CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-603/S-001, S-002, S-003

ADMINISTRATIVE DOCUMENTS

MAR 4 1998

LABELING REVIEW OF NDA

NDA: 20-603(S-001)

Submission Date:	06/20/97
Received:	06/23/97
Review Date:	08/19/97
	10/09/97
	12/10/97
	01/15/98
	03/04/98

Applicant:	McNeil Consumer Products Company
Applicant's Representative:	Vivian Chester 215-233-7010 Willie D. Pagsuyin 215-233-7115
Drug:	Children's Motrin Drops (ibuprofen oral suspension) 40 mg/mL
Pharmacologic Category:	Pain Reliever/Fever Reducer
Submitted:	Special Supplement-Changes Being Effected Final draft labeling in full color scheme for: Cartons: ½ fl oz and ¼ fl oz; and Containers: same as above. Note: The ½ fl. oz is for retail sale. The ¼ fl. oz is a professional sample size.

Reviewer's Comments:

Final draft labeling in full color scheme for the ½ and ¼ fl oz product sizes was submitted for Children's Motrin Drops. The labeling represents changes made, in part, to incorporate a revised allergy warning and storage statement, as per FDA letter of March 31, 1997. The allergy warning and storage statement included in the submitted labeling are consistent with the March 31, 1997 letter.

In addition, to the changes recommended by the Agency, the

sponsor also:

1. Made changes to the "Uses" section to make the labeling consistent with their approved OTC labeling for Children's/Junior Strength Motrin Chewable Tablets (NDA 20-601, approved 11/15/96);

FROM:	*TO:*
USES:	**USES:**
For the Temporary Relief of:	**For Temporary:**
• **Fever**	• **Reduction of Fever**
• **Minor aches and pains** due to colds, flu, sore throat, headaches and toothaches	• **Relief of minor aches and pains** due to colds, flu, sore throat, headaches, and toothaches

2. Revised the declaration of net quantity of contents on all product labels from "x mL (x fl oz)" to "x fl oz (x mL)."

3. Added "Use enclosed dropper only" under the heading "DIRECTIONS."

4. Revised the "IMPORTANT" statement on the container from "See box for complete information and save for future use" to "See box for complete Warnings and other information and save box for future use."

5. Deleted the flag "New" on the front panel and sell copy on the side panel.

6. Changed the color of the bar around "For Ages 2-3" from gold to pink.

These changes are satisfactory and should be approved as submitted.

Recommendations:

1. An **APPROVAL** letter should be sent to the sponsor requesting the submission of final printed labeling.

2. The **APPROVAL** letter should also request that the sponsor revise the labeling at the time of next printing or within 180 days, whichever comes first, as follows:

New or Revised language is highlighted.

A. Read Product Information Statement (All cartons)

Read all product information before using. Keep this box for important information. This product is intended for use in children ages 2-3 years.

B. Headings (All cartons and containers)

All headings and information presented in all capital letters (IMPORTANT, ACTIVE INGREDIENT, USES, DIRECTIONS, WARNINGS, SHAKE WELL BEFORE USING, ASPIRIN SENSITIVE CHILDREN, CALL YOUR DOCTOR IF, DO NOT USE, and AGE, WEIGHT, AND DOSE in the dosing table) should be revised to upper and lower case.

C. Use statement: (All cartons and containers

The "Uses" section should be revised as follows:

Uses: Temporarily:
- Reduces fever
- Relieves minor aches and pains due to the common cold, flu, sore throat, headaches, and toothaches

D. Directions (All cartons and containers)

A fifth statement should be added under "Directions" as follows:

5. If stomach upset occurs while taking this product, give with food or milk.

E. Dosing Table (All cartons and containers)

The dosing table should be revised as shown.

Weight (lb)	Age (yr)	Dose (mL)
Under 24	Under 2	Consult Doctor
24-35	2-3	2 Dropperfuls (2.5 mL)
One Dose Last 6-8 Hours		

D. Aspirin Sensitive Statement (All cartons and containers)

Aspirin Sensitive Children: Although this product does not contain aspirin, it may cause a severe reaction in people allergic to aspirin. Do not give to children who have had any of the following reactions to any pain reliever/fever reducer:

- **allergic reaction**
- **difficulty breathing**
- **shock**
- **asthma**
- **hives**
- **swelling**

(Note: the entire "Aspirin Sensitive Statement" should be in bold type.)

The following information should be deleted from the "Aspirin Sensitive" warning.

Children's MOTRIN can cause serious reactions similar to those listed above, requiring immediate medical attention. These reactions can occur after taking a single dose or any subsequent dose in persons both with, and without, a prior reaction to Children's MOTRIN or other pain reliever/fever reducer.

E. Call Your Doctor If Statements (All containers and cartons)

- Stomach upset gets worse or lasts

(Statement to immediately follow bullet concerning a lack of relief or worsening of symptoms.)

F. Stomach Upset statement (All cartons)

The following statement should be deleted.

If stomach upset occurs while taking this product, give with food or milk. If stomach irritation gets worse or lasts, call your doctor.

The above revisions are recommended to increase the consistency of labeling of Children's OTC ibuprofen products.

