# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-128**

# CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

[redacted]

McNeil Consumer Products Company
Attention: Willie D. Pagsuyuin
Director, Regulatory Affairs
7050 Camp Hill Road
Fort Washington, Pennsylvania 19034-2299

SEP - 7 1999

Dear Mr. Pagsuyuin:

Reference is made to your Proposed Pediatric Study Request submitted on October 22, 1998, for ibuprofen/pseudoephedrine HCl to[redacted]

To obtain needed pediatric information for ibuprofen/pseudoephedrine HCl for the treatment of symptoms associated with sinusitis, common cold, flu, including nasal congestion, headaches, body aches, pains, and fever, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following two studies:

**Type of Studies:**

Study 1: A multiple-dose study of ibuprofen/pseudoephedrine HCl suspension of sufficient duration to assure attainment of steady state concentrations for both ingredients. The total volume of blood to be drawn and the pharmacokinetic methods to be employed in the data analysis should be determined *a priori* and stated in the protocol. If sparse sampling methods (i.e., population pharmacokinetics) are employed, blood samples should be dispersed throughout the absorption and elimination phases of the drugs to ensure proper parameter estimation.

Study 2: A repeated dose study of ibuprofen/pseudoephedrine HCl suspension dosing in at least 75 pediatric patients dosed as in proposed labeling as needed for the duration of an acute illness.

**Indication/Objective:**

Study 1: The primary objectives of the study should be to evaluate the multiple-dose pharmacokinetic parameters of ibuprofen and pseudoephedrine in children when both drugs are administered in combination as a suspension, and to assess the potential for a drug-drug pharmacokinetic interaction by comparing the results with those from previous single-ingredient studies in children in the same age group.

Study 2: The primary objective of the study should be to evaluate the safety of repeated administration of ibuprofen/pseudoephedrine HCl suspension in these patients.

**Age Groups:**

Study 1: Pediatric subjects spanning the age range of 2 through 11 years of age. At least one third of the subjects must be approximately evenly distributed below 7 years of age.

Study 2: Pediatric patients spanning the age range of 2 through 11 years of age. At least one third of the patients must be approximately evenly distributed below 7 years of age.

**Drug Information:**

Dosage Form: Age appropriate formulation

Route of Administration: Oral

**Drug Specific Safety Concerns:**

Study 1 & 2: Clinical safety for each study should include monitoring for development or exacerbation of asthma, anaphylactoid reactions, central nervous system effects, and hemodynamic effects.

**Statistical Analysis:**

Study 1: In order to provide a sufficiently accurate estimate of any dosing adjustments that may be needed in pediatric subjects, the planned pharmacokinetic evaluation should be powered and structured to detect a 30% change in drug clearance and other relevant pharmacokinetic parameters compared to such values for adults and compared to values for the administration of the individual ingredients to children. In addition to the primary analysis, a covariance analysis should be performed across gender, age and body weight.

Study 2: Statistical analyses should include baseline demographics (age, sex, weight, race) summarized by clinical response; incidence rates of adverse events and premature withdrawals; and changes from baseline in laboratory values, vital signs and body weight. All analyses should be summarized and, where appropriate, analyzed with the results of statistical tests declared significant if $p < 0.05$ (two-tailed comparison).

Safety data should be tabulated, including serious and other adverse reactions, deaths, withdrawals and drop-outs. Clinical data should be explored for factors (e.g., dose, baseline severity) that may affect clinical response.

**Labeling:**

Appropriate sections of the label may be changed to incorporate the findings of the studies.

**Format of Reports To Be Submitted:**

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation must be submitted.

**Timeframe:**

These reports must be submitted by June 1, 2001. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not been extended previously or has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please note that you may seek a written agreement with FDA, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act)*. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Sandra Cook, Project Manager, at (301) 827-2090.

