labels for the RLD as requested by Ms. Middleton. These pages will replace page numbers 017 through 022 and include additional pages 022a through 022n.

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REC'D
JUL 28 1999
OGD

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

Through the course of our inspection of our file copy of the original ANDA submission, we discovered typographical errors on pages 067, 1568, 1643, 1767 and 1768, which we want to correct at this time. Replacement pages 067, 1568, 1643, 1767 and 1768 are included in this amendment to our original submission.

We also discovered that we inadvertently omitted Volume 1 (which includes Sections I through V) pages 001 through 066 and Section VII pages 1564 through 1569 of the bioavailability/bioequivalence review copy (orange binder). We are submitting copies of those pages (in an orange binder) for inclusion in the bioavailability/bioequivalence review copy.

This letter also certifies that, concurrently with the submission of this amendment, a true copy of this submission 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 assistance and your prompt handling of this submission.

Sincerely,

BASF CORPORATION

Michael Gill
Regulatory Specialist

BASF Corporation

BASF

August 16, 1999

NDA ORIG AMENDMENT
N/AB

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

RE: ANDA 75-661, Ibuprofen 200 mg Tablets
Telephone call with Jennifer Fan (Division of Bioequivalence) requesting an Information Amendment

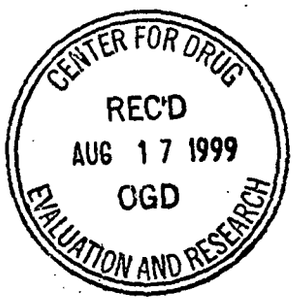
Dear Mr. Sporn:

Pursuant to a telephone call request from Ms. Jennifer Fan (Division of Bioequivalence) on August 13, 1999, we are submitting this information amendment.

Ms. Fan asked for clarification of two questions, which are presented below in bold and italicized type followed by our responses (which were also provided during our telephone conversation):

1. ***Was a bioequivalence study also performed on an 800 mg strength ibuprofen product?***

   Yes, we have performed a separate 800 mg ibuprofen bioequivalence study, which we submitted on July 30, 1999 in an ANDA for an 800 mg ibuprofen tablet formulation. We are also requesting a waiver of in vivo bioequivalence for a 400 mg and a 600 mg ibuprofen tablet formulation in this same application (ANDA 75-682).



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2. ***What was the reference listed drug that we used for our bioequivalence study, Motrin® IB or Nuprin®, and how did we confirm which was the reference listed drug?***

Motrin IB is the reference listed drug used and is the subject of NDA # 019012 (Motrin/ Nuprin) approved on May 18, 1984 and held by McNeil Consumer Products Company. McNeil pharmacist Erica Kobylinski confirmed that Motrin IB is the reference listed drug available to the marketplace and supplied by McNeil to our study site pharmacy. The product brand name listed for NDA # 019012 in the Orange Book (19th Edition, Cumulative Supplement 4, April, 1999) is Nuprin (the brand name of product that is licensed to Bristol-Myers Squibb), however, the brand name product marketed under NDA #019012 is McNeil's Motrin IB.

We have provided a faxed copy of this information amendment to Ms. Fan at 301-594-0181. Should there be any additional questions, I may be reached at phone number 318-861-8103.

Thank you for your prompt handling of this information amendment to ANDA 75-661.

Sincerely,

BASF CORPORATION

Michael Gill
Regulatory Specialist

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 75-661
Intent to Amend the Application

Dear Ms. McNeal:

Pursuant to 21 CFR 314.120, we do intend to amend ANDA 75-661 to address the major deficiencies listed in your facsimile dated January 27, 2000.

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

Sincerely,

Michael Gill
Regulatory Specialist

Noted. NAI
B. McNeal
2/28/00

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EVALUATION AND RESEARCH

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

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 75-661
Intent to Amend the Application

Dear Ms. McNeal:

Pursuant to 21 CFR 314.120, we do intend to amend ANDA 75-661 to address the major deficiencies listed in your facsimile dated January 27, 2000.

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

Sincerely,

Michael Gill
Regulatory Specialist

Noted. NAI
B. McNeal
2/28/00

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 22 2000
DGD

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

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)

RE: ANDA 75-661
Ibuprofen Tablets, USP, 200 mg
Major Amendment

Dear Sir or Madam:

Pursuant to 21 CFR 314.120 we are amending our application, ANDA 75-661, in response to your January 27, 2000 facsimile received from Project Manager Bonnie McNeal, (301) 827-5848, transmitting chemistry and labeling deficiencies from the respective review groups. 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 January 27, 2000 facsimile followed by our response.

A. Deficiencies:

1. ***Please establish specifications for tablet thickness and friability as part of your tablet manufacturing in-process controls. Please submit test data along with the specifications for our evaluation.***

   Tablet weight is used as the control parameter instead of tablet thickness. It is combined with hardness and disintegration control for the core tablet process and provides good tablet quality control. The hardness of the tablet core eliminates the need to measure or control tablet friability. The tablet would not meet the hardness specification if it were very friable. There were no friability related tablet core quality issues seen for the submission batch at the coating stage.

