CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
76-112

APPROVAL LETTER
Dr. Reddy's Laboratories, Inc.
Attention: Paul Campanelli
U.S. Agent for: Dr. Reddy's Laboratories Limited
One Park Way
Upper Saddle River, NJ 07458

Dear Sir:

This is in reference to your abbreviated new drug application dated February 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ibuprofen Tablets USP, 400 mg, 600 mg and 800 mg.

Reference is also made to your amendments dated September 7, October 1, and October 24, 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 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 Co.). 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 that 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,

[Signature]

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

10/31/2001
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
76-112

APPROVED DRAFT LABELING
IBUPROFEN Tablets, USP
400 mg
Rx only

Each tablet contains:
Ibuprofen, USP 400 mg
See accompanying literature for complete product information.
Dispense in a tight container.
Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Mfr. By: Dr. Reddy's Laboratories Limited
Bachupally - 502 325 INDIA

Lot EXP

NDC 55111-002-11
Each tablet contains:
Ibuprofen, USP .......................... 600 mg

See accompanying literature for complete product information.

Dispense in a tight container.

Store at controlled room temperature
20° to 25°C (68° to 77°F) [see USP].

Mfd. By: Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

NDC 55111-003-11
Rx only
IBUPROFEN Tablets, USP
800 mg
Rx only

Each tablet contains:
Ibuprofen, USP 800 mg
See accompanying literature for complete product information.
Dispose in a tight container.
Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Mfd. By: Dr. Reddy's Laboratories Limited
Bachupally - 502 325 INDIA

OCT 31 2001

NDC 55111-004-11

500 Tablets

OCT 31 2001

NDC 55111-004-11
Ibuprofen Tablets, USP
Rx Only
Issued: September 2001

DESCRIPTION
Ibuprofen is a nonsteroidal anti-inflammatory agent, available as 200 mg, 400 mg, and 800 mg tablets for oral administration. Ibuprofen is a white powder with a melting point of approx 170°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:

\[
\text{CH}_3-\text{CH}_2-\text{COOH}
\]

Ibuprofen is a nonsteroidal anti-inflammatory agent (NSAID), used in the treatment of symptoms associated with a variety of inflammatory and painful conditions. It is effective in the treatment of pain, fever, and inflammation caused by acute and chronic conditions.

CLINICAL PHARMACOLOGY
Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits the production of prostaglandins. It acts by inhibiting the COX-2 enzyme, which is responsible for the production of prostaglandins. Prostaglandins are a group of compounds that play a role in the production of pain and inflammation.

Ibuprofen is rapidly absorbed when administered orally, with peak plasma concentrations occurring within 1-2 hours. It is extensively metabolized in the liver and primarily excreted in the urine.

PRECAUTIONS
General Precautions
Ibuprofen is contraindicated in patients with a history of gastrointestinal bleeding, ulceration, or perforation, or in those with a history of peptic ulcer disease, including those with a history of ulcers, bleeding, or perforation.

ALCOHOL INTERACTIONS
Ibuprofen should be used with caution in patients taking alcohol, especially in those with a history of alcohol abuse or dependence.

APPROVED OCT 2001
OVERDOSE
Approximately 11 years 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, asymptomatic and responsive, but with no symptoms of poisoning. Two hours after ingestion the child’s condition seemed stable; she still responded only to painful stimulation and continued to have periods of sleep 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, but held herself and respond to spoken commands. Blood level of ibuprofen was 10.95 μg/ml approximately 11 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 ingested approximately 120 mg/kg, there were no signs of acute intoxication or toxic sequel. Blood level in one child 90 minutes after ingestion was 70 μg/ml; about 10 times the peak levels seen in absorption excursion studies.

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

In cases of acute overdose, 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 alkaline and reduce lesions. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and radioligand of ibuprofen.

DOSEAGE AND ADMINISTRATION

DOSAGE

In controlled clinical trials, doses of ibuprofen greater than 400 mg were not more effective than the 400 mg dose.

Dyspepsia: For the treatment of dyspepsia, beginning with the earliest onset of such pain, ibuprofen should be given in a dose of 600 mg every 4 hours as necessary for the relief of pain.

HOW SUPPLIED

Ibuprofen tablets are available in the following strengths, colors and sizes:

- 400 mg (white, round, beveled film coated tablets embossed “1607” on one side and “390” on other side) 
  Bottles of 100  Bottles of 500
- 600 mg (white, modified capsule shaped film coated tablets embossed “1607” on one side and “600” on other side) 
  Bottles of 100  Bottles of 500
- 800 mg (white, capsule shaped, beveled film coated tablets embossed “1607” on one side and “800” on other side) 
  Bottles of 100  Bottles of 500

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Rx only

Manufactured by:
Dr. Reddy’s Laboratories Limited
Bucharest – 502 325 INDIA

Issued: September 2001

* Reactions occurring in 1% to 10% of patients treated with ibuprofen. (Those reactions occurring in less than 1% of the patients are not listed.)

** Reactions are classified under “Probable Causal Relationship (PCR) if there has been one positive challenge or if three or more cases occur which might be causally related. Reactions are classified under “Causal Relationship Unknown” if several or many events have been reported but the criteria for PCR have not been met.
APPLICATION NUMBER:
76-112

CHEMISTRY REVIEW(S)
38. Chemistry comments to be provided to the applicant.

ANDA 76-112 APPLICANT: Dr. Reddy’s Laboratories Limited

DRUG PRODUCT: Ibuprofen Tablets USP, 400 mg, 600 mg and 800 mg

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. Please identify the composition of the ink, Opadry White OY-LS-58900 by the percent per weight.

2. We request that you submit the limits for each test indicated in your in-process testing protocol, which includes the following stages:
   For monitoring only as a limit is not acceptable.

3. We request that your drug product maximum individual impurity and total impurities limit be the same at the drug substance or demonstrate that the impurities are degradants and increase with storage/time.

4. Your dissolution procedure refers to a General Test procedure, which employs pooled dissolution testing. Also, pages 2947 and 2989 indicate pooled samples for dissolution. Please clarify as to how the dissolution procedure was conducted (individual analysis or pooled analysis) for the ANDA submission, and stability testing. What is the proposed procedure for the future commercial lots? What is your definition of the term “pooled sample”?

5. It is indicated that batch #G001 was divided into batch numbers G001A (400 mg tablet) and G001B (600 mg tablets). Are you using the same batch number (G001) for the 800 mg tablets?

Sincerely yours,

[Signature]
Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
1. CHEMIST'S REVIEW NO. 2

2. ANDA 76-112

3. NAME AND ADDRESS OF APPLICANT
   Dr. Reddy Laboratories Ltd.
   66 South Maple Avenue
   Ridgewood, NJ 07450

4. LEGAL BASIS FOR ANDA SUBMISSION
   Generic version of McNeil’s, MOTRIN® (NDA 17-463). Patent
certification and exclusivity statement are provided (pp. 003-010).

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
   Ibuprofen Tablets

7. PROPRIETARY NAME
   Motrin®

8. SUPPLEMENT(s) PROVIDE(s) FOR
   Original ANDA

9. AMENDMENTS AND OTHER DATES

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<tr>
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<th>FDA</th>
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</thead>
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<tr>
<td>Orig. submission</td>
<td>Acknowledgment letter</td>
</tr>
<tr>
<td>Amendment</td>
<td>3/7/01</td>
</tr>
<tr>
<td>Amendment (phone)</td>
<td>Labeling review</td>
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<tr>
<td></td>
<td>Bio review</td>
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<td></td>
<td>4/6/01</td>
</tr>
<tr>
<td></td>
<td>Deficiency letter</td>
</tr>
<tr>
<td></td>
<td>8/8/01</td>
</tr>
</tbody>
</table>

   Amendment 9/17/01
   Amendment (Major) 10/1/01
   Amendment (Phone) 10/24/01

   This review covers submission dated 10/1 and 10/24/01.

10. (PROPOSED) INDICATION(S) FOR USE
    Anti-inflammatory -
    Indicated for relief of the signs and symptoms of rheumatoid
    arthritis and osteoarthritis, for relief of mild to moderate pain
    and for the treatment of primary dysmenorrhea.