/S/

Marina Y. Chang, R.Ph.
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/S/

Ida Yoder, M.S.
Chemist, HFD-560

/S/

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CC: NDA 20-603
HFD-560/Div Files
HFD-560/Div Dir /S/ 3/30/98
HFD-560/Dep Dir /S/ received 3/30/98 3/9/98
HFD-560/Team Leader /S/ 3/4/98
HFD-560/Neuner___
HFD-560/Yoder
HFD-560/Chang
HFD-560/Mason

LABELING REVIEW OF NDA SUPPLEMENT

NDA: 20-603
SUPPLEMENT: SLR-002

JAN 11 1999

Submission Date:	June 1, 1998
Received:	June 2, 1998
Review Date:	July 29, 1998
Amended:	November 18, 1998
Amended:	December 1, 1998

Applicant: McNeil Consumer Healthcare
7050 Camp Hill Road
Fort Washington, PA 19034

Applicant's Representative: Vivian A. Chester
Vice President, Regulatory Affairs
(215-233-7010)

Drug: Children's Motrin Ibuprofen Drops
Ibuprofen oral suspension, 50 mg/1.25mL

Pharmacologic Category: Pain reliever/fever reducer

Submitted: Special Supplement-Changes Being Effected-Labeling Changes
Final color labeling for the Children's Motrin Drops - ½ fl oz (15 mL), ¼ fl oz (7.5 mL) bottle/carton

Reviewer: Stephanie A. Mason
Reviewer's Comments:

Final color labeling for Children's Motrin Drops, ½ fl oz (15 mL), ¼ fl oz (7.5 mL), was submitted as changes being effected. The submitted labeling represents the following changes:

1. Revised language to Aspirin Warning Statement.

Reviewer's comments: The change is not acceptable. The Agency has completed its evaluation relating to potential allergic reactions, including those in aspirin-sensitive individuals, and has recommended the following warning statements: (Refer to letter dated September 15, 1998.)

> **Allergy alert**: ibuprofen may cause a severe allergic reaction which may include:
> • hives • facial swelling • asthma (wheezing) • shock
>
> **Do not use** if you have ever had an allergic reaction to any other pain reliever fever reducer.

Stop use and ask a doctor if an allergic reaction occurs. Seek medical help right away.

For pediatric products, the heading of "Aspirin Sensitive Children" will no longer be used. In addition, for products with drug fact format labeling, the last two warning statements must be placed under their respective subheadings as the first bulleted statement.

2. Incorporated the following changes per FDA's June 12, 1998 letter:

a. The phrase: "7. If stomach upset occurs while taking this product, give with food or milk," located under the "**DIRECTION**" section.

b. A fourth bullet statement under the "**CALL YOUR DOCTOR IF**" section: "Stomach upset gets worse or lasts."

Reviewer's Comments: These changes are acceptable. However, the sponsor did not revise labeling in this supplement to reflect the other following changes per the FDA's approval letter dated June 12, 1998, for 20-603/S-001:

c. Under the heading "Read Product Information" statement": "The product is intended for use in children ages 2-3 years.

d. Under "Heading': Change all headings (e.g., IMPORTANT, ACTIVE INGREDIENTS etc.) And information presented in all capital letters to be revised to upper and lower case.

e. Under the "Uses" statement - Align bullets and revise to read:

Temporarily:
- reduces fever
- relieves minor aches and pains due to the common cold, flu, sore throat, headaches, and toothaches

f. Under "Dosing Table" the header Dose (mL) should follow, and on the second line, column 3, (2.5 mL) should follow 2 Dropperfuls.

3. Revised the **DIRECTION** section to improve product dosing instructions (bolding shows changes):

"**DIRECTIONS:**
1. **Shake well before using.**
2. Find right dose on chart below. If possible use weight to dose; otherwise use age.
3. **Only use enclosed dropper; fill to prescribed level and dispense liquid slowly into child's mouth, toward inner cheek.**
4. **Replace original bottle cap to maintain child resistance.**
5. If needed, repeat dose every **6-8 hours.**
6. Do not use more than **4 times a day.**
7. **If stomach upset occurs while taking this product, give with food or milk.**

[Dosing Chart]

"**Attention: Specially designed for use with enclosed dropper. Use only enclosed dropper to dose this product. Do not use any other dosing device.**"

Reviewer's Comments: These changes are acceptable.

4. Strengthened the overdose warning under the "**IMPORTANT**" section of the labeling:

> "**IMPORTANT**:
> **Do not exceed recommended dose**. Taking more than the recommended dose (overdose) may not provide more relief and could cause serious health problems. **Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately**."

Reviewer's comments: This is not acceptable. The header "Important" should be deleted. The phrase "Do not exceed recommended dose . . ." should be revised to read "Do not take more than directed" and placed under the "Directions" section as the first bullet. The second sentence following "Do not exceed recommended dose" should be deleted.

5. Other following revisions: (1) advising consumers that they can contact other health care professionals about the product. and (2) alphabetized all inactive ingredients, including colorants under the "**INACTIVE INGREDIENT**" section.

Reviewer's Comment: This is acceptable.

6. The sponsor added "Concentrated" to the Children's Motrin Drops name to better differentiate the product in name from the less concentrated Children's Motrin Suspension.

Reviewer's Comment: This is acceptable.

7. The tamper-evident statement on the label has been revised to read:

> "**DO NOT USE:**
> **If plastic bottle wrap imprinted "Safety Seal®" and "Use With Enclosed Dropper Only" is broken or missing**.