2. ***On page 1817 of your application, you have provided a tablet coating weight gain specification of ( ) mg. This specification is too wide. Please revise your specification based on actual tablet coating weight gains. Tablet coating weight gain test data must be submitted for our evaluation.***

Coating is applied for pharmaceutical elegance. Page 1819 of the application shows the weight gain during the coating process. The application batch has a weight gain of mg, which is within mg (9%) of the upper range. Coating towards the upper range has no effect on product quality or stability. As stated on page 1770, the upper range has been reduced to mg (125% of target) and the lower target is mg, for a working range of mg. The weight range of mg is an action range that requires additional coating as needed to achieve pharmaceutical elegance. The Master Formula page (that reflects batch page 1817 of the application) has been revised to this lower limit and is found on page 1685 of the application.

3. ***We note that you have provided package sizes of 5000 tablets and 50,000 tablets for your LDPE bags. Please clarify if you intend to repack these bulk tablets. If so, please provide the evidence of a proposed written agreement with the repackager to comply with 21 CFR 201.150 (a)(2) requirements.***

   The packaging, labeling and stability data provided to support these two package sizes is included since we intend to market a bulk tablet configuration to customers that may have a demand for large tablet quantities. We do not currently have any agreements to repackage these products within the context of 21 CFR 201.150 (a)(2), however should we enter into such an agreement, a copy of the agreement will be provided for the ANDA in an annual report.

4. ***Please revise your Ibuprofen Tablet identification test to include IR testing to conform to the current USP specifications.***

   A corrected copy to replace page 2037 of the original application is included in Tab C.

5. ***We note your data on impurities in the drug product and comment regarding the testing of impurities at the expiry date on pages 2090-2092 of your application. Please include a validated test and specifications for both the unknown and known individual and total impurities in your release and stability protocols, in addition to the required analysis for These tests should be performed at each stability test station.***

   The USP Chromatographic Purity monograph test method is used for the analysis of impurities, as shown in the analysis provided by the drug substance manufacturer (see example chromatogram in original application pages 2293 and 2294) and included in DMF

The historic trends listed on page 1579 of the original application and the stability data in the DMF are comparable to the impurities found in the drug substance used for the application batch and the stability data generated to support the application.

The use of the Ibuprofen drug substance specifications for Chromatographic Purity to release material for product manufacturing is sufficient to control the impurity limits in the finished dosage form. We have revised the stability protocol and associated stability test requirements to include the impurity analysis at each test station, using an individual limit of ( )%, and a total limit of(.)%. The revised protocol and associated stability test requirements are found on page 011 in Tab D.

6. ***We note that you have eliminated( )from your Ibuprofen tablet routine stability testing program. Please revise your finished drug product stability specifications to include the testing of Specifications must be established based on actual test data observed. In addition, please include appearance as part of your drug product stability testing specifications.***

The stability protocol and associated stability test requirements has been revised to reflect ;and appearance and can be found on page 011 in Tab D. As noted in the original report, variation in( )is not correlated to any effect on product performance. The stability results in each of the container/closure configurations reflect the excellent performance noted in the open dish study. This supports our conclusion that the product formula is robust and that the USP specification limits used are acceptable to ensure product quality through expiration (See 12 month report in response to question 7 found in Tab E.)

7. ***We note that some of your LDPE bags do not meet USP <661> Multiple Internal Reflectance or Thermal Analysis test specifications. Please provide test data to demonstrate that these LDPE bags are suitable or compatible for packaging your bulk Ibuprofen tablets. The submission of three months of accelerated and RT stability data from the drug product is not adequate for this purpose.***

In addition to the USP <661> test results, the original application included USP <87> (Biological Reactivity Test) results (page 1963-1970). Additionally we have included comparative infrared spectra of tablets that were in direct contact with the bag (through 6 months at 40°C/75% RH) to tablets stored in the HDPE bottle (at 25°C/60% RH). Each of the spectra is comparable, supporting our contention that the bag has no adverse effect on the product. The comparative spectra can be found in Tab F.

Additionally, a 6 month accelerated/12 month room temperature stability report is included. The report concludes that the product is stable in any of the selected configurations and equivalent to open dish studies, which further supports the stability of the tablet in any of the container/closure configurations, including the bags. (See Stability Report in Tab E.)

We commit to qualifying an alternative LDPE bag that meets all applicable USP tests for use post-approval, and will include the bag test results in the annual report.

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

The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMP(s) at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

We do note and acknowledge that all firms referenced in our application relative to the manufacture and testing of the product are in compliance with cGMP(s) and will be in compliance at the time of approval.

Labeling Deficiencies:

GENERAL COMMENTS

We acknowledge your comments regarding labeling revised to meet the requirements published in the Over-the-Counter Human drugs; Labeling Requirements; Final Rule[Federal Register:March 17, 1999(Volume 64, Number51)]. However, the Drug Facts format has not been approved for the reference listed drug, Motrin IB, at this time. Revise your labels and labelling to be in accordance with the most recently approved labeling format of the reference listed drug, approved March 31, 1997.