11. Rx or OTC
    Rx

12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
   Tablets (Oral)

14. STRENGTH(S)
   400 mg, 600 mg and 800 mg

15. CHEMICAL NAME AND STRUCTURE
    USP 23 (pp. 1360-1361)

   Drug substance and drug product are official USP 23 items.

16. RECORDS AND REPORTS
    None

17. COMMENTS
   a. Application ADEQUATE for approval.
   b. Labeling: ACCEPTABLE dated 10/12/01.
   c. Bio review: ADEQUATE dated 4/30/01
   d. Drug Master File ADEQUATE dated 4/00.
   e. Methods validation: Not required
   f. Establishment evaluation: ACCEPTABLE, dated 3/16/01.

18. CONCLUSIONS AND RECOMMENDATIONS
    APPROVED

19. REVIEWER:
    Raymond Brown

    DATE COMPLETED:
    October 24, 2001
Contain Trade Secret, Commercial/Confidential Information and are not releasable.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
76-112

Bioequivalence Review(s)
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-112        APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen tablets USP, 400 mg, 600 mg, and 800 mg

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

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

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

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Ibuprofen Tablets, USP 400, 600 & 800 mg
ANDA 76-112
Reviewer: Lin-Whei Chuang

Dr. Reddy’s Laboratories Limited
(Formerly Cheminor Drugs Limited)
Ridgewood, NJ
Submission Date:
February 2, 2001

Review of One Fasting and One Non-Fasting Bioequivalence Studies; Dissolution Data; and Waiver Request

Background:

Chemical Nature:
Ibuprofen is a colorless crystalline stable solid. It is relatively insoluble in water and readily soluble in most organic solvent.

Reference Listed Drug (RLD):
Motrin 800 mg tablets of McNeil Consumers - Pharmacia & Upjohn approved through NDA #17463. It is also available as prescription drugs in 300 mg, 400 mg and 600 mg tablets, and 100 mg and 200 mg tablets in OTC drugs.

Pharmacology:
NSAID

Food Effects:
It was stated in the labeling of RLD that “Take with food or milk if occasional and mild heartburn, upset stomach or stomach pain occurs with use”.

Indications and Recommended dose:
800 mg every 4-6 hours indicated as pain reliever and/or fever reducer.

Submission History:
1. This is not an EVA submission.

2. There are many generic ibuprofen tablets currently available in the market. Present submission of Dr. Reddy’s Laboratories Limited contains 1 fasting BE study and 1 non-fasting, food study on the 800 mg tablet; dissolution data for all 3
strengths; and waiver requests for the 400 mg and 600 mg strengths.

Comparative Formulations - Not For Release through FOI:

The formulation data submitted by the firm (see attached copy from p. 180, Vol. 1.2) indicated that all 3 strengths of test product are proportionally similar per definition 1 of the general BA/BE guidance.

In Vivo Fasting Bioequivalence Study - 1 x 800 mg:

Objective:
To compare the single-dose bioavailability of Reddy’s ibuprofen 800 mg tablet and Motrin® 800 mg tablets of Pharmacia & Upjohn under fasting conditions.

Sites, Dates, and Principal Investigator:
Clinical: Phoenix International Life Sciences, Montreal, Canada
   3/13-14/00 (period 1)
   3/16-17/00 (period 2)
   S. Serfaty, M.D.

Analytical: Phoenix International Life Sciences, Montreal, Canada
   3/23-4/12/00

The maximal storage period for the study samples was 29 days.

Design and IRB:
A randomized, 2-way crossover study conducted in 24+2 male subjects under fasting conditions.

Protocol and the informed consent form were approved by the Institutional Review Board of Phoenix International Life Sciences on 2/29/00.

Washout Period:
3 days

Subject Selection:
Twenty-six (26) male Caucasian subjects with 21-45 years of age were selected based on the screening procedure and exclusion
criteria stated in the protocol (pp. 125-126, Vol. 1.2). They had the mean age of 32.9 years, mean height of 176.5 cm, and mean weight of 75.5 Kg.

**Restriction:**
Subjects were instructed of the prohibitions stated in the protocol (p. 126, Vol. 1.2).

**Treatments:**
Subjects fasted overnight before receiving one of the following drug treatments with 240 mL of water in the morning of 3/14/00 according to the randomly assigned sequence (AB for #4, 5, 8, 9, 11, 12, 15, 16, 18, 20, 22, 23, 25; and BA for the rest of subjects):

**Treatment A - Test Drug:** One ibuprofen 800 mg tablet, USP, Cheminor Drugs, batch #G001, potency 98.6%, batch size tablets.

**Treatment B - Reference Drug:** One Motrin® 800 mg tablet (ibuprofen 800 mg tablet, USP, Pharmacia & Upjohn Company, lot #33CTT, potency 101.6%, expires 10/03.

In the morning of 3/17/00, subjects received the alternate treatment.

**Post-dose Procedure:**
1. Subjects remained fasted and ambulatory for 4 hours post-dose.
2. Fluids were restricted from 1 hour before to 1 hour after dosing except water administered with the study drug.
3. Blood samples were drawn at 0, 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after dosing. Plasma samples were stored in duplicate tubes at -22°C pending assay of ibuprofen.
4. Subjects left the clinical facility after the 12-hour blood draw.

**Study Drug Accountability:**
It was stated in the protocol that any unused study drug would be retained per Agency's requirements.
Analytical Method:
Ibuprofen and internal standards were extracted from plasma by and injected onto with

Pre-study and during-study validations are presented below in Tables 1&2:

**TABLE 1: PRE-STUDY ASSAY VALIDATION FOR IBUPROFEN ASSAY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Quality Control Samples</th>
<th>Standard Curve Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>QC or Std. Curve Conc. (ng/mL)</td>
<td>0.3, 20.012, 40.024, 0.1, 100.059</td>
<td>0.1, 0.2, 2.504, 7.511, 25.037, 38.057, 45.067, 50.075, 90.134, 125.187</td>
</tr>
<tr>
<td>Between-Batch Precision (%CV)</td>
<td>1.3 - 15.7</td>
<td>0.5 - 6.8</td>
</tr>
<tr>
<td>Between-Batch Accuracy (% Actual)</td>
<td>94.8 - 98.5</td>
<td>95.1 - 110.4</td>
</tr>
<tr>
<td>Within-Batch Precision of QC (%CV)</td>
<td>1.3 - 10.7</td>
<td></td>
</tr>
<tr>
<td>Within-Batch Accuracy of QC (% Actual)</td>
<td>92.5 - 99.8</td>
<td></td>
</tr>
<tr>
<td>Linearity</td>
<td>R &gt;0.9990</td>
<td></td>
</tr>
<tr>
<td>Linear Range (ng/mL)</td>
<td>0.1 - 125.187</td>
<td></td>
</tr>
<tr>
<td>Sensitivity/LOQ (ng/mL)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Recovery (%)</td>
<td>91.5 - 99.7 (4 QC samples of 0.3-100.059 ng/mL) 101.97-103.24 (internal std. of 0.808-3.203 ug/mL)</td>
<td></td>
</tr>
<tr>
<td>Stability in Plasma/Serum (%)</td>
<td>a) 99.2 - 100.9</td>
<td></td>
</tr>
<tr>
<td>a) 5.5 Hr @ 22°C</td>
<td>b) 100.1 - 100.8</td>
<td></td>
</tr>
<tr>
<td>b) 3 Freeze-Thaw Cycles</td>
<td>c) 90.0 - 103.0</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>Specific, no interference noted in blank plasma.</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2: DURING STUDY ASSAY VALIDATION -- FASTING STUDY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Quality Control Samples</th>
<th>Standard Curve Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>QC or Std. Curve Conc. (ng/mL)</td>
<td>0.299, 39.928, 99.82</td>
<td>0.101, 0.202, 2.5, 7.501, 25.003, 37.908, 45.167, 50.007, 112.918, 125.017</td>
</tr>
<tr>
<td>Between-Batch Precision (%CV)</td>
<td>1.3 - 5.5</td>
<td>0.7 - 7.9</td>
</tr>
<tr>
<td>Between-Batch Accuracy (% Actual)</td>
<td>97.3 - 98.8</td>
<td>97.7 - 103.2</td>
</tr>
<tr>
<td>Linearity</td>
<td>r&gt;0.9996</td>
<td></td>
</tr>
<tr>
<td>Linear Range (ng/mL)</td>
<td>0.101 - 125.017</td>
<td></td>
</tr>
<tr>
<td>Sensitivity/LOQ (ng/mL)</td>
<td>0.101</td>
<td></td>
</tr>
</tbody>
</table>

Comments on the Analytical Method:
The method and data presented in this analytical section are acceptable.
Results:

Drop-out:
None

Protocol Deviation:
None

Adverse Events:
Two (2) cases of mild headaches were reported, both occurred during treatment A and were judged possibly related to the study drug.