*The labeling has been changed because a plastic carton overwrap has been included as a new tamper evident feature. The inner foil cap liner is no longer heat sealed.

Reviewer's Comment: This change is acceptable.

This reviewer notes that the sponsor removed the Statement of Identity - "Fever Reducer/Pain Reliever" from the top panel of the carton and replaced with "Read Instructions Carefully." In addition, the statement "See New Label" has been added to the PDP.

Recommendations:
An approval letter should be sent to the sponsor stating the following:

1. The "Aspirin Sensitive Children" statement should be replaced with the "Allergy alert" in accordance with the Agency's September 15, 1998 letter; within the time frame outlined in that letter.

2. The header "Important" should be deleted. The phrase "Do not exceed recommended dose . . ." should be revised to read "Do not take more than directed." This should be placed under the "Directions" section as the first bullet. The second sentence following "Do not exceed recommended dose" should be deleted. This can be done at the next printing or within 180 days, whichever comes first.

3. The sponsor will be expected to modify their label to conform with the OTC Labeling Format Final Rule once published.

4. The flag statement "See New Label" should be removed after 6 months.

5. The storage statement should be modified to conform with the current recommendation given by the Division of New Drug Chemistry which states: "Store at 20-25°C (68-77°F)."

/S/

Stephanie A. Mason
IDS, HFD-560

/S/

Debbie Lumpkins, Team Leader
Microbiologist, HFD-560

cc:
NDA 20-603
HFD-560/Div Files
HFD-560/Mason
HFD-560/Rothschild
HFD-560/Div Dir:
HFD-560/Dep Dir:11/30/98
HFD-560/Team Leader:11/23/98
R/D:SMason:7/9/98
Redrafted:7/29/98
Revised:9/10/98:10/21/98:11/18/98
F/T:sam:12/1/98

APR 15 1999

LABELING REVIEW OF NDA SUPPLEMENT

NDA: 20-603
SUPPLEMENT: SE5-003

Submission Date:	June 15, 1998
Received:	June 15, 1998
Review Date:	March 9, 1999
Amended:	March 19, 1999
Amended:	March 25, 1999
Amended:	March 31, 1999

Applicant: McNeil Consumer Healthcare
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Applicant's Representative: Vivian A. Chester, Vice President
Regulatory Affairs, (215-233-7010)

Drug: Children's Motrin
(ibuprofen oral suspension) Drops 50 mg/1.25mL

Pharmacologic Category: Fever reducer/pain reliever

Submitted: Efficacy Supplement - draft labeling carton/bottle size ½ fl oz (15 mL) - berry-flavored

Reviewer: Stephanie A. Mason

Background: Under Section 505A(c) of the Federal and Cosmetic Act and 21 CFR 314.70(b), the sponsor submitted information requesting expansion of the approved age group for the Children's Motrin Drops product to include dosing instructions for children 2 months to 3 years of age by adding dosing instructions for children 2 months to less than 2 years of age. The sponsor also requested approval to change the current product name to Infants' Motrin Concentrated Drops to better reflect the intended population of use and to differentiate the product in name from the less concentrated NDA 20-516 Children's Motrin suspension (100 mg per 5 mL). The sponsor submitted representative labeling to reflect the carton bottle component of a single size only, intended to illustrate the proposed change.

Reviewer's comments:

1. Per the Agency's September 15, 1998 letter, the following revisions need to be made: (1) Modify the allergy warning to state "Allergy alert: ibuprofen may cause a severe allergic reaction which may include: ▪ hives ▪ facial swelling ▪ asthma (wheezing) ▪ shock. (2) under the "**Do not use**" section, the first bulleted statement should read "if you have ever had an allergic reaction to any OTC pain reliever/fever reducer" and under "**Stop use and ask a doctor if**" section, the first bulleted statement should read "an allergic reaction occurs. Seek medical help

right away."

2. The sore throat warning (see § 201.315) will need to be included in the labeling and listed with the appropriate subheading highlighted in bold type.

3. The sponsor has removed the age reference "For Ages 2-3" that was located at the top of the principal display panel because this is now inappropriate given the new proposed name of the product, i.e., Infants' Motrin Concentrated Drops ibuprofen oral suspension, 50 mg 1.25 mL. This is acceptable.

4. The sponsor added a new warning "your child is under 4 months of age and has a fever. Fever may be sign of serious illness and prompt medical attention is especially important in this age group" under the "**Call your doctor if**" section. This added warning has been deleted because the product will not be approved for that age range. Also, deleted was the statement "Always Call Doctor For Fever in Child Under Age 4 Months." This subheader was deleted because it is obsolete.

5. In the approved labeling for Children's Motrin Drops, the bottle label contained the statement of identity (i.e., pharmacological category, fever reducer/pain reliever). However, on the draft labeling submitted, this information was not present. The sponsor should include the statement of identity on the bottle label.

6. The tamper-evident statement "Do not use if plastic bottle wrap imprinted 'SAFETY SEAL' and 'USE WITH ENCLOSED DROPPER ONLY' is broken or missing" is located on the top flap panel of the carton. Per § 201.66(c)(7), the agency will continue to allow flexibility as to where the statement appears in the labeling and is not requiring that it be included within the "**Drug Facts**" area. However, if the statement is included in the "**Drug Facts**" area, it should be placed under "**Other information**."