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 labeling as instructed and are providing draft prints for your review. A side-by-side comparison with annotations is also included. (Refer to Tab G.) This replaces application pages 015-022f. The container labeling has been revised with annotations included. (Refer to Tab H). This replaces application pages 023-066. The corresponding Motrin® IB label samples can be found in the original application, pages 022g-022n. 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

BASF Corporation

BASF

April 20, 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)

ORIG AMENDMENT
N/AB

RE: ANDA 75-661
Ibuprofen Tablets, USP, 200 mg
Bioequivalency Amendment

Dear Sir or Madam:

Pursuant to 21 CFR 314.96, we are providing our response to the November 19, 1999 facsimile received from Project Manager Jennifer Fan, (301) 827-5847. Our Bioequivalency Amendment is provided in hard copy format with two (2) diskettes, each containing the data files for their respectively labelled 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 19, 1999 facsimile followed by our response.

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

   The two bio-studies included in the original submission have been re-organized into two separate volumes. Both reports follow the outline provided by the Office of Generic Drugs. In addition, for the convenience of the reviewer, appendices appearing in the original report and referenced in these reports have been included with this submission.

2. ***It is not clear why the firm has used the MIXED EFFECTS model instead of the GENERAL LINEAR model for the statistical analysis of the fasting study data. Please explain.***

   When the original report was prepared the biostatistical office of our clinical study site analyzed the data using both the mixed effects and general linear models. These resulted in similar results demonstrating bioequivalence and a comparable food effect. However, the office inadvertently provided the mixed effects model in the report. Included in this report are the results of the general linear model for the statistical analysis.

3. ***It is not understood why the "food challenge" study was conducted using only 12 subjects leading to only 2 subjects per sequence. Please clarify.***

   This subject number is based on the recommendations of the guidance document provided to the applicant (included in Appendix A of these reports) titled, "A Guidance: Naproxen Tablets in Vivo Bioequivalence and In Vitro Dissolution." This guidance states the study should include a minimum of 12 subjects, with equal numbers assigned to each of the six dosing sequences, resulting in 2 subjects per dosing sequence and a total of 12 subjects in each treatment arm.

4. ***The firm should complete the "How Supplied" section of the labelling. It is pointed out that the firm may not make changes such as "scoring" to the test product, unless it is also seen with the innovator product.***

   The "How Supplied" section has been completed. A replacement page for page number 022 has been provided in this submission on page 009 immediately following the facsimile copy of the Bioequivalence Deficiency letter.

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
Manager, Regulatory Services and Compliance

BASF Corporation

BASF

June 23, 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)

BIOAVAILABILITY
NDA ORIG AMENDMENT
N/AB

RE: ANDA 75-661
Ibuprofen Tablets, USP, 200 mg
Bioequivalency Amendment

Dear Sir or Madam:

Pursuant to 21 CFR 314.96, we are providing our response to the June 20, 2000 facsimile received from Project Manager Jennifer Fan. 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 June 20, 2000 facsimile followed by our response.

1. The ( ) assay was not fully validated.

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

Accuracy - The accuracy of this assay was %, which was similar to that reported above. This was demonstrated using 17 samples run on two separate days by comparing the concentration in those samples determined by this assay with the actual concentration of ibuprofen in the samples.

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Precision - The precision of this assay was demonstrated with coefficients of variation for both the intra-assay variability and the inter-assay variability being well within acceptable limits, being 5.6% and 6.2%, respectively. Inter-assay variability was evaluated using 9 samples run on 3/26/98 and 8 samples on 4/1/98 while intra-assay variability was evaluated using 8 samples run on one day (4/1/98).

Stability - The stability of this assay was demonstrated by the finding that there was minimal variation in samples used to assess freeze-thaw stability (4.0% variation when samples were frozen, thawed, refrozen, thawed and analyzed), stability at room temperature for 3 hours (2.0% variation), in process stability assessing preparation time up to autosampler injection (6.0% variation) and long term stability (3.1% variation over 8 weeks).

Specificity - This was a highly specific assay with the peak for ibuprofen consistently being eluted at 10.7 minutes and the internal standard, naproxen, eluting at 5.6 minutes. There were no interfering peaks identified at these times in blank plasma. There were also no peaks identified at these times in pre-dose samples during the sample analysis portion of the study.

Recovery - The recovery of ibuprofen for this assay was 87% being determined by comparing the peak areas for 3 unextracted and 3 extracted samples.

2. ***The assay validation data provided in the ANDA submissions were generated using a single standard curve.***

The use of standard curves and quality control samples during the validation process and the analysis of study specimens was consistent with standards described for accreditation of a ( )is a national organization which, among other activities, establishes quality improvement standards for clinical laboratories and is responsible for accreditation of clinical laboratories nationwide, including clinical laboratories at this institution. The guidelines used were consistent with the document, "Commission on Laboratory Accreditation: Inspection Checklist, Section 3B, Toxicology, 1998.1 edition."

Precision, accuracy, recovery, freeze thaw stability and room temperature stability were determined during a consecutive five day period (3/26/98 to 4/1/98) using a standard curve obtained that time. Because long term stability was evaluated during the course of the analysis of the subject samples different standard curves were used for this parameter.