Plasma Concentration and Pharmacokinetic Analysis
A total of 768 plasma samples from 24 subjects were assayed for ibuprofen in 14 batches of assay. A total of 12 samples were repeated because of poor chromatography, anomalous value, or high/low standard missing. The 4 samples repeated due to anomalous value were each repeated twice and the median values were reported:

<table>
<thead>
<tr>
<th>Subject</th>
<th>Period (TRT)</th>
<th>Hour</th>
<th>Initial</th>
<th>1st Repeat</th>
<th>2nd Repeat</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>1 (B)</td>
<td>4</td>
<td>42.062</td>
<td>42.526</td>
<td>44.785</td>
<td>42.526</td>
</tr>
<tr>
<td>16</td>
<td>1 (A)</td>
<td>4</td>
<td>47.736</td>
<td>46.992</td>
<td>48.397</td>
<td>47.736</td>
</tr>
<tr>
<td>12</td>
<td>2 (B)</td>
<td>6</td>
<td>35.902</td>
<td>8.857</td>
<td>9.211</td>
<td>9.211</td>
</tr>
<tr>
<td>23</td>
<td>2 (B)</td>
<td>6</td>
<td>42.583</td>
<td>42.792</td>
<td>44.291</td>
<td>42.792</td>
</tr>
</tbody>
</table>

Among the above 4 samples, 3 coincided with the observed Tmax of the time-concentration profile. The one from subject #12 was not, or adjacent to, the Tmax.

The mean plasma concentrations of ibuprofen at each sampling time point after both treatments are presented in Figure 1. The same data and the mean pharmacokinetic parameters of ibuprofen are presented in Tables 3-4.
### TABLE 3: ARITHMETIC MEAN PLASMA IBUPROFEN CONCENTRATIONS [ng/mL] VERSUS TIME AFTER 1 X 800 MG TABLET UNDER FASTING CONDITIONS (N=24)

<table>
<thead>
<tr>
<th>TIME HR</th>
<th>TEST MEAN</th>
<th>SD</th>
<th>REF. MEAN</th>
<th>SD</th>
<th>TEST/REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>.</td>
</tr>
<tr>
<td>0.167</td>
<td>2.500</td>
<td>2.963</td>
<td>6.125</td>
<td>7.182</td>
<td>0.408</td>
</tr>
<tr>
<td>0.33</td>
<td>16.060</td>
<td>11.668</td>
<td>22.026</td>
<td>14.020</td>
<td>0.730</td>
</tr>
<tr>
<td>0.5</td>
<td>26.411</td>
<td>14.359</td>
<td>32.876</td>
<td>17.637</td>
<td>0.803</td>
</tr>
<tr>
<td>0.75</td>
<td>34.475</td>
<td>16.116</td>
<td>40.266</td>
<td>19.311</td>
<td>0.856</td>
</tr>
<tr>
<td>1</td>
<td>37.595</td>
<td>16.267</td>
<td>42.471</td>
<td>19.346</td>
<td>0.885</td>
</tr>
<tr>
<td>1.25</td>
<td>38.397</td>
<td>16.064</td>
<td>42.486</td>
<td>18.035</td>
<td>0.904</td>
</tr>
<tr>
<td>1.5</td>
<td>38.972</td>
<td>14.673</td>
<td>42.518</td>
<td>15.584</td>
<td>0.917</td>
</tr>
<tr>
<td>2</td>
<td>38.331</td>
<td>13.304</td>
<td>39.571</td>
<td>12.547</td>
<td>0.969</td>
</tr>
<tr>
<td>2.5</td>
<td>35.445</td>
<td>12.725</td>
<td>35.566</td>
<td>10.819</td>
<td>0.997</td>
</tr>
<tr>
<td>3</td>
<td>32.264</td>
<td>11.405</td>
<td>30.326</td>
<td>9.050</td>
<td>1.064</td>
</tr>
<tr>
<td>4</td>
<td>25.292</td>
<td>8.690</td>
<td>22.811</td>
<td>8.117</td>
<td>1.109</td>
</tr>
<tr>
<td>8</td>
<td>5.589</td>
<td>2.795</td>
<td>5.482</td>
<td>3.026</td>
<td>1.019</td>
</tr>
<tr>
<td>10</td>
<td>2.882</td>
<td>1.536</td>
<td>2.870</td>
<td>1.597</td>
<td>1.004</td>
</tr>
<tr>
<td>12</td>
<td>1.587</td>
<td>0.916</td>
<td>1.578</td>
<td>0.904</td>
<td>1.005</td>
</tr>
</tbody>
</table>

### TABLE 4: ARITHMETIC MEANS OF PHARMACOKINETIC PARAMETERS OF IBUPROFEN AFTER 1 X 800 MG TABLET UNDER FASTING CONDITIONS (N=24)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TEST MEAN</th>
<th>SD</th>
<th>REF. MEAN</th>
<th>SD</th>
<th>TEST/REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCI (NG*HR/ML)</td>
<td>196.83</td>
<td>43.51</td>
<td>199.83</td>
<td>45.97</td>
<td>0.98</td>
</tr>
<tr>
<td>AUCT (NG*HR/ML)</td>
<td>191.71</td>
<td>41.09</td>
<td>194.75</td>
<td>43.99</td>
<td>0.98</td>
</tr>
<tr>
<td>CMAX (NG/ML)</td>
<td>48.32</td>
<td>10.00</td>
<td>51.36</td>
<td>11.97</td>
<td>0.94</td>
</tr>
<tr>
<td>KE</td>
<td>0.34</td>
<td>0.05</td>
<td>0.33</td>
<td>0.04</td>
<td>1.02</td>
</tr>
<tr>
<td>LAUCI</td>
<td>192.53a</td>
<td>0.21c</td>
<td>195.03a</td>
<td>0.22c</td>
<td>0.99b</td>
</tr>
<tr>
<td>LAUCT</td>
<td>187.77a</td>
<td>0.21c</td>
<td>190.24a</td>
<td>0.22c</td>
<td>0.99b</td>
</tr>
<tr>
<td>DLCMAX</td>
<td>47.29a</td>
<td>0.22c</td>
<td>49.93a</td>
<td>0.25c</td>
<td>0.95b</td>
</tr>
<tr>
<td>THALF</td>
<td>2.11</td>
<td>0.35</td>
<td>2.14</td>
<td>0.27</td>
<td>0.99</td>
</tr>
<tr>
<td>TMAX</td>
<td>1.52-3.23</td>
<td>1.29</td>
<td>1.72-2.82</td>
<td>1.28</td>
<td>1.11</td>
</tr>
</tbody>
</table>

*a = GEOMETRIC MEANS  
b = RATIO OF GEOMETRIC MEANS  
c = SD OF LOG-TRANSFORMED PARAMETER
FIG 1: PLASMA IBUPROFEN LEVELS

IBUPROFEN TABLETS, 1000 MG, ANDA 076-112
UNDER FASTING CONDITIONS
DOSE=1 X 1000 MG

TIME, HRS
0 1 2 3 4 5 6 7 8 9 10 11 12

PLASMA LEVEL, MG/ML

1-TEST (DR. KEGD) 2=REF (PHARMAGIA & UPJOHN)
Statistical Analysis:
ANOVA was conducted by the firm on the non-transformed and log-transformed AUCT, AUCI and CMAX of ibuprofen using SAS GLM with model including sequence, subject within sequence, treatment and period as factors. No significant treatment effect was detected for any of the parameters. Results presented in Table 5 are from ANOVA conducted by the reviewer which are identical to those reported by the firm:

**TABLE 5: LEAST-SQUARES MEANS AND 90% CONFIDENCE INTERVALS FOR IBUPROFEN PHARMACOKINETIC PARAMETERS AFTER 1 X 800 MG TABLET UNDER FASTING CONDITIONS (N=24)**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TEST LSM</th>
<th>REF. LSM</th>
<th>TEST/REF.</th>
<th>90% CONF. INT.</th>
<th>Root MSE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCI [ng·hr/mL]</td>
<td>196.83</td>
<td>199.83</td>
<td>0.98</td>
<td>95.29 - 107.71</td>
<td>...</td>
</tr>
<tr>
<td>AUCT [ng·hr/mL]</td>
<td>191.71</td>
<td>194.75</td>
<td>0.98</td>
<td>95.23 - 101.65</td>
<td>...</td>
</tr>
<tr>
<td>CMAX [ng/mL]</td>
<td>48.32</td>
<td>51.36</td>
<td>0.94</td>
<td>84.19 - 103.98</td>
<td>...</td>
</tr>
<tr>
<td>LAUCI*</td>
<td>192.53</td>
<td>195.03</td>
<td>0.99</td>
<td>95.44 - 102.11</td>
<td>0.068648</td>
</tr>
<tr>
<td>LAUCT*</td>
<td>187.77</td>
<td>190.24</td>
<td>0.99</td>
<td>95.45 - 102.07</td>
<td>0.068025</td>
</tr>
<tr>
<td>LCMAX*</td>
<td>47.29</td>
<td>49.93</td>
<td>0.95</td>
<td>84.62 - 106.00</td>
<td>0.227249</td>
</tr>
</tbody>
</table>

a = From ANOVA Table  
b = Geometric LS Mean

Comments on Results of Fasting Bioequivalence Study:

1. The computation of pharmacokinetic parameters and the 90% confidence intervals conducted by the firm has been confirmed by the reviewer using data submitted in the data diskette. The 90% confidence intervals of LNAUCT, LNAUCI and LNCMAX are all within the acceptable range of 80-125%.

2. Three re-assayed samples due to pharmacokinetic anomaly coincided with the observed Tmax of time-concentration profile (subject #14, hour 4, treatment B; #16, hour 4, treatment A; and #23, hour 6, treatment B). However, after deleting data from these 3 subjects, the outcome of the study remains unchanged.

3. Results of this fasting bioequivalence study are acceptable.
In Vivo Non-Fasting Bioequivalence Study - 1 x 800 mg:

Objective:
To compare the single-dose bioavailability of Reddy's ibuprofen 800 mg tablet and Motrin® 800 mg tablets of Pharmacia & Upjohn under fed conditions; and to compare the bioavailability of Reddy's ibuprofen 800 mg tablet under fed and fasted conditions.

Sites, Dates, and Principal Investigator:
Clinical: Phoenix International Life Sciences, Montreal, Canada
5/18-19/00 (period 1)
5/25-26/00 (period 2)
6/1-2/00 (period 3)
S. Serfaty, M.D.

Analytical: Phoenix International Life Sciences, Montreal, Canada
6/8-7/7/00

The maximal storage period for the study samples was 49 days.

Design and IRB:
A randomized, 3-way crossover study conducted in 18 male subjects under non-fasting and fasting conditions.

Protocol and the informed consent form were approved by the Institutional Review Board of Phoenix International Life Sciences on 5/2/00.

Washout Period:
7 days

Subject Selection:
Eighteen (18) male Caucasian subjects with 18-45 years of age were selected based on the screening procedure and exclusion criteria stated in the protocol (pp. 1079-1080, Vol. 1.5). They had the mean age of 31.1 years, mean height of 173.9 cm, and mean weight of 69.7 Kg.

Restriction:
Subjects were instructed of the prohibitions stated in the protocol (p. 1080, Vol. 1.5).
Treatments:
Subjects fasted overnight before receiving one of the following drug treatments with 240 mL of water in the mornings of 5/19/00, 5/26/00, and 6/2/00 according to one of the following randomly assigned sequences:

ABC: #1, 2, 11  BCA: #9, 13, 14  CAB: #5, 15, 17
ACB: #6, 7, 10  BAC: #12, 16, 18  CBA: #3, 4, 8

Treatment A - Test Drug: One ibuprofen 800 mg tablet, USP, Cheminor Drugs, batch #G001, given under fasting conditions.

Treatment B - Test Drug: One ibuprofen 800 mg tablet, USP, Cheminor Drugs, given 30 minutes after the initiation of a standard breakfast*.

Treatment C - Reference Drug: One Motrin® 800 mg tablet (ibuprofen 800 mg tablet, USP, Pharmacia & Upjohn Company, lot #33CTT, given 30 minutes after the initiation of a standard breakfast*.

* = 240 mL of whole milk, 180 mL of orange juice, buttered English muffin, 1 fried egg, hash brown potatoes, 1 slice of American cheese and 1 slice of Canadian bacon.

Post-dose Procedure, safety monitoring and study drug accountability were the same as those conducted for the fasting study except that blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours post-dose.

Analytical Method:
The analytical method is the same as that in the fasting study. The during study validation data are presented in Table 6:

**TABLE 6: DURING STUDY ASSAY VALIDATION - NON-FASTING STUDY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Quality Control Samples</th>
<th>Standard Curve Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>QC or Std. Curve Conc. (ng/mL)</td>
<td>0.3, 29.994, 59.988</td>
<td>0.1, 0.2, 3.753, 11.009, 35.028, 45.036, 57.546, 67.554, 75.06</td>
</tr>
<tr>
<td>Between-Batch Precision (%CV)</td>
<td>2.0 - 7.9</td>
<td>1.2 - 7.1</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Between-Batch Accuracy (% Actual)</td>
<td>97.8 - 104.8</td>
<td>96.2 - 102.8</td>
</tr>
<tr>
<td>Linearity</td>
<td>$r &gt; 0.9993$</td>
<td></td>
</tr>
<tr>
<td>Linear Range (ng/mL)</td>
<td>0.1 - 75.06</td>
<td></td>
</tr>
<tr>
<td>Sensitivity/LOQ (ng/mL)</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

**Comments on the Analytical Method:**
Data presented in this analytical section are acceptable.

**Results:**

**Drop-out:**
One (1) subject, #11 assigned sequence of ABC, chose to withdraw from the study after the completion of period 2 due to personal reason. It was stated in the protocol that samples from subjects who completed at least 2 periods will be assayed and included in statistical analysis. Therefore his samples were included in the analysis.

**Protocol Deviation:**
None

**Adverse Events:**
Only 1 case of mild headache was reported which occurred during treatment A (test-fasting) and was judged possibly related to the study drug.

**Plasma Concentration and Pharmacokinetic Analysis**
A total of 954 plasma samples from 18 subjects (subject # 11 only gave samples for treatment A and B) were assayed for ibuprofen in 19 batches of assay. A total of 7 samples were repeated because of exceeding curve limits, loss in processing, or anomalous value. Only 1 sample was repeated due to anomalous value which was a none-zero (0.108 ng/mL) pre-dose value and was repeated twice, both confirms the zero value.

The mean plasma concentrations of ibuprofen at each sampling time point after both treatments are presented in Figure 2. The same data and the mean pharmacokinetic parameters of ibuprofen are presented in Tables 7-8.
### TABLE 7: ARITHMETIC MEAN PLASMA IBUPROFEN CONCENTRATIONS [ng/mL] VERSUS TIME AFTER 1 X 800 MG TABLET UNDER NON-FASTING AND FASTING CONDITIONS (N=18 EXCEPT FOR REF.-FED WHERE N=17)