Sincerely yours,

/S/ 07 SEPTEMBER 1999

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research



APPEARS THIS WAY
ON ORIGINAL

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Central Document Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

SEP 30 1999

RE: Children's MOTRIN® Cold Suspension
Ibuprofen (100 mg/5 mL) and Pseudoephedrine HCl (15 mg/ 5 mL)

**SUBMISSION OF PEDIATRIC STUDY REPORTS –**
**PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**

New Drug Application 21-128

Dear Sir or Madam:

In accordance with 21 CFR 314, enclosed is a New Drug Application for Children's MOTRIN® Cold Suspension, which combines Ibuprofen (100mg/5mL) and Pseudoephedrine HCl (15 mg/5 mL). This combination product has been developed as an over-the-counter (OTC) medication for children 2 to 11 years old to temporarily relieve symptoms associated with the common cold, flu or sinusitis including nasal and sinus congestion, stuffy nose, headache, sore throat, body aches and pains and to temporarily reduce fever.

Ibuprofen and pseudoephedrine are frequently co-administered, since nasal congestion often accompanies headaches, pain, and fever in association with the common cold, flu or sinusitis. OTC adult combination ibuprofen-pseudoephedrine products have been available since 1990. A similar combination is of particular benefit in children because two separate drug administrations can be difficult for parents and can lead to noncompliance and misadministration. The availability of an OTC ibuprofen-pseudoephedrine combination product in an age-appropriate dosage form would provide children with the efficacy, safety and convenience that are currently available to adults.

The proposed ibuprofen/ pseudoephedrine HCl combination product, Children's MOTRIN Cold Suspension, is indicated for the following uses: 1) temporarily reduces fever and 2) temporarily relieves symptoms associated with the common cold, flu or sinusitis including nasal and sinus congestion, stuffy nose, headache, sore throat, body aches and pains. The dosing regimen proposed for Children's MOTRIN Cold Suspension is based on the currently approved regimen for OTC pediatric ibuprofen, which uses the standard age and weight groupings described in "Pediatric Dosing Information for Over-the-Counter Human Drugs; Intent and Request for Information; Notice of Intent [53 FR 23180, June 20, 1988]". The proposed dosing schedule maintains consistent dosing across age groups and keeps dosing within established safe and effective ranges for each ingredient.

The clinical development program was discussed with FDA at meetings held on July 30, 1997 and May 10, 1999. The clinical studies performed in support of OTC approval of Children's MOTRIN Cold Suspension were conducted by McNeil Consumer Healthcare under [redacted] Three clinical studies are reported in this NDA, including a clinical safety study conducted in children 2 to 11 years old (Study 99-086), a pharmacokinetics drug interaction study conducted in children 4 to 11 years old, (including an analysis and extrapolation in support of dosing down to 2 years old) (Study 98-057), and a bioequivalence study conducted in adults (Study 97-024).

On September 7, 1999, McNeil received an official WRITTEN REQUEST from FDA for two pediatric studies. The clinical safety study (Study 99-086) and the pharmacokinetics drug interaction study (Study 98-057) contained in this NDA are provided in response to FDA's WRITTEN REQUEST. Please refer to the Pediatric Exclusivity Summary that immediately follows this cover letter.

The formulation for Children's MOTRIN Cold Suspension has been developed in two flavors: Berry (Formula C-822-4) and Grape (Formula C-846-3). In support of this application, stability data are provided on 6 batches of finished product including 3 of each flavor. This application requests a 36 month expiration period for the drug product packaged in 1 oz. and 4 oz. bottles. This request is supported by stability data collected for [redacted]

We were notified by our supplier of pseudoephedrine hydrochloride that their Drug Master File [redacted] has been updated to reflect a change in the synthesis process of the key intermediates with no change to the pseudoephedrine synthesis process. The drug product batches supporting this NDA were manufactured using pseudephedrine from the previous process. On August 13, 1999, we requested guidance from the Division regarding the stability requirements to support this change. A copy of our request immediately follows this cover letter. To date, we have not received feedback on the proposal we submitted. In accordance with our proposal, we hereby commit to placing the first three commercial production batches of each formulation packaged in the largest and smallest bottles in our marketed product stability program. We also commit to reporting the results in Annual Reports to the NDA.