3. ***Horse serum instead of blank plasma was used to prepare calibration and control standards during assay validation.***

During the assay development and validation process in this laboratory, horse serum was initially used to avoid any concerns that impurities would confuse the results. Since ibuprofen is a protein bound drug, the decision was made to use human plasma for subsequent standard curves and controls to be most consistent with the clinical sampling procedure (in which human plasma was collected). Tests at that time demonstrated that there would be no matrix effect. Therefore human plasma was used for controls.

Following the inspection by the Division of Scientific Investigations and the Little Rock Post of the FDA Dallas District, an additional experiment was performed to further demonstrate that there was, in fact, no matrix difference. Six samples in human plasma and six samples in horse serum were prepared at each of four concentrations representing the range of concentrations observed in these studies. These were extracted and analyzed according to the methods of the study. The retention times were identical for serum and plasma. The following table demonstrates that there is no matrix effect.

Ibuprofen Concentration	Coefficient of Variation	Percent Difference between Means
1.56 ug/ml	4.1%	0%
12.5 ug/ml	4.5%	0.5%
25 ug/ml	5.3%	6.2%
75 ug/ml	4.4%	5.5%

4. A standard curve was not generated with each analytical run.

The laboratory analysis for this study was performed according to the guidelines for certification of a clinical laboratory by the( ) The ( )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 Inspection Checklist. For each specific guideline, the second column describes how these guidelines for the use of standard curves were met in this study.

guideline	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 200 mg studies was 6.7% and for all the controls in the 800 mg studies the c.v. was also 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. In both of the 200 mg studies, a total of 3 QC samples (1.3% of 236 QC samples) had a variation of 16-18%. There were a

	total of 6 QC 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 200 mg studies was 9 weeks and for both of the 800 mg studies was study 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. 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.

5. ***Quality control (QC) samples with a concentration only near the mid-range (e.g. 10mcg/ml) of the standard curve was used.***

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 on the standard curves used during different phases of assay development and obtained under a variety of conditions (different stock solutions, columns and 2 different 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 that quality of each analysis.

6. ***The standard curve used for the study has a lower limit of quantitation 1.56 mcg/ml and not 0.5 mcg/ml as was reported.***

The LOQ for ibuprofen used in the 200 mg study was 0.5 mcg/ml. This point was chosen because: (1) drug concentrations were easily measured in these samples, (2) it was an extrapolation of the point at which the percent deviation from the curve began to significantly deteriorate, and (3) it was the point below which the majority of concentrations with highly variable duplicates (>25% deviation) occurred (65% of disparate duplicates were at concentrations <0.5 mcg/ml). Concentrations below the LOQ while reported on the data sheets were not used in the statistical analysis of the data. In the statistical analysis concentrations below the LOQ were set as missing in the calculations.

The two parameters used to determine bioequivalence are the AUC and Cmax. The Cmax would not be affected by the LOQ. It is not expected that the AUC would be affected by this difference in LOQ because at all sampling points the ratio of the ibuprofen concentration in test and reference arms was very similar. Thus, raising the LOQ from 0.5ug/ml to 1.56 ug/ml would not alter the ratio of the AUC which is used to define bioequivalence.

7. ***The identity of persons recording all data in case report forms including dosing of test and reference formulations is missing.***

All data reported on these source documents were completed by the three clinical research nurses in the pharmacology section. The study site's SOP has been updated stating that personnel completing a source document sign these entries.

8. ***The thermometer in the -20 ℃ freezer used to store plasma samples would not read below -10 ℃.***

After samples were collected and the plasma separated, the samples were stored in the -20 degree F freezer until they were transferred to the -70 degree F freezer at the end of the study day. Thus, this -20 degree F freezer was only used for temporary storage (less than 12 hours) prior to the long term storage in the -70 degree F freezer.

The thermometer that is currently in the -20 degree F freezer does read to -20 degrees (and is traceable to a reference standard) indicating that this freezer is at the desired temperature +/-1 degree F. At the time of the study the thermometer used did not read down to -20 degrees but gave a reading of less than -10 degrees F. This thermometer is giving the same reading of less than -10 now while the -20 thermometer is reading -20 degrees F.

Because this freezer was used for temporary storage, the difference between –10 degrees and –20 degrees did not affect the stability of these samples. The purpose of the thermometer was to ensure that the freezer was operational.

9. ***The thermometers in both –20 ℃ freezer and in the –70 ℃ freezer used to store plasma samples were not traceable to a reference standard.***

The –70 degree F freezer was used for long term storage of the plasma samples prior to analysis. This freezer assured the long term stability of the plasma samples. The long term stability in this study was excellent with a variation of 4% in control samples before and after the storage period. Thus, although these thermometers were not traceable to a reference standard, this did not affect the stability of the samples.

The study site has developed SOP's for the regular calibration of the thermometers for these freezers with thermometers which are traceable to a reference standard. Calibration of the freezers will occur four times yearly.

10. ***Subject #307 was not within 10% of the ideal body weight for his height and was not excluded from the study.***

The subject's weight was actually 16% for frame size. The reason for this occurrance was that the subject was very muscular for his frame size. As this was a crossover study, this difference would not affect the outcome of the study since the subject would have received all treatments. However, a letter was drafted to the institutional review board by the investigator stating that a subject was enrolled in these studies who did not meet all inclusion criteria.