<table>
<thead>
<tr>
<th>TIME HR</th>
<th>TEST-FED</th>
<th>SD</th>
<th>REF.-FED</th>
<th>SD</th>
<th>TEST-FAST</th>
<th>SD</th>
<th>TEST-FED/REF.-FED</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>.</td>
</tr>
<tr>
<td>0.25</td>
<td>1.069</td>
<td>2.751</td>
<td>1.824</td>
<td>4.516</td>
<td>8.688</td>
<td>7.357</td>
<td>0.586</td>
</tr>
<tr>
<td>0.5</td>
<td>4.754</td>
<td>9.886</td>
<td>11.202</td>
<td>15.584</td>
<td>25.700</td>
<td>15.768</td>
<td>0.424</td>
</tr>
<tr>
<td>0.75</td>
<td>10.303</td>
<td>14.740</td>
<td>22.292</td>
<td>22.635</td>
<td>36.381</td>
<td>18.422</td>
<td>0.462</td>
</tr>
<tr>
<td>1</td>
<td>15.660</td>
<td>17.020</td>
<td>27.287</td>
<td>21.725</td>
<td>40.856</td>
<td>19.970</td>
<td>0.574</td>
</tr>
<tr>
<td>1.25</td>
<td>21.187</td>
<td>18.029</td>
<td>30.435</td>
<td>19.038</td>
<td>42.153</td>
<td>19.970</td>
<td>0.696</td>
</tr>
<tr>
<td>1.5</td>
<td>25.800</td>
<td>19.751</td>
<td>32.927</td>
<td>18.059</td>
<td>41.731</td>
<td>18.450</td>
<td>0.784</td>
</tr>
<tr>
<td>1.75</td>
<td>28.238</td>
<td>18.820</td>
<td>33.464</td>
<td>16.358</td>
<td>40.825</td>
<td>16.290</td>
<td>0.844</td>
</tr>
<tr>
<td>2</td>
<td>30.412</td>
<td>18.315</td>
<td>33.542</td>
<td>15.083</td>
<td>40.987</td>
<td>14.575</td>
<td>0.907</td>
</tr>
<tr>
<td>2.5</td>
<td>30.362</td>
<td>11.767</td>
<td>32.388</td>
<td>12.917</td>
<td>37.541</td>
<td>12.113</td>
<td>0.937</td>
</tr>
<tr>
<td>3</td>
<td>31.140</td>
<td>8.497</td>
<td>31.631</td>
<td>9.626</td>
<td>33.615</td>
<td>9.936</td>
<td>0.984</td>
</tr>
<tr>
<td>3.5</td>
<td>31.734</td>
<td>7.703</td>
<td>30.992</td>
<td>10.532</td>
<td>30.397</td>
<td>7.943</td>
<td>1.024</td>
</tr>
<tr>
<td>4</td>
<td>33.650</td>
<td>8.777</td>
<td>30.201</td>
<td>13.214</td>
<td>27.208</td>
<td>7.333</td>
<td>1.114</td>
</tr>
<tr>
<td>8</td>
<td>7.857</td>
<td>2.506</td>
<td>6.880</td>
<td>3.318</td>
<td>5.824</td>
<td>2.738</td>
<td>1.142</td>
</tr>
<tr>
<td>10</td>
<td>3.820</td>
<td>1.553</td>
<td>3.403</td>
<td>1.628</td>
<td>2.829</td>
<td>1.338</td>
<td>1.123</td>
</tr>
<tr>
<td>12</td>
<td>2.088</td>
<td>1.085</td>
<td>1.721</td>
<td>0.870</td>
<td>1.394</td>
<td>0.772</td>
<td>1.213</td>
</tr>
</tbody>
</table>

### TABLE 8: ARITHMETIC MEANS OF PHARMACOKINETIC PARAMETERS OF IBUPROFEN AFTER 1 X 800 MG TABLET UNDER FASTING CONDITIONS (N=18 EXCEPT FOR REF.-FED WHERE N=17)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TEST-FED</th>
<th>SD</th>
<th>REF.-FED</th>
<th>SD</th>
<th>TEST-FAST</th>
<th>SD</th>
<th>TEST-FED/ REF.-FED</th>
<th>TEST-FED/ TEST-FAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCl</td>
<td>191.89</td>
<td>23.65</td>
<td>193.29</td>
<td>29.56</td>
<td>207.89</td>
<td>30.39</td>
<td>0.99</td>
<td>0.92</td>
</tr>
<tr>
<td>AUCl</td>
<td>184.61</td>
<td>24.33</td>
<td>186.24</td>
<td>28.51</td>
<td>203.94</td>
<td>29.50</td>
<td>0.98</td>
<td>0.91</td>
</tr>
<tr>
<td>CMax</td>
<td>45.96</td>
<td>11.75</td>
<td>50.11</td>
<td>9.29</td>
<td>54.43</td>
<td>9.61</td>
<td>0.92</td>
<td>0.84</td>
</tr>
<tr>
<td>Ke</td>
<td>0.35</td>
<td>0.07</td>
<td>0.35</td>
<td>0.05</td>
<td>0.37</td>
<td>0.04</td>
<td>0.98</td>
<td>0.94</td>
</tr>
<tr>
<td>LAUCl</td>
<td>190.56a</td>
<td>0.12c</td>
<td>191.06a</td>
<td>0.16c</td>
<td>205.79a</td>
<td>0.15c</td>
<td>1.00b</td>
<td>0.93b</td>
</tr>
<tr>
<td>LAUCL</td>
<td>183.17a</td>
<td>0.13c</td>
<td>186.13c</td>
<td>0.16c</td>
<td>201.93a</td>
<td>0.15c</td>
<td>0.98b</td>
<td>0.91b</td>
</tr>
<tr>
<td>LCMax</td>
<td>44.71a</td>
<td>0.24c</td>
<td>49.23a</td>
<td>0.20c</td>
<td>53.61a</td>
<td>0.18c</td>
<td>0.91b</td>
<td>0.83b</td>
</tr>
<tr>
<td>THALF</td>
<td>2.11</td>
<td>0.64</td>
<td>2.00</td>
<td>0.31</td>
<td>1.89</td>
<td>0.19</td>
<td>1.06</td>
<td>1.12</td>
</tr>
<tr>
<td>TMAX</td>
<td>2.89</td>
<td>1.25</td>
<td>2.01</td>
<td>1.09</td>
<td>2.15</td>
<td>1.32</td>
<td>1.43</td>
<td>1.34</td>
</tr>
</tbody>
</table>

a = GEOMETRIC MEANS  
b = RATIO OF GEOMETRIC MEANS  
c = SD OF LOG-TRANSFORMED PARAMETERS
FIG 2. PLASMA IBUPROFEN LEVELS

IBUPROFEN TABLET, 300 MG, ANDA 775-112
UNDER NONFASTING/FASTING CONDITIONS
DOSE=1 X BID MG

PLASMA LEVEL, NG/ML

TIME, HRS

1: TEST(DR. REDDY-FAST)
2: REFERENCE(PHARMA: AUPJOHN-FED)
3: TEST(DR. REDDY-FED)
Statistical Analysis:
The firm conducted ANOVA on non-transformed and log-transformed AUCT, AUCI and CMAX of ibuprofen using SAS GLM with model including sequence, subject within sequence, treatment and period as factors. Results presented in Table 9 are from ANOVA conducted by the reviewer which are identical to those reported by the firm.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TEST-FED</th>
<th>REF.-FED</th>
<th>TEST-FAST</th>
<th>TEST-FED/ REF.-FED</th>
<th>TEST-FED/ TEST-FAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCI</td>
<td>191.89</td>
<td>192.94</td>
<td>207.89</td>
<td>0.99</td>
<td>0.92</td>
</tr>
<tr>
<td>AUCT</td>
<td>184.61</td>
<td>188.03</td>
<td>203.94</td>
<td>0.98</td>
<td>0.91</td>
</tr>
<tr>
<td>CMAX</td>
<td>45.96</td>
<td>50.04</td>
<td>54.43</td>
<td>0.92</td>
<td>0.84</td>
</tr>
<tr>
<td>LAUCI</td>
<td>190.56</td>
<td>190.82</td>
<td>205.79</td>
<td>1.00</td>
<td>0.93</td>
</tr>
<tr>
<td>LAUCT</td>
<td>183.17</td>
<td>186.03</td>
<td>201.93</td>
<td>0.98</td>
<td>0.91</td>
</tr>
<tr>
<td>LCMAX</td>
<td>44.71</td>
<td>49.22</td>
<td>53.61</td>
<td>0.91</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Comments on Results of Non-Fasting Bioequivalence Study:

1. The computation of pharmacokinetic parameters, LS means, and ratios of means has been confirmed by the reviewer.

2. When comparing the test to reference drugs under fed conditions, the ratios of LS means of LNAUCT, LNAUCI, and LNCMAX are all within the acceptable range of 0.8-1.25.