In addition to the paper archive and review copies included with this submission, we are also providing the following items electronically:

| | |
|---|---|
| Section 6 | Human Pharmacokinetics and Bioavailability Summary in WORD 6.0 |
| Section 8 | Integrated Safety and Efficacy Summaries in WORD 6.0 |
| Section 11 | Protocol 99-086 Data Tabulations in SAS Transport Files |
| | Protocol 99-086 Patient Profiles for Serious Adverse Experiences and Discontinuations as PDF Files |

Other sections are available electronically upon request.

We have remitted the appropriate application fee specified in FDA User Fee Guidance. Under separate cover, a field copy has been sent to the Philadelphia District Office.

Please contact me at (215) 273-8368 for any questions that may arise during the review process. Correspondence may be sent to me via telefacsimile at (215) 273-4049.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz
Associate Director, Regulatory Affairs

cc: S. Cook, (HFD-550)
D. Pagano, Field Copy, PAI Coordinator, Philadelphia District Office

Enclosures: Archival Copy
Chemistry Review Copy
Biopharmaceutics Review Copy
Clinical Review Copy
Statistical Review Copy
Methods Validation Package (3 copies)
Summary Section (Volume 1- 10 additional desk copies)

Jau010.doc

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

McNeil

NEW CORRESP
NC

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NOV - 5 1999

Karen Midthun, MD-
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

DATE 11/18/99 Villalba

RE: Children's MOTRIN® Cold Suspension
Ibuprofen (100 mg/5 mL) and Pseudoephedrine HCl (15 mg/5 mL)
NDA 21-128
Correspondence

Dear Dr. Midthun:

In section 19.2 of our NDA, we stated that "none of the studies submitted in this NDA meet the requirements of a 'covered clinical study' under 21 CFR 54.2". According to 21 CFR 54.2 (e), large open safety studies conducted at multiple sites were not considered 'covered clinical studies' for the purposes of providing financial disclosure information. Financial disclosure information was not included in the original submission of this NDA because the only study submitted in this NDA that was conducted after the implementation date of the final rule was study 99-086, "An open-label study of the safety of an ibuprofen-pseudoephedrine HCl suspension in children", which included 114 children enrolled at 16 investigative sites.

On October 26, 1999, Sandy Cook, Project Manager, FDA, called to request that McNeil provide financial disclosure information for Study 99-086. As required by 21CFR 54.4(1), attached is a completed Form FDA 3454 listing all investigators and subinvestigators for Study 99-086.

Please contact me at (215) 273-8368 if you have any further questions.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs -

NOV 05 1999

cc: S. Cook, Project Manager (HFD-550)
jau014.doc

McNeil

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Karen Midthun, MD -
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NOV 16 1999

ORIG AMENDMENT
BC

NOV 17 1999

RE: Children's MOTRIN® Cold Suspension
Ibuprofen (100 mg/5 mL) and Pseudoephedrine HCl (15 mg/5 mL)
NDA 21-128
Minor Amendment No.1

Dear Dr. Midthun:

We wish to formally amend this application to include the information faxed to Dr. Rao Puttagunta, FDA Chemistry Reviewer, in response to his phone conversation with Paula J. Oliver, Senior Director of Regulatory Compliance, regarding manufacturers' identification as listed in NDA 21-128 (Vol. 2, Section 4, Pg. 65/66). Please note the following with regard to the four listed firms:

1. [redacted]
The address, as listed in the application is correct.

2. [redacted]
We were able to determine more specific information from [redacted] as follows:

[redacted]

3. McNeil Consumer Healthcare
The company name and address as listed in the application is correct.

4. [redacted]
The company address, as listed in the application, is correct.

We have learned that [redacted] does not include Inc. in its name. The proper name of the company is [redacted]

ORIGINAL

We have revised Vol. 2, Section 4, Pg. 65/66 to include the updated information listed above. The revised pages are included as Attachment 1.

In regards to the readiness of these sites for FDA inspection, all sites are ready for inspection.