11. ***Measurements were not taken to determine study subjects frame size even though the height and weight table used specified ideal heights and weights for small, medium and large frames.***

Subjects frame size was subjectively estimated and then the appropriate weight for that frame was used. Any variation resulting from these estimates would not be expected to affect the outcome in this crossover study since all subjects would have received the same treatments. In the future, if the frame size charts are used, their appropriate use for the specific protocol will be noted.

12. ***The case report forms indicated that corrections to the data were not routinely initialed and dated.***

Corrections to data on source documents are routinely initialed and dated as is the policy at this institution. Two exceptions to this policy were noted by the reviewer during the site inspection. All data reported on these source documents were completed by the three clinical research nurses of the pharmacology section. It is standard procedure for the nurses to sign and date these source documents. Study personnel have been reminded to follow this guideline.

13. Subject #402's Case Report Form showed that the subject received treatment 2:3 (reference fed) on 12/14/98 when subject #402 actually received the treatment on 12/18/98.

In this particular situation the date in one of the entries indicated a date of 12/14/98 while on other entries on the same document the date indicated was 12/18/98. Other data corroborated the fact that the actual date was 12/18/98. Thus, the date of 12/18/98 was correct and the single entry of the date of 12/14/98 was in error. This error was easily discernable and was corrected in the presence of the FDA investigator with that investigator's approval.

14. No record of radomization was seen for the 200mg and 800mg studies.

The randomization was performed by the research pharmacist at the research institute. This randomization was done in a manner consistent with the written protocol for the study. The randomization schedule has been included with the deficiency responses.

A computer generated randomization was not done by the biostatistical department. The randomization was performed by the research pharmacist. Future randomization schemes will be according to written protocol.

15. There was no documentation to show that the SAS subroutines used to calculate pharmacokinetic parameters (e.g. AUC, Cmax) and 90% confidence interval limits were validated.

The pharmacokinetic parameters obtained through the SAS subroutines were verified manually to assure the accuracy of these calculations. The data generated was checked manually by two people independently, as part of data verification, prior to the utilization of the data or report generation. These values were found to have been correctly calculated.

16. There was no SOP for data handling and for conduct of pharmacokinetic analysis.

All data handling, pharmacokinetic analyses and statistical analyses for these studies were performed by a single biostatistician. For any studies where data handling, pharmacokinetic analyses and statistical analyses are to be done by multiple biostatisticians, then these analyses will be performed with all biostatisticians using the same written procedures.

The deficiencies listed above were identified in the Form FDA 483, which was issued to ( ) as result of the inspection by the Division of Scientific Investigations (Martin Yau, Pharmacologist) and the Resident in Charge of the Little Rock Post (A. Blake Bevill), Dallas District Office of FDA which occurred on January 24 through January 27, 2000. As agreed with the investigator, these deficiencies were addressed in ( )response to the FDA 483, which was submitted to Mr. Bevill for use by the Dallas District and the Division of Scientific Investigations of the FDA on March 3, 2000. A copy of this correspondence is provided on page 06 of this submission for your convenience.

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 and Compliance Manager

BASF Corporation

BASF

BIOAVAILABILITY

N/AB

October 31, 2000

ORIG AMENDMENT

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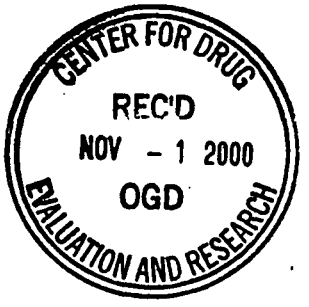
(301-594-0320)



RE: ANDA 75-661
Ibuprofen Tablets, USP, 200 mg
Bioequivalency Amendment

Dear Sir or Madam:

Pursuant to 21 CFR 314.96, we are providing our response to the October 3, 2000 facsimile received from Project Manager Steven Mazzella. 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 October 3, 2000 facsimile followed by our response.

1. ***You have not stated whether the validation information reported in response 1 refers to a pre or post study validation. In all likelihood it appears to be a post-study validation, which is not acceptable. This is a serious flaw.***

   The validation information reported in response 1 refers to pre-study validation work (March, April and December of 1998 as indicated on page 2 of the response). This work was completed nine (9) months before the initiation of the ibuprofen 200 mg bio study. Regarding the statement: "In all likelihood it appears to be a post-study validation", we are bewildered as to how this could possibly be concluded based on the data that was submitted in the original application and the June 23, 2000 submission and inspected at the clinical study site. The following table illustrates the method validation time lines:

ACTIVITY	DATES
Pre-validation	1/28/98 – 3/25/98
Validation	3/26/98, 4/1/98 and 12/3/98 – 12/7/98
Clinical Study	12/7/98 – 1/4/99
Analytical Analysis	12/9/98 – 2/9/99

Based on the misinterpretation of the data submitted, we disagree with the statement: "This is a serious flaw."