3. When comparing the test drug under fed to fasting conditions, results in Tables 8 & 9 indicated a small decrease of mean AUC (8-9%), a 16-17% decrease of mean Cmax, and a 0.75-hour delay of mean Tmax (2.89 under test-fed conditions versus 2.15 hours under test-fasting conditions).

4. Because subject #11 did not complete both treatments under fed conditions, the reviewer re-conducted ANOVA without his data and the outcome of the study remains unchanged.

5. Results of this non-fasting bioequivalence study are acceptable.
IN-VITRO DISSOLUTION TESTING RESULTS:
Ibuprofen tablet is a USP product with the following recommended method and tolerance:

Medium: pH 7.2 phosphate buffer; 900 mL.
Apparatus 2: 50 rpm.
Time: 60 minutes.
Tolerance: NLT in 60 minutes.

The firm conducted comparative dissolution testing for the test and reference products using the USP method as presented in Table 10:

<table>
<thead>
<tr>
<th>Table 10: In Vitro Dissolution Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug: Ibuprofen Tablets</td>
</tr>
<tr>
<td>Dosage Strength: 400 mg, 600 mg, &amp; 800 mg</td>
</tr>
<tr>
<td>ANDA No: 76-112</td>
</tr>
<tr>
<td>Submission Date: 2/2/01</td>
</tr>
</tbody>
</table>

Conditions for Dissolution/Release Testing
Apparatus: Apparatus II (Paddle) RPM: 50
Medium: pH 7.2 phosphate buffer Volume: 900 mL
No. Units Tested: 12
Tolerance (Q): in 60 minutes
Reference Drug: M/s. Pharmacia & Upjohn Company

Results of In Vitro Dissolution

<table>
<thead>
<tr>
<th>Sampling Time (min)</th>
<th>Test Product: Ibuprofen Tablets</th>
<th>Reference Product: Motrin Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Batch #: G001A 400 mg</td>
<td>Lot #: 90CPTA 400 mg</td>
</tr>
<tr>
<td>Mean %</td>
<td>Range</td>
<td>% CV</td>
</tr>
<tr>
<td>10</td>
<td>96</td>
<td>2.0</td>
</tr>
<tr>
<td>20</td>
<td>97</td>
<td>1.5</td>
</tr>
<tr>
<td>30</td>
<td>97</td>
<td>1.5</td>
</tr>
<tr>
<td>45</td>
<td>98</td>
<td>1.7</td>
</tr>
<tr>
<td>60</td>
<td>98</td>
<td>1.8</td>
</tr>
<tr>
<td>75</td>
<td>99</td>
<td>1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling Time (min)</th>
<th>Test Product: Ibuprofen Tablets</th>
<th>Reference Product: Motrin Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Batch #: G001B 600 mg</td>
<td>Lot #: 45CST 600 mg</td>
</tr>
<tr>
<td>Mean %</td>
<td>Range</td>
<td>% CV</td>
</tr>
<tr>
<td>10</td>
<td>97</td>
<td>1.5</td>
</tr>
<tr>
<td>20</td>
<td>98</td>
<td>1.7</td>
</tr>
<tr>
<td>30</td>
<td>99</td>
<td>1.4</td>
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<tr>
<td>45</td>
<td>99</td>
<td>1.8</td>
</tr>
<tr>
<td>60</td>
<td>99</td>
<td>1.7</td>
</tr>
<tr>
<td>75</td>
<td>100</td>
<td>2.0</td>
</tr>
<tr>
<td>Sampling Time (min)</td>
<td>Test Product:</td>
<td>Reference Product:</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen Tablets</td>
<td>Motrin Tablets</td>
</tr>
<tr>
<td></td>
<td>Batch #: G001</td>
<td>Lot #: 33CTT</td>
</tr>
<tr>
<td></td>
<td>Strength: 800 mg</td>
<td>Strength: 800 mg</td>
</tr>
<tr>
<td>Mean %</td>
<td>% CV</td>
<td>Mean %</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>--------</td>
</tr>
<tr>
<td>10</td>
<td>96</td>
<td>2.0</td>
</tr>
<tr>
<td>20</td>
<td>98</td>
<td>0.9</td>
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<tr>
<td>30</td>
<td>98</td>
<td>1.3</td>
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<tr>
<td>45</td>
<td>99</td>
<td>1.0</td>
</tr>
<tr>
<td>60</td>
<td>99</td>
<td>0.9</td>
</tr>
<tr>
<td>75</td>
<td>100</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**Comments on Dissolution Tests:**

1. Results of all 3 strengths of the test and reference products comply with the specification of "in 60 minutes".

2. All 3 strengths of the test and reference products are rapidly dissolved, i.e., more than 90% are dissolved within 10 minutes.

**REQUEST FOR WAIVER OF IN-VIVO BIOEQUIVALENCE:**

The firm is requesting waiver of the in-vivo bioequivalence study requirements for its 400 mg and 600 mg strengths of the test product based on the fasting and non-fasting in vivo bioequivalence studies conducted on the 800 mg strength, the proportionality of formulations, and comparative dissolution data.

**Comments on Waiver Request:**

1. The fasting and non-fasting bioequivalence studies conducted on the 800 mg strength are acceptable.

2. The dissolution data of all 3 strengths of the test product meet the specification of "in 60 minutes".

3. The formulations of the 2 lower strengths are proportionally similar to the formulation of the 800 mg tablets.

4. Therefore the waiver for the firm’s 400 mg and 600 mg tablets can be granted per 21 CFR 320.22(d)(2).
Recommendation:

1. Both fasting and non-fasting bioequivalence studies conducted by Dr. Reddy’s Laboratories Limited on its ibuprofen 800 mg tablet, batch #G001, comparing it to Motrin® 800 mg tablet, lot #33CTT, have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Dr. Reddy’s Laboratories’ ibuprofen 800 mg tablet is bioequivalent to the reference product, Motrin® 800 mg Tablet manufactured by Pharmacia & Upjohn under fasting and non-fasting conditions.

2. The dissolution tests conducted by Dr. Reddy’s Laboratories Limited on its ibuprofen 400 mg, 600 mg, and 800 mg tablets, batch #G001A, #G001B, and #G001, respectively, comparing them to Motrin® 400 mg, 600 mg, and 800 mg tablets, lot #90CPTA, #45CST, and #33CTT, respectively, have been found acceptable by the Division of Bioequivalence.

The formulations of the 400 mg and 600 mg strengths are both proportionally similar to the 800 mg test product which underwent in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 400 mg and 600 mg tablets is granted per 21 CFR 320.22(d)(2). The 400 mg and 600 mg tablets of the test product are therefore deemed bioequivalent, respectively, to the 400 mg and 600 mg tablets of Motrin® manufactured by Pharmacia & Upjohn.

3. The dissolution testing should be incorporated into the firm’s manufacturing controls and stability program and conducted in 900 mL of pH 7.2 phosphate buffer at 37°C using USP 24 apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

Not less than the labeled amount of ibuprofen in the dosage form is dissolved in 60 minutes.

Lin-Whei Chuang 4/7/01

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I
RD INITIALLED YHUANG
FT INITIALLED YHUANG

G [illegible] 4/6/2001

Concur: [illegible] Date: 4/30/2001

For Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-112     APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Ibuprofen tablets USP, 400 mg, 600 mg, and 800 mg

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

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

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

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
APPLICATION NUMBER:
76-112

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

ANDA Number: 76-112  Date of Submission: February 2, 2001
Applicant's Name: Dr. Reddy's Laboratories Limited
Established Name: Ibuprofen Tablets USP, 400 mg, 600 mg & 800 mg

Labeling Deficiencies:

1. CONTAINER – Bottles of 100 and 500 tablets
   
   Satisfactory in draft as of the February 2, 2001 submission.

2. PACKAGE INSERT
   
   a. Title:
      Revise to read "Ibuprofen Tablets, USP" [capitalize "Tablets"] [see General Comments below]
   
   b. General Comments
      Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or of the title of a package insert.
   
   c. Adverse Reactions
      Relocate the table found in your Dosage and Administration section to the end of this section (Adverse Reactions) and directly above the Overdosage section.

   d. Dosage and Administration
      Rheumatoid arthritis and osteoarthritis, including flareups of chronic disease:

      i. First sentence; revise to read -

         **Suggested Dosage:** 1200 mg – 3200 mg daily (400 mg, 600 mg or 800 mg tid or qid).
         Individual...

      ii. Second to the last paragraph; revise to read -

         The availability of three tablet strengths facilitates dosage adjustment.