Please contact me at (215) 273-8368 if you have any further questions.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

cc: S. Cook, Project Manager (HFD-550)
R. Puttagunta, Chemistry Reviewer (HFD-550)

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APPEARS THIS WAY
ON ORIGINAL

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NC

DEC 8 1999


Karen Midthun, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research.
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: Children's MOTRIN® Cold Suspension
Ibuprofen (100 mg/15 mL) and Pseudoephedrine HCl (15 mg/mL)
NDA 21-128
Correspondence

Dear Dr. Midthun:

On December 2, 1999, Sandy Cook called to request the pharmacokinetics data supporting this application electronically in EXCEL 97 format. The electronic files were sent via e-mail to Sandy Cook on December 7, 1999. Attachment 1 contains the requested data files on diskette for Studies 97-024 and 98-057. Please note that the electronic copy of Suppl2.xls that was sent on 12/7/99 contained redundant data that have been removed from the Suppl2.xls file on the enclosed diskette. A description of the data files and hard copies of the tabulations are provided in Attachment 2.

If you have any further questions, please contact me at (215) 273-8368.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz

ORIGINAL

Janet A. Uetz
Associate Director, Regulatory Affairs

/S/

JAU:dtg
Attachment

cc: S. Cook, Prcject Manager (HFD-550)

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McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

JAN 28 2000

Karen Midthun, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-128
Correspondence

Dear Dr. Midthun:

Enclosed are 4 additional desk copies of volume 1 of NDA 21-128 requested by Sandy Cook on behalf of the OTC Division.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz
Associate Director, Regulatory Affairs

JAU:dtg
Attachment

cc: S. Cook (HFD-550) (cover letter only)
B. Merritt (HFD-560) (4 desk copies)

p:\nda\corresp\midthun3.doc

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Karen Midthun, MD
Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

FEB 1 2000

RE: Children's MOTRIN® Cold Suspension
NDA 21-128
Correspondence

Dear Dr. Midthun:

Enclosed are the following items requested by Sandy Cook on behalf of the OTC Division:

1. Attachment 1 contains copies of the carton and bottle labels in Drug Facts format for both the berry and the grape flavors as provided in volume 1 of the original submission. Labeling format information is provided for each item.

2. Attachment 2 contains a hard copy and electronic copy (Word 97) of the labeling content in Drug Facts format.

Please contact me at (215) 273-8368 if you have any further questions.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

JAU:dtg
Attachment

cc: S. Cook (HFD-550) (cover letter only)
B. Merritt (HFD-560) (review copy)

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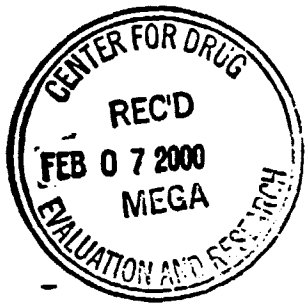
McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NDA CHG AMENDMENT

FEB 4 2000 S4

Karen Midthun, MD
Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850




RE: Children's Motrin® Cold Suspension
NDA 21-128
Safety Update

Dear Dr. Midthun:

In accordance with 21 CFR 314.50(d)(5)(vi), we are providing the 4-month safety update for Children's Motrin Cold Suspension. This update includes commercial marketing experience safety data for OTC adult ibuprofen-pseudoephedrine combination products from FDA Spontaneous Reporting System from January 1, 1999 through October 18, 1999 and from the McNeil Spontaneous Reporting System from January 1, 1999 through December 31, 1999.

Should you have any questions, please contact me at 215-273-8368.

Sincerely.

MCNEIL CONSUMER HEALTHCARE

Janet A. Uetz
Janet A. Uetz
Associate Director, Regulatory Affairs

cc: S. Cook (HFD-550), cover letter only

ORIGINAL

Midthun5.doc

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Karen Midthun, MD
Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

FEB 11 2000

RE: Children's MOTRIN® Cold Suspension
Ibuprofen (100 mg/5 mL) and Pseudoephedrine HCl (15 mg/5 mL)
NDA 21-128
Minor Amendment No.2

Dear Dr. Midthun:

We wish to formally amend this application to include the information faxed to Dr. Rao Puttagunta, FDA Chemistry Reviewer, on January 24, 2000, in response to his phone conversation with Jackie Linse, Associate Director, Regulatory Affairs, regarding the tabular listing of all samples to be submitted to the FDA. The tabular listing is included as Attachment 1.