2. ***You have given explanation for using only one standard curve. This explanation is not sufficient for the acceptance of the validation results. This is a serious flaw.***

The analytical method was validated for the essential parameters of method validation (accuracy, precision, sensitivity, specificity, linearity and reproducibility) on 3/26/98, 4/1/98 and 12/3/98 – 12/7/98 as described in the "*Draft-Not for Implementation* Guidance for Industry "Bioanalytical Method Validation for Human Studies" (Issued 12/1998, Posted 1/5/1999). Additional "in-study" validation studies were conducted to ensure precision and accuracy of the method. The in-study validation was assured through the following activities:

- Duplicate injections of samples for better estimate of analyte values, although not required based on meeting the acceptance criteria from validation data, but performed for analytical assurance.

- Samples for the application were processed in an analytical run using a calibration curve generated for the single analyte (ibuprofen).

- System suitability samples were injected each day of the analytical run.

- Injection of plasma blanks (pre-dose) for each patient sampling group.

- Injection of QC samples at run concentration (10 μg/mL) throughout sample processing.

The analytical method validation and sample analytical runs are viewed in context of the overall analytical study being conducted by this laboratory utilizing this analytical method. The Ibuprofen 200 mg bioequivalence study samples represented half of the study samples analyzed. Ibuprofen 800 mg bioequivalence study samples (subject of ANDA #75-682) were analyzed as part of the overall study analytical process. The 800 mg bioequivalence study also included the essential validation parameters stated above and the "in-study" validation, including duplicate injection of samples, a separate calibration curve for the sample analytical run, system suitability, plasma blanks, and QC samples at the upper run concentration (30 μg/mL). Calibration curves provided comparable values to the original method development calibration curve. All system suitability and QC control samples exhibit a high level of reproducibility and provided assurance that the method continues to perform satisfactorily.

We believe the validation data provided supports the conclusion of the method validity. Additionally the data supports the in-study validity, although it varies from the draft guidance language.

The draft guidance references articles and conferences from the 1980's and early 1990's. The aspects of method validation that demonstrate that an analytical process is "suitable for intended purpose" (specificity, accuracy, precision, reproducibility, and robustness) are applicable to all types of analytical methodologies. The issues of in-study performance should be influenced by method robustness, using quality control procedures to show how the method performs routinely (Buick, 1990). We acknowledge that the three concentration levels described for QC samples utilizing duplicate injections per concentration are used to provide analytical run statistical assessment for analytical methods that have potential for drift or lack of control throughout the run. We also acknowledge that a confidence interval approach yielding comparable accuracy and precision is an acceptable alternative (Shah, 1992). The state-of-art chromatography equipment currently available to laboratories has reduced the amount of instrument variability that may have reduced method precision and accuracy over the time of the studies. The robustness of the method used, plus the short time frame for the study, supports our approach used for the calibration curves and QC controls. We had previous experience with the analytical method used (for a bioequivalence study not submitted to the agency) that also supported this approach.

During the course of the Ibuprofen 200 mg analytical study period, 236 QC samples (10 µg/mL) were analyzed. A confidence interval approach (Shah, 1992) was used to analyze the QC sample data. Below is a summary of the confidence interval analysis.

Nominal Value	10 µg/mL
Mean	9.6 µg/mL
S.D.	0.6 µg/mL
%CV	6.7%
95% c.i.	9.5 - 9.7 µg/mL
Nominal +/- 20 %	8 - 12 µg/mL

The validated method was used to assess clinical samples of the reference listed drug (RLD) and the application formulation. The samples were run concurrently, eliminating time or instrument bias. Pursuant to 21 CFR 320.29, the statutory requirements for analytical methods for an in vivo bioavailability/bioequivalence study have been met. The comparability of the bioequivalency values provides the necessary data to assure bioequivalence of the application formulation. The comparability is also supported by the in-vitro dissolution studies comparing the RLD to the application drug.

References: *Draft – Not for Implementation* Guidance for Industry "Bioanalytical Method Validation for Human Studies" (Issued 12/1998, Posted 1/5/1999).

Buick, A.R., M.V. Doig, S.C. Jeal, G.S. Land, and R.D. McDowall, "Method Validation in the Bioanalytical Laboratory," *Journal of Pharmaceutical and Biomedical Analysis* 1990;8:629-637.

Shah, V.P., K.K. Midha, S.V. Dighe, et al., Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies (Conference report). *Pharmaceutical Research* 1992;9:588-592.

3. ***You have provided the information comparing the horse and human serums. The correlation between the animal (in this case horse) and the human data have never been accepted by the Division as a substituted [sic] for the adequate assay validation using only human plasma samples. This is a serious flaw.***

   You have misinterpreted the relevance of the information comparing horse serum to human plasma. The use of the horse serum was used during the early method development phase only and prior to the actual method validation process, which took place 3/26/98, 4/1/98 and 12/3/98 – 12/7/98. The actual method validation was performed using human plasma only. The reason this became an issue and was cited on the FDA 483 was because of a typographical error on the analytical method SOP that referred to serum. This typographic error was corrected at the time of the clinical inspection and should not have been included on the FDA 483 because it was explained and addressed to the satisfaction of the FDA investigators. The actual validation data included calibration and control standards that were prepared ONLY with human plasma. The horse serum versus human plasma information submitted in our response dated June 23, 2000 was intended only to provide the reviewer supporting information that demonstrates that the use of horse serum for early development work prior to the initiation of the validation process was an efficient way to initially determine peak assignments and instrument responses, etc. The definitive validation work was initiated with and performed with human plasma.