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

[Signature]

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

<table>
<thead>
<tr>
<th>ANDA Number: 76-112</th>
<th>Date of Submission: February 2, 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicant's Name: Dr. Reddy's Laboratories Limited</td>
<td></td>
</tr>
<tr>
<td>Established Name: Ibuprofen Tablets USP, 400 mg, 600 mg &amp; 800 mg</td>
<td></td>
</tr>
</tbody>
</table>

Labeling Deficiencies:

1. **CONTAINER** - Bottles of 100 and 500 tablets
   
   Satisfactory in **draft** as of the February 2, 2001 submission.

2. **PACKAGE INSERT**
   
   a. **Title:**
      Revise to read *"Ibuprofen Tablets, USP"* [capitalize "Tablets"] [see **General Comments** below]

   b. **General Comments**
      Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or of the title of a package insert.

   c. **Adverse Reactions**
      Relocate the table found in your **Dosage and Administration** section to the end of this section (Adverse Reactions) and directly above the **Overdosage** section.

   d. **Dosage and Administration**
      Rheumatoid arthritis and osteoarthritis, including flareups of chronic disease:
      
      i. First sentence; revise to read -
         
         **Suggested Dosage:** 1200 mg – 3200 mg daily (400 mg, 600 mg or 800 mg tid or qid). Individual...

      ii. Second to the last paragraph; revise to read -
         
         The availability of three tablet strengths facilitates dosage adjustment.

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

_________________________________________________________________

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
# REVIEW OF PROFESSIONAL LABELING CHECK LIST

<table>
<thead>
<tr>
<th>Established Name</th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this product a USP item? If so, USP supplement in which verification was assured. USP 24</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this name different than that used in the Orange Book?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If not USP, has the product name been proposed in the PF?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Error Prevention Analysis

| Has the firm proposed a proprietary name? If yes, complete this subsection. | X |    |      |
| Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? | X |    |      |
| Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? | X |    |      |

## Packaging

| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | X |    |      |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | X |    |      |
| Does the package proposed have any safety and/or regulatory concerns? | X |    |      |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | X |    |      |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | X |    |      |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | X |    |      |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | X |    |      |
| Are there any other safety concerns? | X |    |      |

## Labeling

| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | X |    |      |
| Has applicant failed to clearly differentiate multiple product strengths? | X |    |      |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | X |    |      |

## Labeling(continued)

| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | X |    |      |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | X |    |      |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | X |    |      |
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.

<table>
<thead>
<tr>
<th>Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the scoring configuration different than the RLD?</td>
<td>X</td>
</tr>
<tr>
<td>Has the firm failed to describe the scoring in the HOW SUPPLIED section?</td>
<td>X</td>
</tr>
<tr>
<td>Inactive Ingredients: (FTR: List page # in application where inactives are listed)</td>
<td></td>
</tr>
<tr>
<td>Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?</td>
<td>X</td>
</tr>
<tr>
<td>Do any of the inactives differ in concentration for this route of administration?</td>
<td>X</td>
</tr>
<tr>
<td>Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?</td>
<td>X</td>
</tr>
<tr>
<td>Is there a discrepancy in inactives between DESCRIPTION and the composition statement?</td>
<td>X</td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, is claim supported?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td>X</td>
</tr>
<tr>
<td>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</td>
<td></td>
</tr>
<tr>
<td>Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?</td>
<td>X</td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does ANDA meet them?</td>
<td>X</td>
</tr>
<tr>
<td>Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?</td>
<td>X</td>
</tr>
<tr>
<td>Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.</td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)</td>
<td></td>
</tr>
<tr>
<td>Insert labeling references a food effect or a no-effect? If so, was a food study done?</td>
<td>X</td>
</tr>
<tr>
<td>Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.</td>
<td>X</td>
</tr>
<tr>
<td>Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.</td>
<td></td>
</tr>
</tbody>
</table>

**FOR THE RECORD:**

1. Professional Package Insert:
   Model labeling used by the firm for Motrin was approved February 16, 1988; revised September 1987. **This is the correct model to use.**

2. In the opinion of the applicant and to the best of our knowledge, there is no patent in existence. (Page 12 in Vol. B. 1.1)

3. Storage/Dispensing Conditions:
   - NDA: Store at controlled room temperature 20°-25°C (68°-77°F) (400 mg & 800 mg)
   - Store at controlled room temperature 15°-30°C (59°-86°F) (600 mg tablets)
   - ANDA: Store at controlled room temperature 20°-25°C (68°-77°F) [See USP]

4. Product Line:
   The innovator markets their product in 30, 50, 60, 90, 100, 120 & 500 & unit-dose packages of 100. The
applicant proposes to market their product in bottles of 100 & 500 tablets.

5. Inactive Ingredients:
The listing of the inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pg.1978 vol. B. 1.3.

6. All manufacturing will be performed by Dr Reddy Laboratories Limited (See pg 2418 in Volume B. 1.4.)

7. Container/Closure: (400, 600 and 800mg tablets) Bottles of 100 will utilize a CRC-closure and bottles of 500 will utilize a non-CRC closure. All bottle sizes will utilize HDPE containers (Page 3008-3012 in volume B.1.5.)

8. The description of the drug product found in the HOW SUPPLIED section of the package insert is in accordance with the description of the product found in the Finished Dosage Form. (see pgs. 3272, 3275 and 3278 in vol. A. 1.12.)

Date of Review: 3/21/01
Primary Reviewer: J Barlow
Team Leader: J Grace
Date of Submission: 2/02/01
Date: 3/21/01
Date: 3/30/01
cc:
APPLICATION NUMBER:
76-112

CORRESPONDENCE
DELIVERED VIA FAX and Federal Express
301- 443-3839

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: ANDA # 76-112 Ibuprofen Tablets, USP, 400 mg, 600 mg and 800 mg
TELEPHONE AMENDMENT

Dear Sir or Madam:

Dr. Reddy's Laboratories Inc., US Agent for Dr. Reddy's Laboratories Limited, is providing on
their behalf this response to the Telephone deficiency communicated on October 24, 2001.
Reference is made to the original submission and the amendment dated September 7,

Agency Comment:

Your Reprocessing Statement references Code of Federal Regulations Title 21
§314.70. Please be advised that this section is no longer in force. Please revise your
statement to eliminate all references to this regulatory section.

As requested, the reprocessing statement has been revised. The following page supercedes
the previously submitted reprocessing statement. This concludes our submission. Should you
have any further issues, we can be contacted at 410-309-3145, FAX 410-309-6145.

Sincerely yours,

C. Jeanne Taborsky
C. Jeanne Taborsky
Regulatory Affairs
Hand delivered

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: ANDA #76-112 Ibuprofen Tablets, USP, 400 mg, 600 mg and 800 mg
MINOR AMENDMENT

Dear Sir or Madam:

Dr. Reddy's Laboratories Inc., US Agent for Dr. Reddy's Laboratories Limited, is providing this response to the Minor NA dated August 8, 2001 on their behalf. Reference is made to the original submission and the amendment dated September 7, 2001 and the original submission dated February 2, 2001.

The foreign firm inadvertently submitted the amendment without the knowledge of the US agent. At the request of the agency, the US agent obtained a copy from the foreign firm, and it is hereby being resubmitted at this time. As requested, the US agent has informed the foreign firm of the legal requirements to submit through the US agent. The firm apologizes for this misunderstanding on their part and for any inconvenience that this has caused. The following submission supercedes the minor amendment response previously provided.

A. Chemistry Deficiencies:
Page(s) / 

Contain Trade Secret, Commercial/Confidential Information and are not releasable.
B. Labeling Deficiencies

1) CONTAINER - Bottles of 100 and 500 tablets
   Satisfactory in draft as of the February 2, 2001 submission

   Twelve copies of the Final Printed Labels (FPL) for the containers (HDPE bottle) are provided in Section V.