At this time we would also like to provide the preservative efficacy challenge data which demonstrate that the sodium benzoate at the [redacted]

Please contact Jackie Linse at (215) 273-8733 or me at (215) 273-8368 if you have any questions.

Sincerely,

McNeil CONSUMER HEALTHCARE

Janet A. Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

cc: S. Cook, Project Manager (HFD-550)
R. Puttagunta, Chemistry Reviewer (HFD-550)

Mmbput2.doc

McNeil

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Karen Midthun, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

APR 27 2000


NDA ORIG AMENDMEN

RE: Children's Motrin® Cold Suspension
NDA 21-128
Amendment No. 3

BM

Dear Dr. Midthun:

This Amendment to NDA 21-128 provides a response to the additional pediatric safety information that was requested by FDA via telefacsimile on March 21, 2000 Immediately following this cover letter is a guide to the location of the information requested. Each FDA request is restated in bold face type followed by a reference to the section of this amendment where the requested information is presented. The Amendment is organized as follows:

Section 1 – Overview
Section 2 – Clinical Study Safety Data
Section 3 – Marketing History
Section 4.1 – Safety Profile Data for Ibuprofen and Pseudoephedrine
Section 4.2 – Safety Profile Data for Pseudoephedrine
Section 4.3 – Safety Profile Data for Ibuprofen

Should you have any questions, please contact me at 215-273-8368.

Very truly yours,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

ORIGINAL

cc: Sandy Cook, Project Manager, HFD-550 (cover letter only)
JAU/joc
Attachment
Jau101.doc

Received 5/3/00
Villalba

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

APR 27 2000

Karen Midthun, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850


BL

RE: Children's Motrin® Cold Suspension
NDA 21-128
Amendment No. 4

NDA ORIG AMENDMENT

Dear Dr. Midthun:

This Amendment provides updated draft labeling for Children's Motrin Cold Suspension. (Carton and Bottle labels for 1oz and 4oz berry and 1oz and 4oz grape.) The revisions include:

1) addition of the symptom bullets, "• fever • stuffy nose • sore throat" to the front panel,
2) relocation of "see bottom of box for lot number and expiration date" to the **"Other information"** section and
3) addition of a hyphen to "toll-free" and addition of bolding to the phone number in the **"Questions or comments?"** section.

Should you have any questions, please contact me at 215-273-8368.

Very truly yours,

McNEIL CONSUMER HEALTHCARE

Janet A Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

cc: Sandy Cook, Project Manager, (HFD-550)
JAU/joc
Attachment

ORIGINAL

Jau102.doc

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NDA ORIG AMENDMENT APR 27 2000

Karen Midthun, MD
Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

BC

Re: Children's MOTRIN® Cold Suspension
Ibuprofen (100mg/5mL) and Pseudoephedrine HCl (15mg/5mL)
NDA 21-128
Amendment No. 5

Dear Dr. Midthun:

We wish to amend NDA 21-128 to include updated analytical methods for both the berry and grape flavor Children's MOTRIN® Cold Suspension. These updates are improvements recommended by the investigator at the time of our pre-approval inspection. We indicated to the investigator that we would amend our application with them.

If you have any questions regarding this amendment, please contact Jackie Linse at (215) 273-8733 or me at (215) 273-8368.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

cc: S. Cook, Project Manager (HFD-550)
R. Puttagunta, Chemistry Reviewer (HFD-550)

ORIGINAL

Mmbput3:kt

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

Karen Midthun, MD
Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

JUN 8 2000

NEW CORRESPONDENCE
NC

Re: Children's MOTRIN® Cold Suspension
NDA 21-128
Correspondence

Dear Dr. Midthun:

On June 1, 2000, Ms. Sandra Cook, Project Manager called with a request by the medical reviewer for information regarding market withdrawals of two products by Proctor and Gamble. The products in question were:

Vicks Action, an ibuprofen pseudoephedrine product withdrawn from the market in the United Kingdom in 1998 and

Vicks Action Profen, an ibuprofen pseudoephedrine product withdrawn from the market in Indonesia in 1999.

After contacting our U.K. affiliates, who in turn contacted Proctor and Gamble in the UK, it was confirmed that these market withdrawals were solely for commercial reasons.