4. ***Please refer to comment 2 above.***

   Please refer to response to comment 2 above.

5. ***You have not satisfactorily answered why only one QC sample with a concentration only near the mid-range of the standard curve was used in the original validation.***

   Please refer to response to comment 2 above.

6. ***You have not satisfactorily answered why the original validation reported a standard curve lower limit of quantitation as 0.5 mcg/ml instead of 1.56 mcg/ml.***

   The original validation report included a standard curve lower limit of quantitation of 0.5 μg/mL, as determined by criteria defined in March 1998 as part of the pre-study validation of the ibuprofen analytical method. These criteria were provided in our deficiency response dated June 23, 2000 and are restated below:

This point was chosen because:

(1) drug concentrations were easily measured in these samples, (2) it was an extrapolation of the point at which the percent deviation from the curve began to significantly deteriorate, and (3) it was the point below which the majority of concentrations with highly variable duplicates (>25% deviation) occurred (65% of disparate duplicates were at concentrations <0.5 mcg/ml). Concentrations below the LOQ were reported on the data sheets, but were not used in the statistical analysis of the data. In the statistical analysis calculation concentrations below the LOQ were not used (set as missing in the calculations).

We acknowledge the definition for limit of quantitation used by the analytical laboratory and included in the original validation report is different than the definition provided in the *Draft – Not For Implementation* Guidance for Industry "Bioanalytical Method Validation for Human Studies" (Issued 12/1998, Posted 1/5/1999) and that FDA's Division of Bioequivalence appears to have referenced in its review of bioequivalence study data. Several points must be remembered:

(1) The definition for limit of quantitation was established during the pre-study validation. This was ten (10) months prior to the issuance of the draft guidance definition of LOQ.

(2) The definition was established as a standard to use for acceptance of analytical data generated and was written prior to the initiation of any analytical work. We feel it would be inappropriate to use a re-defined criterion that was not in place at the time of the pre-study validation. We do not believe there is only one scientifically valid definition for LOQ that should be deemed acceptable. It was not created to allow acceptance of data that you have determined by use of a different definition would be below the limit of quantitation value.

(3) The two parameters used to determine bioequivalence are the AUC and Cmax. The Cmax would not be affected by the LOQ. All sampling points for the ratio of the ibuprofen concentration in test and reference arms were very similar. Thus, raising the LOQ from 0.5 µg/mL as utilized in the original validation report to 1.56 µg/mL as defined using the draft guidance would not alter the ratio of the AUC as used to define bioequivalence, which the test product readily meets.

(4) Pursuant to 21 CFR 320.26 the study design should provide for collection of blood samples with sufficient frequency to permit an estimate of peak concentration in the blood of the active drug ingredient and the total area under the curve for a time at least three times the half-life of the active drug ingredient measured. The half-life of ibuprofen measured was 1.7 hours and 1.6 hours for the application product and reference listed drug, respectively. Three times the half-life would be at 5.1 hours for the longer of the two values; consequently

any sample collected beyond the six-hour blood sample collection point exceeds the statutory requirements for the determination of the area under the curve. Plasma sample concentration values that approached either of the defined LOQ values were at the later blood sample collection times and are irrelevant in calculation of AUC values pursuant to the statutory requirements. The ratio for AUC (0-12) originally reported in the submission was 103.0% with a 90% CI of 96.7% - 109.6%. The recalculated value for the ratio of AUC (0-6) eliminating all data points of less than 1.5 µg/mL is 102.3% with a 90% CI of 95.4% - 109%.

7. ***You have accepted the responsibility of the deficiencies 8 through 16: Even though not serious flaws, these refer to the inadequate and loose practices related to the assay conduct and data reporting.***

We have adequately addressed the 483 deficiencies cited in 8 through 16. We have not, however, acknowledged that the items cited rise to the level of study-effecting deficiencies due to the minor nature of the particular observations. We most stringently disagree with your reference to our assay conduct and data reporting as "inadequate and loose practices." Due to the broad scope of suitability approaches to use for BE studies and the influence of that on the FDA's review of our bioequivalence study, we recognize that there may be disagreement regarding the approach to technical aspects of the bioequivalence study method validation and analysis. We have endeavored to address all such disagreements with interpretation and implementation of scientifically valid principles of analytical method validation and conduct with the respect due one scientist to another. We are dismayed by the inappropriate tone of the letter's comments and believe these comments violate the spirit of legitimate scientific discourse of complex analytical concepts. The assay and data reporting were not inadequate nor were the assay conduct practices "loose."

The in vivo and in vitro study data previously submitted to the application to address prior deficiencies met all statutory requirements pursuant to 21 CFR 320 for approval of this application. 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 A. Gill
Manager Regulatory Compliance

BASF Corporation

BASF

January 19, 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)

NDA ORIG AMENDMENT
N/Ac

RE: ANDA 75-661
Ibuprofen Tablets, USP, 200 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 75-661, in response to your December 5, 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.