7. The flag statement "See New Label" on the carton's principal display panel should be deleted after six months of marketing.

8. The word "the" should precede "common cold" in the second bulleted statement under the **Uses** section.

9. The sponsor submitted a proposed dosage chart to provide dosing for the following age ranges: 2 to 3 months, 4 to 11 months, 12 to 23 months, and 2 to 3 years. This is not acceptable. Concerns about the safety of treating fever in children as young as 2 months without consulting a physician make dosing directions for that young an age group unacceptable. Further, we are not convinced that the proposed additional warning would be heeded by consumers. At the present time, the agency will allow dosing directions down to 6 months of age as this is the lowest age that is supported by the data submitted in this application. To avoid the potential for

overlapping within the age ranges, the agency recommends that the sponsor delete the age ranges under 2 months, 2 to 3 months, and 2 to 3 years of age from the dosage chart. Thus, the product should only be labeled for ages 6 months to 23 months of age.

10. A new subheading "**Ask a doctor before use if the child has**" has been added and the following bullets have been included under this heading:

- not been drinking
- lost a lot of fluid due to continued vomiting or diarrhea
- problems or serious side effects from taking fever reducers or pain relievers
- stomach pain

11. Concerning the immediate container bottle label, the active ingredient(s) and purpose(s) should be retained on the bottle label. Per the final rule, for products that are sold with an outer package, the Agency encourages manufacturers to try to meet all of the labeling requirements in this rule on the immediate container as well. If the immediate container is too small to meet the format requirements, the agency encourages manufacturers to include the required information as provided in the small package format in § 201.66(d)(10). The sponsor will also need to delete the age ranges for under 2 months, 2 to 3 months, and 2 to 3 years of age from the dosage chart as well as the statement located under the chart which reads "Always Call Doctor For Fever in Child Under Age 4 Months."

12. The statements under the dosage chart have been deleted. The statement "▪ do not use with any other device" has been added as an additional bulleted statement under **Directions**. The statement "use only the enclosed dropper" was already a bulleted statement.

Additional Recommended Changes Per the OTC Proposed Labeling Requirements; Final Rule dated March 17, 1999 (64 FR 13254):

1. All headers (drug facts, active ingredient(s), uses, warnings, directions, other information, dietary information, and inactive ingredient(s)) should be bolded, italicized, and flush with the left margin except for the header "Purpose." The first letter of the first word of each heading and subheading shall appear in upper case, all other words will be lower case. In addition, all colons following headers and subheaders should be deleted.

2. Section 201.66(c)(1) requires the title "**Drug Facts**" as the first heading in the standardized format. If the drug facts labeling appears on more than one panel, the title "Drug Facts (continued)" shall appear at the top of each subsequent panel containing such information.

3. Section 201.66(c)(3) requires the heading "**Purpose**" or **Purposes**," followed by the general pharmacological category(ies) or the principal intended actions of the drug of each active ingredient.

4. The dosage unit stated in the directions for use (e.g., in each 1.25 mL) should be in parenthesis and follow the heading "**Active ingredient.**"

5. All applicable warnings (such as the allergy alert and sore throat warning) should be listed with the appropriate subheading highlighted in bold type. Thus, the bulleted statement concerning sore throat located under the subheading "**Call your doctor if**" has been deleted and placed under a separate warning heading (see prototype attached). In addition, the header "**Directions**" is not in the required order and should be listed after the header "Warnings."

6. The sore throat warning (see § 201.315) will need to be included in the labeling and listed with the appropriate subheading in bold type.

7. The sponsor should delete the numerals and replace with bullet points to distinguish each piece of information found under each heading and subheading. The bullet style is limited to uniform solid squares or circles.

8. Under § 201.66(d)(8) of the final rule for OTC labeling requirements, a horizontal line is required to separate the information under each major heading.

9. The sponsor will need to revise their subheadings and place them in the required order as stated in final rule for OTC labeling requirements (see § 201.66(c)). For example, "Do not use," "Ask a doctor before use if the child has," "Ask a doctor or pharmacist before use if the child is," When using this product," and "Stop use and ask a doctor if."

10. Warnings to be placed under the "**Do not use**" subheading are for absolute contraindications for the use of the product. The bulleted statement "for more than 3 days for fever or pain unless directed by a doctor" should be deleted from under the "**Do not use**" section. The revised bulleted statement "fever or pain gets worse or last more than 3 days" should be located under the new subheading "**Stop use and ask a doctor if.**"

11. A new subheading "**Ask a doctor or pharmacist before use if the child is**" has been added and the subheading "**Call your doctor if**" has been deleted. The bulleted statements "your child is under a doctor's care for any serious condition." "taking any other drug (has been added), and your child is taking any other product that contains ibuprofen or any other pain reliever/fever reducer" are now located under the new subheading. The bulleted statements "problems or serious side effects from taking fever reducers or pain relievers," "lost a lot of fluid due to continued vomiting or diarrhea and "not been drinking" are now located under the subheading "**Ask a doctor before use if the child has.**" All other bulleted statements previously located under "**Call your doctor if**" and not mentioned above, are now located under the new subheading "**Stop use and ask a doctor if.**"

12. The "Keep out of reach" warning in § 330.1(g) has been modified to read "**Keep out of reach of children**. In case of overdose, get medical help or contact a Poison Control Center right away."