If you have any additional questions, please contact me at (215) 273-8733.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Jacqueline U. Linse
Associate Director, Regulatory Affairs

JL0068

DUPLICATE

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NDA ORIG AMENDMENT JUN 16 2000

Karen Midthun, MD, Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850


BB

RE: Children's Motrin Cold Suspension
NDA 21-128
Correspondence

Dear Dr. Midthun:

This submission provides a response to the biopharmaceutics review questions on NDA 21-128 received by telefacsimile on June 14, 2000 (copy attached).

Should you have any further questions, please contact Jackie Linse at (215) 273-8733 or me at (215) 273-8368.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Janet A. Uetz

Janet A. Uetz
Associate Director, Regulatory Affairs

cc: S. Cook, Project Manager (HFD-550), via fax

Jau015.doc

ORIGINAL

McNeil

ORIGINAL

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NEW CORRESP

JUN 2 2 2000

NC

Karen Midthun, MD
Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850


Re: Children's Motrin Cold Suspension
NDA 21-128
Correspondence

Dear Dr Midthun:

At the request of Sandra Cook, enclosed please find a revised NDA Debarment Certification page including signature and date.

Sincerely,
McNEIL CONSUMER HEALTHCARE

Jacqueline U. Linse
Associate Director, Regulatory Affairs

cc: S. Cook

MB0622:kt

McNeil

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NDA [illegible] AMENDMENT JUN 2 7 2000

Karen Midthun, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850


RE: Children's MOTRIN® Cold Suspension
NDA 21-128
Correspondence

BC

Dear Dr. Midthun:

On April 27, 2000, we submitted an amendment to the above NDA providing updated analytical methods. The method updates were minor modifications recommended by the FDA Investigator during our Pre-approval inspection. On June 26, 2000, Dr. Puttagunta, Reviewing Chemist, called to request that we update our methods validation package with the new methods. In response to his request, we are providing four copies of the methods validation package with the new methods included.

Please contact me at (215) 273-8733 if you have any questions and to arrange the teleconference.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Jacqueline U. Linse
Associate Director, Regulatory Affairs

cc: S. Cook, Project Manager (HFD-550)
R. Puttagunta (HFD-550)

ORIGINAL

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McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

JUL 7 2000

NEW CORRES

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 10 2000
MEGA

Karen Midthun, MD, Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: Children's Motrin Cold Suspension
NDA 21-128
Amendment to Pending Application

NC

Dear Dr. Midthun:

In response to Dr. Puttagunta's request of July 5, 2000, we are formally withdrawing the Package Interchangeability Protocol from our pending New Drug Application.

Should you have any further questions, please contact Jackie Linse at (215) 273-8733 or me at (215) 273-7010.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Vivian A. Chester

Vivian A. Chester
Vice President, Regulatory Affairs

cc: S. Cook, Project Manager (HFD-550), via fax

pmj00016.doc

ORIGINAL

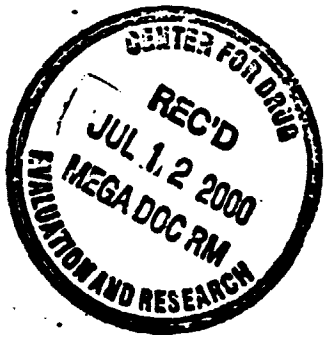
McNeil

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NDA ORIG AMENDMENT JUL 11 2000

Karen Midthun, MD -
Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

BC




Re: Children's MOTRIN® (ibuprofen) Cold Suspension
NDA 21-128
Amendment No. 7 (CMC)

Dear Dr. Midthun:

In response to Dr. Puttagunta's request of 7/7/00, we are submitting updated stability tables containing 12-month data.

Should you have further questions, please call me at (215) 273-8733.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Jacqueline U. Linse
Associate Director, Regulatory Affairs

cc: R. Puttagunta, Chemistry Reviewer (HFD-550)

JL000711:sco

ORIGINAL

ARCHIVAL COPY

McNeil

McNeil Consumer Healthcare, 7050 Camp Hill Road, Fort Washington, PA 19034-2299 (215) 273-7000

NDA ORIG AMENDMENT JUL 17 2000

Karen Midthun, MD
Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

BC

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 18 2000
MEGA DOC RM

Re: Children's MOTRIN® (ibuprofen) Cold Suspension
NDA 21-128
Amendment No. 8 (CMC)

Dear Dr. Midthun:

In response to Dr. Puttagunta's request of 7/7/00, we are submitting updated stability tables containing 18-month data and the statistical analysis report.