2) PACKAGE INSERT
   a. Title
      Revise to read "Ibuprofen Tablets, USP" (capitalize "Tablets") (see General Comment below)

   b. General Comments
      Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case), Upper case may be used when the USAN name stands alone as on labels or of the title or a package insert.

   c. Adverse Reactions
      Relocate the table found in your Dosage and Administration section to the end of this section (Adverse Reactions) and directly above the Overdosage section.
d. Dosage and administration
Rheumatoid arthritis and osteoarthritis, including flare-ups or chronic disease

i. First sentence: revise to read

Suggested Dosage: 1200 mg – 3200 mg daily (400 mg, 600 mg or 800 mg or qid), individual.

ii. Second to the last paragraph; revise to read
The availability of three tablet strengths facilitates dosage adjustment.

Please revise you labels and labeling as instructed above, and submit the final prints.

The Package Insert Labeling (PIL) has been revised to include all the changes as recommended by the agency. 12 copies each for the final printed inserts are provided in Section V. Similarities and Differences between Previously Submitted labeling against Proposed labeling is provided in Section IV.

The Firm acknowledges that it may be necessary to further revise the labeling subsequent to approved changes for the Reference Listed Drug.

The Firm commits to incorporate the dissolution test into the stability and quality control programs as specified in USP 24.

Please communicate any remaining questions or issues to C. Jeanne Taborsky, and they will be addressed and a response submitted. This concludes our submission. Please feel free to contact me if you have any questions, tele (410) 309-3145, Fax (410) 309-6145.

Sincerely yours,

C. Jeanne Taborsky
Regulatory Affairs
SENT VIA FEDERAL EXPRESS

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: ANDA # 76-112 Ibuprofen Tablets USP 400 mg, 600 mg, and 800 mg Correspondence

SEP 14 2001

Dear Sir/ Madam:

Dr. Reddy's Laboratories, Inc. US Agent for Dr. Reddy's Laboratories Limited, Bacheapalli 502 325, INDIA, is submitting this correspondence to the previously submitted ANDA dated February 2, 2001.

Please be advised that the name of the US agent has changed. A Letter of Authorization for US Agent is also provided herein with the updated information.

Pursuant to Code of Federal Regulations Title 21 §314.440 (a) (4), a third copy of this communication is being provided. This is the required field copy and we certify that it is a true copy of the technical section as described in Code of Federal Regulations Title 21 §314.50 (d) (1).

This concludes our correspondence. Please contact C. Jeanne Taborsky at (410) 309-3145 or Paul V. Campanelli, Vice President Formulations Business, Reddy-Cheminor, Inc. at (201) 760-2880 ext 203, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky
Regulatory Affairs Consultant

Attachment: US Agent LOA
March 19, 2001

Via Facsimile – 12 pages/Via Courier

Office of Generic Drugs
Center for drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Saundra Middleton

Reference: Ibuprofen Tablets 400 mg, 600 mg & 800 mg
ANDA: 76-112

Dear Ms. Middleton:

This is in reference to our telephone amendment on March 14th with respect to Copovidone used in the above referenced submission by Dr. Reddy's Laboratories, Ltd.

For your review we have attached the following documentation:

- Quantity of Copovidone (Plasdone S-630) used in Ibuprofen Tablets.
- Technical Profile for Plasdone S-630
- ISP Technical Data Sheet for Plasdone S-630
- PDR excerpt of listing Copovidone as an inactive ingredient.

Please contact the undersigned at (201) 444-4424 or by fax at (201) 444-1456, if you have any questions concerning this submission.

Very truly yours,
REDDY-CHEMINOR, INC.

[Signature]
Paul V. Campanelli
Vice President, Formulations Business

Attachments
Reddy-Cheminor, Inc.
U.S. Agent for Dr. Reddy's Laboratories Limited
Attention: Paul V. Campanelli
66 South Maple Avenue
Ridgewood, NJ 07450

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 made to the telephone conversation dated March 2, 2001 and your correspondence dated March 2, 2001.

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

DATE OF APPLICATION: February 2, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 5, 2001

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

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

[Signature]

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
March 2, 2001

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention:
Emily Thomas

Dear Emily:

Per your telephone conversation with Paul Campanelli, attached please find our response to the Telephone Deficiency regarding our Ibuprofen 400, 600 and 800 mg ANDA # 76-112 submission.

Should you have any questions or require additional information, please feel free to contact us.

Thanks and best regards,

REDDY-CHEMINOR, INC.

Robert A. Campanelli
Manager Formulations Business
February 2, 2001

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg
Abbreviated New Drug Application

Dear Sir/Madam:

Dr. Reddy's Laboratories Limited (Formerly Cheminor Drugs Limited) herewith submits an abbreviated new drug application (ANDA) for Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drug, MOTRIN® (Ibuprofen) Tablets 400 mg, 600 mg and 800 mg which is manufactured by Pharmacia and Upjohn Co., the holder of the approved application and which is listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book).

Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg have been developed and will be manufactured, tested and packaged by Dr. Reddy's Laboratories Limited (Formerly Cheminor Drugs Limited), Bacheapally, Post Bag No.15, Kukatpally P.O., Hyderabad 500 072, INDIA manufacturing facility, in accordance with 21 CFR § 210 and 211.

The manufacturer of the drug substance used to produce the ANDA / Biobatch of this product is Dr. Reddy's Laboratories Limited-Bulk drugs division(formerly Cheminor Drugs Limited-Bulk Drug Division), Plot No. 9/A, Phase 3, I.D.A. Jeedimetla, Hyderabad – 500 055, INDIA DMF

The required bioavailability / bioequivalence studies were conducted on Dr Reddy's(formerly Cheminor's) Ibuprofen Tablets, USP 800 mg and MOTRIN® (Ibuprofen) Tablets 800 mg by Phoenix International Life Sciences Inc., 2350 Cohen Street, Saint-Laurent (Montreal), Quebec, Canada H4R2N6. These studies indicate that Ibuprofen Tablets USP, 800 mg are bioequivalent to MOTRIN® (Ibuprofen) Tablets, 800 mg.

The in vitro dissolution profiles for Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg are comparable to those of MOTRIN® (Ibuprofen) Tablets, 400 mg and 600 mg and 800 mg respectively. The formulations of Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg are dose proportional to Ibuprofen Tablets USP 800 mg. Based on the above, a waiver for the bioavailability/bioequivalence study for the 400 mg and 600 mg is requested.
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Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg are stable and a two year expiration dating is requested. The two year expiration dating for these products is supported by one, two and three months accelerated stability data (40°C ± 2°C/75% ± 5% Relative Humidity) in the smallest and largest fill size of the container / closure system proposed for marketing. The stability studies were conducted under a stability protocol that is in conformance with the current FDA Stability guidelines.

The dosage form, route of administration, active ingredient, potency and labeling (except DESCRIPTION & HOW SUPPLIED) for Ibuprofen Tablets, USP 400 mg, 600 mg and 800 mg are same as those for MOTRIN® (ibuprofen) Tablets, 400 mg, 600 mg and 800 mg.

This ANDA is submitted in thirteen volumes:

- Volume I : Section I through Section V
- Volume II through Volume VIII : Section VI
- Volume IX : Section VII through Section VIII
- Volume X : Section IX through Section XII
- Volume XI : Section XII through Section XIII
- Volume XII : Section XIV through Section XXII

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self addressed stamped envelope provided for your convenience.
February 2, 2001

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Pursuant to 21 CFR 314.440 (a) (4), a third copy of this application is also enclosed. This is the required field copy and we certify that it is a true copy of the technical section as described in 21 CFR 314.50 (d) (1).

We also notify the agency that due to the recent merger of Cheminor Drugs Limited into Dr. Reddy's Laboratories Limited, our company name has been changed from Cheminor Drugs Limited — Pharma Division to Dr. Reddy's Laboratories Limited.

As far as this ANDA is concerned, as most of the documents have been executed prior to the change of name, we have maintained the company name as Cheminor Drugs Limited — Pharma Division throughout this ANDA. However, the labeling includes Dr Reddy's Laboratories Limited as the name of the manufacturer.

We request the agency, to henceforth to consider our company name as Dr. Reddy's Laboratories Limited for correspondence purpose. All the addresses remains the same.

Should you have any questions on this submission, please feel free to contact the undersigned at (201)444-4424 or by fax at (201)444-1456.

Sincerely,

[Signature]

Paul V. Campanelli
Vice President – Formulation Business