13. The header "**Important**" should be deleted. The phrase "Do not exceed recommended dose..." should be revised to read "Do not take more than directed." This should be placed under the "**Directions**" heading as the first bullet. The sentence following "Do not exceed recommended dose" (e.g, taking more than recommended....) should be deleted.

14. The statement "**Read all product Information** ...." may remain on the back or side panel of the outside container or wrapper of the immediate container label but the sponsor should separate the statement so that it does not intermingle with the required information section. (See § 201.66(e) of the OTC labeling requirements final rule.)

15. Concerning the tamper-evident statement "Do not use if plastic bottle wrap imprinted 'SAFETY SEAL' AND 'USE WITH ENCLOSED DROPPER ONLY' is broken or missing" the Agency continues to allow flexibility as to where this statement appears in labeling and is not requiring that it be included within the "**Drug Facts**" area. However, if the statement is included in the "**Drug Facts**" area, it should be placed under "**Other information**." (See § 201.66(c)(7).)

16. A new bolded and italicized subheading "**Other information**" has been added with the recommended storage instructions for all OTC drug products following.

17. The storage statement located on both the carton and bottle label needs to be modified to conform with the current recommendations for all OTC drug products given by the Division of New Drug Chemistry to read: "Store at 20-25°C (68-77°F)."

18. The term "artificial flavors" should be the first ingredient listed under **Inactive ingredients.**

19. The flag statement "See New Label" should be deleted after six months of marketing.

Recommendations: The labeling is approvable contingent upon agreement of the following revisions requirements. The prototype does not reflect true specifications (i.e., font, typeface and size) that are required in the OTC labeling Requirements final rule. The sponsor will be responsible for inserting this information in their future labeling submission within the time frames stated in that rule.

1. The sponsor will need to modify its allergy warning to conform with the Agency's recommended Allergy alert warning as stated in a letter dated September 15, 1998, requiring that the warning be implemented within the time frame outlined in that letter. In addition, the sponsor will need to also add the two warning statements below as the first bulleted statement under the respective subheadings. They are as follows:

Allergy alert: ibuprofen may cause a severe allergic reaction which may include:
- hives - facial swelling - asthma (wheezing) - shock

Do not use
- if you have ever had an allergic reaction to any other pain reliever/fever reducer

Stop use and ask a doctor if
- an allergic reaction occurs. Seek medical help right away

2. The sponsor will need to delete all references to the ages ranging from "under 2 months," "2 to 3 months," and "2 to 3 years" from the labeling. The product should be labeled only for children 6 months to 23 months of age.

3. The sore throat warning (see § 201.315) will need to be included in the labeling and listed with the appropriate subheading in bold type.

4. The sponsor will need to revise the warning regarding dehydration to read as follows:

Ask a doctor before use if the child has
- lost a lot of fluid due to continued vomiting or diarrhea
- not been drinking

5. The storage statement should be modified to conform with the current recommendations for all OTC drug products given by the Division of New Drug Chemistry to read: "Store at 20-25°C (68-77°F)."

6. The flag statement "See New Label" should be deleted after six months of marketing.

7. The labeling will need to be modified to conform with the proper format and content as required by the OTC labeling format final rule, which published on March 17, 1999, (64 FR 13254), within the time frames stated in the final rule. The sponsor should try to meet all of the labeling requirements in the final rule for OTC on the immediate container as well. If the immediate container is too small to meet the format requirements, the sponsor may include the required information as provided in the small package format in § 201.66(d)(10) as stated in that rule.

8. Final printed labeling should be submitted for all packaging that the sponsor intends to market.

/S/
Stephanie A. Mason, IDS

/S/
Debbie L. Lumpkins, Microbiologist
Team Leader 3

cc:
NDA 20-859
HFD-560/Div File
HFD-560/K. Rothschild
HFD-560/D. Lumpkins:3/16/99:3/18/99:3/25/99
HFD-560/S. Mason
HFD-560/Yoder
HFD-560/Dr. L. Katz:3/16/99:3/23/99:3/29/99 /S/
HFD-560/Dr. D. Bowen:3/16/99
HFD-560/Dr. R. Neuner:4/8/99 /S/
R/D:SMason:3/5/99:Revised:3/17/99:3/31/99
F/T:LKatz:sam:4/7/99

U.S. Food and Drug Administration
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation-III

APR 22 1999

OTC Consult

To: Rosemarie Neuner, M.D., M.P.H.

/S/

Through: Arzu Selen, Ph.D., Dep. Director, Div. of Pharmaceutical Evaluation-III

From: E. Dennis Bashaw, Pharm.D., DPE-III 4/22/99

4/22/99

Date: 04/22/99

Re: NDA 20-603, Children's Motrin Age Range Supplement (SES-003)

Background

This supplement has been submitted by the applicant to allow for OTC dosing of ibuprofen down to the age of 2months. In this submission the sponsor cites the recommendation of an Non-Prescription Drugs Advisory Committee (NDAC) meeting in Nov. 1997 which indicated that data may exist to lower the current OTC labeled dosing regimen from 2yrs to a lower value. In this supplement, the applicant is providing supportive information to lower the age range down to 2mos. old. This supplement has been referred to the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products for comment. The pharmacokinetic issues have been referred to the Division of Pharmaceutical Evaluation-III for comment.