The reanalysis of bioequivalence analytical samples using the attached protocol (see Volume 2, Attachment 4) is intended to confirm the demonstration of bioequivalence for the fasting and limited food effects studies that are the subject of the application amendment dated April 20, 2000, and in response to the deficiency letter dated November 20, 2000, using the three QC controlled samples suggested in the FDA's draft guidance, "Bioanalytical Method Validation for Human Studies." We would respectfully suggest a reanalysis of analytical samples for six (6) patients from the fasting study and analytical samples for six (6) patients from the limited food effect study in order to confirm the validity of the results of the original analysis that used one QC control sample versus the reanalysis using three QC control samples as referenced in the draft guidance document.

For ease of review, we have provided in bold Italics the specific deficiencies listed in the December 5, 2000 facsimile followed by our response.

1. ***We acknowledge your statement that tablet weight is used as an in-process control parameter instead of tablet thickness and that the testing of hardness and disintegration of tablet core eliminates the need to measure tablet friability. Please provide test data to demonstrate the correlation between tablet weight and tablet thickness and correlation between tablet hardness/disintegration and tablet friability. We recommend that the testing of tablet thickness and friability be part of your tablet manufacturing in-process controls. Please revise your drug product manufacturing in-process control specifications accordingly.***

By this response we amend the application with the addition of tablet friability and tablet thickness specifications to our in-process controls contained in Section XII of the application.

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

Tablet Friability: perform according to USP
Specification: target value %
Tablet Thickness: measure the width of the tablet
Specification: mm

Data Summary:

Lot Number	Friability ≤1.0%	Thickness
WO11406	0.08 – 0.75	4.4 – 4.8

The tablet master formula has been updated to include these test specifications. Please see the example pages in Attachment 1.

2. ***You have established your drug product stability chromatographic impurity specifications as NMT(% individual and NMT(% total. Please provide stability data to justify these impurity specifications.***

The specifications were chosen based on available information regarding ibuprofen drug products with chromatographic purity specifications. As discussed, the stability specification for chromatographic purity specification has been revised to reflect the drug substance specification for chromatographic purity % individual and % total impurity) and is included in Attachment 2.

Regarding the labeling comments provided to us in the December 5, 2000 facsimile, we are providing revised draft labels and labeling as instructed. We have revised our draft labels to reflect the changes made and incorporated into the currently approved Motrin IB® labels and labeling (approved August 25, 2000). We will revise our draft labels to reflect the changes requested in the August 25, 2000 approval letter to McNeil Consumer Healthcare at the time that we submit labels and labeling in final print format. We have provided the draft labels and labeling in the current format so as to accurately reflect the content and format of the currently approved Motrin IB labels. We commit to revising final labeling to reflect any other approved changes to the Motrin IB labels, if additional changes are made.

To facilitate review of these labels and in accordance with 21 CFR 314.94(a)(8)(iv), we are providing side-by-side comparison of our draft labels with the Motrin IB labels with all differences annotated and explained. These labels are provided in Attachment 3.

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

BASF Corporation

To Team Leader for assignment.
10/17/01

BASF

October 9, 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)

RE: ANDA 75-661
Ibuprofen Tablets, USP, 200 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 May 2, 2001 facsimile received from Project Manager Nina Nwaba. 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 75-661, in response to your June 8, 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 May 2, 2001 facsimile. This minor amendment contains twelve (12) copies of Final Printed Labeling which have been revised, as instructed in your June 8, 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 the labeling guidance provided us in the June 8, 2001 facsimile.

This amendment addresses all deficiencies listed from the May 2, 2001 and June 8, 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/rp
Michael Gill
Manager Regulatory Compliance

8800 Line Avenue, Shreveport, Louisiana 71106 (318) 861-8200

BASF Corporation

BASF

November 13, 2001

Office of Generic Drugs, CDER, FDA
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NEW CORRESP
NC

RE: ANDA 75-661
Ibuprofen Tablets, USP, 200 mg

INFORMATION AMENDMENT - Withdrawal of Draft Carton Labels for 24-Count Blister Packs and 24-Count Bottle Cartons

Pursuant to my telephone conversation with Mr. Jim Barlow, FDA Reviewer, Labeling Review Branch on November 13, 2001, I am withdrawing the individual blister pack labels contained on pages 028, 029, 030 and 031 and the draft carton labels for the 24-count bottle cartons and the 24-count blister pack cartons contained on pages 020, 021, 022, 023, 024, 025, 026 and 027 of our October 9, 2001 submission of Final Printed Labels. We are requesting approval of all other Final Printed Labeling contained in our October 9, 2001 submission.

As per our telephone discussion, we will submit the Final Printed Labels or printer's proofs for the above-identified cartons as a Labeling Supplement to ANDA 75-661 after approval of the application as soon as the printer's proofs of these cartons are available.

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/rp

Michael Gill
Manager Regulatory Compliance

CENTER FOR DRUG
NOV 14 2001
OGD
EVALUATION AND RESEARCH

8800 Line Avenue, Shreveport, Louisiana 71106 (318) 861-8200