Should you have further questions, please contact me at (215) 273-8733.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Maureen M Barron for

Jacqueline U. Linse
Associate Director, Regulatory Affairs

cc: R. Puttagunta, Chemistry Reviewer (HFD-550)

JL000714:sco

ORIGINAL

PRIORITY

McNeil
Consumer Healthcare
7050 Camp Hill Road, Fort Washington , PA 19034-2299 Main Phone 215.273.7900

**URGENT DELIVERY REQUESTED**
**FAX TRANSMITTAL**

**DATE:** July 28, 2000

**TO:** Sandra Cook **FAX:** 301-827-2531

**FROM:** Judy O'Connor for Paula Oliver

**PHONE:** 215-273-8502 **FAX:** 215-273-4049

---

**RE: NDA 21-128**

Dear Sandy:

Just got off the phone with Paula and she has given me the go ahead to send the attached documents to you.

I will also be sending you electronically the Drug Facts document. If for some reason you do receive it please let me know.

Judy O'Connor
Administrative Assistant to Paula Oliver
☎ 215-273-8502
Fax: 215-273-4049

Attachment

*NO. PAGES (INCLUDING COVER SHEET):* 5

**CONFIDENTIALITY NOTICE:**

McNeil
Consumer Healthcare
7050 Camp Hill Road, Fort Washington , PA 19034-2299 Main Phone 215.273.7900

**URGENT DELIVERY REQUESTED**
**FAX TRANSMITTAL**

**DATE:** July 28, 2000

**TO:** Sandra Cook **FAX:** 301-827-2531

**FROM:** Paula Oliver

**PHONE:** 215-273-7878 **FAX:** 215-273-4049

---

**RE: NDA 21-128**

Dear Sandy:

In follow-up to our teleconference of July 27, 2000 to discuss the agency's proposed labeling for McNeil Consumer Healthcare's pending NDA 21-128, we have updated the ***Drug Facts*** presentation (attached).

The dosing chart has been revised in accordance with the proposed labeling provided to us on July 21, 2000, and the dosing interval has been revised to 6 hours instead of 6-8 hours. In addition, as discussed during our teleconference: we have moved the bullet point that tells the consumer to replace the original bottle cap, making it consistent with the agency's June 2, 2000 labeling comments on Children's Motrin® Suspension; we have included our original bullet point referencing our dosage cup; we have included the reference to tamper-evident features under the ***Other Information*** header; and we have included a ***Questions or Comments*** header.

With regard to the **Stop Use and Ask a Doctor** subheader, we continue to believe that the fourth bulleted statement should read as follows:

- stomach pain or upset gets worse or lasts

Current pediatric ibuprofen products have labeling which directs the parent to give the child milk or food if stomach upset occurs when using these products. Additionally, all current pediatric ibuprofen products have labeling which directs the parent to stop using the products and call a doctor if stomach pain or upset gets worse or lasts. The proposed labeling provided to us on July 21, 2000 revised this bullet to read as follows:

[redacted]

We believe that our current labeling is more appropriate and less confusing because it tells the parent that if stomach upset occurs initially, they can try food or milk, but if it persists or gets worse they should contact their doctor.

Additionally, under that same subheading, a bullet was added which reads:

- symptoms continue or get worse

This bullet is also not included in current approved ibuprofen labeling and seems redundant since the third bulleted statement reads:

- fever, pain or nasal congestion gets worse, or lasts for more than 3 days

We would appreciate your review of these two points.

Thank you for your assistance.

Thank you very much.

Maureen M Barron for

Paula J. Oliver
Senior Director, Regulatory Compliance
☎ 215-273-7878
Fax: 215-273-4049

Attachment

PJO/joc

F:\scook728.doc

*NO. PAGES (INCLUDING COVER SHEET):*