Available Pharmacokinetic (PK) /Pharmacodynamic (PD) Data

As part of their supplement the sponsor has provided copies of 12 articles developed from a literature search on the pharmacokinetics of ibuprofen in children <2yrs old (see attached table 1). Of these 12 articles, eight of them are in fact abstracts of papers that were presented at scientific meetings and contain no primary data of any value. The remaining four articles have been previously reviewed by this reviewer as part of a presentation given by this reviewer at the Nov. 1997 advisory committee. A brief overview of each article will be presented below:

Article 1: Rey, E, et al. Stereoselective disposition of ibuprofen enantiomers in infants., Br. J. of Clin. Pharmacol., 1996; 38, 373-375.

As noted in the title this article is primarily about the disposition of ibuprofen enantiomers in infants. A total of 11 infants between the ages of 6 to 18months were given a single dose of ~7.6mg/kg of ibuprofen syrup following minor surgery. Blood samples were collected for 8 hrs after dosing and analyzed using a stereo-specific method for ibuprofen. The results of this study are attached as attachment 2. Unfortunately the authors while providing individual data for each infant in the study did not provide the ages, such that it is unclear what the distribution of ages. Lacking the both the age data and an older control group, this data is of little value for the extension of dosing below the age of 6mos.

Article 2: Brown, R., et al Single-dose pharmacokinetics of ibuprofen and acetaminophen in febrile children., J. Clin. Pharmacol., 1992; 32, 231-241.

This article compared the pk of ibuprofen and acetaminophen in febrile children, aged 3mos-12yrs. A total of 158 febrile infants were either given ibuprofen 5mg/kg (n=49), ibuprofen 10mg/kg (n=50), or acetaminophen 12.5mg/kg (n=54). In this article the authors give a wealth of pharmacokinetic data as derived parameters. No raw data was presented, nor was there a breakdown of ages for any of the treatment groups. The closest that the authors approach the effect of age is to say that there was no statistical difference in the pharmacokinetics of children <2.5yrs old compared to those older than

2.5yrs. It was noted that there was a pharmacodynamic difference between younger children in the study and recommended that future studies be done to evaluate these differences.

Article 3: Kauffman, RE, Nelson MV, Effect of age on ibuprofen pharmacokinetics and antipyretic response., J. Pediatr., 1992; 121, 969-973

This study looked at the pk and pd of ibuprofen in 49 subjects between the age of 3mos and 10.4 yrs. Following the diagnosis of a febrile illness, a single 8mg/kg dose of ibuprofen suspension was administered to all subjects. Following dosing, plasma samples were collected for up to 8 hrs post-dose. Pk analysis was conducted on 38 of the 49 infants (9 did not fit the model selection criteria, and 2 had erratic pd results). While the mean pk data was reported in this article, again no analysis by age was provided. While the authors indicate that there was not a statistical difference in pk parameters across age, without a clear idea as to the distribution of the data (i.e., how many subjects were below 6mos, 9mos, 1yr, etc.), this conclusion is of dubious validity for the purposes of extending the dosage range.

Article 4: Kelley, M., et al. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children., Clin Pharmacol Ther., 1992; 52, 181-189.

This study followed the pk and pd effect of ibuprofen and acetaminophen in children between the ages of 11months and 11.5yrs. A total of 36 subjects completed the trial and 33 had evaluable pk and pd datasets. The three subjects that did not have complete data were dropped due to sampling errors. A total of 18 subjects received a single dose of 6mg/kg of ibuprofen while the other 18 subjects received a single mean acetaminophen dose of 11.6mg/kg. In this report individual demographic, pk and pd data was provided for both study groups. This article is clearly the most useful article from a pk/pd standpoint, however, the age range used (11mos-11.5yrs) is not relevant to the question at hand, i.e., extending the dose range.

Discussion

Examination of the provided pk/pd information provided by the sponsor confirms the conclusion reached at the Nov. 1997 NDAC meeting. Namely that there is little pk data in children below the age of two. The data of Rey, E., et al does, however, suggest that the pk of ibuprofen does not change over the age range of 6mo to 18mo. Abundant pk data in children above the age of two does exist in the McNeil ibuprofen database (NDA 20-135, ibuprofen chewable tablets). There is also a fairly large clinical experience using ibuprofen in this population (6mos-2yrs old). At best the pk database is weakly supportive of the extension of dosing to a 6mo. age group. There is absolutely no pk data to support the extension of dosing down to 2mo. of age. Given that various authors, including those summarized above, have detected a difference in dynamic response in the very young, extension of dosing without supportive data is not supportable from either a regulatory or public health standpoint. While such dosing may be safe, the scientific database, from a pharmacokinetic standpoint does not exist.

Recommendation

Based on the information presented by the applicant, there is no supportive pk data for the extension of ibuprofen OTC dosing to the 2-month-old population. Limited pk data (1 article in 11 infants) is available to suggest that there are no significant pharmacokinetic differences between the ages of 6 and 18 months. Provided that acequate safety data exists in the clinical database, the Division of Pharmaceutical Evaluation-III supports the lowering of OTC ibuprofen dosing down to 6 months of age. We do not believe that further age reductions are possible given the available data.

CC: NDA 20-603(ORIG)
HFD-560/Lumpkins
HFD-560/Neuner
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy
HFD-880 (DRUG FILES)

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

Debra L. Bowen, MD
Acting Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Boulevard, Room S-212
Rockville, MD 20850

APR 15 1999

Re: Infant's Motrin Concentrated Drops
NDA 20-603/S-003
Revised Commitment Letter

Dear Dr. Bowen:

We acknowledge your fax of 4/15/99 (copy attached) regarding S-003/NDA 20-603. As requested, we agree to the following:

- Labeling described in your fax of 4/15/99 will serve as a basis of approval for S-003;
- Submit Final Printed Labeling consistent with the above.

We trust we have adequately responded to your request. Should you have any questions, please call me at (215) 273-7115.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Willie D. Pagsuyoin
Director, Regulatory Affairs

WDP:dtg
Attachment

cc: Kerry Rothschild (HFD-560)
p:\nda\corresp\bowen3.doc

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

Debra L. Bowen, MD
Acting Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Boulevard, Room S-212
Rockville, MD 20850

APR 1 4 1999

Re: NDA 20-603/S-003
Children's MOTRIN® Oral Drops

Dear Dr. Bowen:

We acknowledge your fax of 4/14/99 (copy attached) regarding S-003/NDA 20-603. As requested, we commit to the following:

1. Labeling outlined in your fax will serve as a basis of approval for S-003/NDA 20-603. with the following revisions:

   Elimination of the word "OTC" from the instructions to not use the product if the child "has ever had an allergic reaction to any OTC pain reliever/fever reducer".

   Addition of the word "is" to the end of the following subheading: "Ask a doctor or pharmacist before use if the child"

   Under the above subheading, elimination of the word "OTC" in the phrase, "taking any other product that contains ibuprofen, or any other OTC pain reliever/fever reducer."

2. Final printed labeling identical to the labeling described herein will be submitted to FDA.

We trust we have adequately responded to your request.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Paula DeLuis For
Willie D. Pagsuyuin
Director, Regulatory Affairs

WDP:dtg
Attachment
p:\nda\corresp\bowen4.doc

cc: Kerry Rothschild (HFD-560)

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

APR 13 1999

Debra L. Bowen, MD
Acting Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Boulevard, Room S-212
Rockville, MD 20850

Re: Children's Motrin Drops
NDA 20-603/S-003
Response to FDA Comments

Dear Dr. Bowen:

We refer to your fax of 4/12/99 (copy attached) which outlined FDA proposed changes to our draft labeling for Children's Motrin Drops. We agree to the changes outlined by FDA in your fax of 4/12/99, as modified below (changes in italics):

A. We acknowledge FDA's recommended alternate name, Baby Motrin Concentrated Drops; however, our preference is to market this product with our original proposed name of Infant's Motrin Concentrated Drops.

B. For clarity, we propose the following change under Important section:

From: **Read all product information before using. Keep this box for important information. This product is intended for use in ages 6 months to 23 months of age.**

To: **Read all product information before using. Keep this box for important information. This product is intended for use *in children* ages 6 months to 23 months.**

C. For clarity, we propose the following changes Under Warnings:

From: **Sore throat warning**: severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician.

To*: **Sore throat warning**: severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult *a doctor* promptly. Do not use more than 2 days or administer to children under 3 years of age *for sore throat* unless directed by a *doctor.*

*Please note that we have changed any reference from "physician" to "doctor".

From: **Ask a doctor before us if the child has**...not been drinking

To: **Ask a doctor before use if the child has**...not been drinking *fluids*

D. We have included the warning if stomach upset lasts or gets worse in the Stop use and ask a doctor section, as follows:

From: **Stop use and ask a doctor if**...stomach pain gets worse or lasts

To: **Stop use and ask a doctor if**...stomach pain *or upset* gets worse or lasts

E. For clarity, we propose the following changes Under Directions:

From: **Directions**...do not take more than directed

To: **Directions**...do not *give* more than directed

From: **Directions**...use only the enclosed dropper. Do not use any other dosing device. Fill to prescribed level.

To: **Directions**...use only *with* enclosed dropper. Fill to *dose* level. Do not use any other dosing device.

To emphasize the importance of using only the appropriate device to dose the product, we wish to include this information under Directions, as well as retain the current information following the dosing chart, i.e., "**Attention: Specifically designed for use with enclosed dropper. Use only enclosed dropper to dose this product. Do not use any other dosing device.**"

F. To be consistent with the 3/17/99 Final Rule on OTC labeling requirements for human drugs, we propose moving information concerning action to take in the event of stomach upset with use of the product to the appropriate subheading:

"**When using this product**, give with food or milk if stomach upset occurs."

Therefore, this information is deleted from the Directions section (as last bullet: "if stomach upset occurs while taking this product; give with food or milk").

For your convenience, we have attached revised, draft labeling with the above changes. We trust we have adequately responded to your request. Should you have any questions, please call me at (215) 273-7115.

Sincerely,

McNEIL CONSUMER HEALTHCARE

Willie D. Pagsuyoin
Director, Regulatory Affairs

WDP:dtg
Attachment

cc: Kerry Rothschild (HFD-560)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-603/S-003

JUN 18 1998

McNeil Consumer Products
Camp Hill Road
Fort Washington, PA 19034

Attention: Vivian A. Chester
Vice President, Regulatory Affairs

Dear Ms. Chester:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Children's Motrin® (ibuprofen oral suspension) Drops

NDA Number: 20-603

Supplement Number: S-003

Date of Supplement: June 15, 1998

Date of Receipt: June 15, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 14, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Over-the-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Maria Rossana R. Cook, M.B.A.
Chief, Project Management Staff
Division of Over-the-Counter Drug Products, HFD-560
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-603/S-003
HFD-560/Div. Files
HFD-560/CSO/Mason, S.

SUPPLEMENT ACKNOWLEDGEMENT

NDA NO. 20603 SUPP. NO. 003
NDA SUPPL FOR SE5

McNEIL

ORIGINAL

McNEIL CONSUMER PRODUCTS COMPANY, 7050 CAMP HILL ROAD, FORT WASHINGTON, PA 19034-2299 (215) 233-7000

JUN 15 1998

Debra L. Bowen, MD
Director
Division of Over-the-Counter Drug Products (HFD-560)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: Children's MOTRIN® (ibuprofen oral suspension) Drops, 50mg/1.25mL
NDA 20-603
Supplemental New Drug Application - Priority Review Requested

SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Dr. Bowen:

In response to the FDA letters of June 8 and 11, 1998 (copies attached), and in accordance with 21 CFR 314.70(b), we are submitting an SNDA requesting an expansion of the approved age group for Children's Motrin Drops product to include dosing instructions for children two months to two years of age. In addition, this SNDA requests approval to change the current product name to Infants' Motrin Concentrated Drops to better reflect the intended population of use and to differentiate the product in name from the less concentrated Children's MOTRIN Suspension.

This request is consistent with the well established ibuprofen efficacy and safety in children with over eight years of prescription use and over two years of use as an OTC medication. Efficacy support for children less than two years of age is provided by prescription labeling for Motrin drops and suspension products which are currently indicated for the relief of fever and mild to moderate pain in children six months and older. In addition, numerous randomized controlled trials demonstrating the efficacy of ibuprofen have included children as young as two months of age. The widespread use of OTC pediatric ibuprofen products has established that ibuprofen has a safety profile appropriate for expanding OTC availability to include children as young as two months.

Data confirming the OTC safety of pediatric ibuprofen in children less than two years of age from a special subgroup analysis of more than 27,000 children from the Boston University Fever Study provide pivotal support for this labeling change. Further support is provided by recommendations regarding pediatric OTC dosing and labeling from meetings

of the FDA Nonprescription Drugs Advisory Committee. Specifically, on September 18, 1997, NDAC recommended specifying a minimum patient age of two months for which dosing instructions should appear on OTC labeling of pediatric ibuprofen liquid products.

It is well-recognized that physicians recommend pediatric analgesics for children under two years of age. Availability of OTC dosing instructions for the drops product for children as young as two months of age should enhance the safe use of this product in this young age group by allowing consumers to validate verbal dosing recommendations from physicians and other health care providers and help to minimize potential miscommunication in this regard. The proposed additional consumer dosing instructions are outlined in the attached labeling which also includes warnings that would direct the consumer to consult a doctor concerning fever in children less than four months of age; these warnings address the potential risks in this age group.

Under the provisions of the new section 505A of the FD&C Act, we believe this SNDA would be entitled to an additional six months of exclusivity beyond the expiration of Children's Motrin exclusivity on June 16, 1998. In particular, new section 505A(c) provides for an additional six months of exclusivity if the Secretary requests pediatric studies and the studies are completed. Importantly, this provision does not appear to be limited to studies conducted after the date of enactment. This SNDA provides the information requested by the agency in its Written Request correspondence of June 8 and 11, 1998. Therefore, it complies with this provision, especially in the light of the fact that it relies upon pivotal data (a new subgroup analysis) from the Boston University Fever Study, a randomized, double-blind, office-based, acetaminophen-controlled study involving 84,000 children. This study was sponsored and funded solely by McNeil Consumer Products Company.

In view of the important medical benefits the added OTC dosing instructions for younger children would offer consumers, we request a priority review of this SNDA. Please call me at (215) 233-7010 if you have any questions regarding this supplemental application.

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester

Vivian A. Chester
Vice President, Regulatory Affairs

cc: M. Weintraub, MD, HFD-550 (letter only)
D. Sporn, HFD-600 (letter only)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
McNeil CONSUMER HEALTHCARE

DATE OF SUBMISSION
APR 13 1999

TELEPHONE NO. *(Include Area Code)*
(215) 273-7115

FACSIMILE (FAX) Number *(Include Area Code)*
(215) 273-4049

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
Camp Hill Road, Fort Washington PA 19034

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-603

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Ibuprofen

PROPRIETARY NAME *(trade name)* IF ANY Children's MOTRIN Oral Drops

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*

CODE NAME *(if any)*

DOSAGE FORM: Drops

STRENGTHS: 40mg/mL

ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: For the temporary relief of fever and minor aches and pains due to colds, flu, sore throat, headaches and toothaches

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Corres: Response to FDA Comments

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Willie D. Pagsuyuin, Director, Regulatory Affairs	APR 13 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Camp Hill Road, Fort Washington, PA 19034	(215)273-7115

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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