CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-448

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

CONSULTS:

Division	Consult Date	Status	Comment
Division of Biopharmaceutics	28Jun94	Pending	dissolution method and specification
Division of Biometrics	25May94	Pending	expiration dating 18 mo. stability data
	07Feb95	Pending	expiration dating 36 mo. stability data.

REMARKS/COMMENTS:
McNeil is responding to deficiencies noted in the "Approvable" letter of September 27, 1994 from chemistry review #1. The deficiency questions are reviewed under the appropriate section of the review format. The alpha-numeric designation of the deficiency questions have been maintained.

The consult to the Division of Biopharmaceutics regarding the dissolution test method and specification for the chewable tablet remains outstanding.

The consult to the Division of Biometric regarding an "approvable" expiration dating period remains outstanding.

The deficiency questions with regard to the environmental assessment were not addressed. McNeil has requested a meeting to clarify requirements (see Cover Letter of AC Amendment 13Dec94).

CONCLUSIONS & RECOMMENDATIONS:
This application is "approvable" (AE). The major outstanding deficiencies are McNeil's request to store coated granulation and compressed tablets up to two years before marketing without reducing the expiration date. The adequacy of the sampling plan to assure the drug product will have the appropriate quality remains to be resolved. The environmental assessment deficiencies have not been addressed.

3/9/95

George Chen, Ph.D.
Review Chemist, HFD-180

3/9/95

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:
HFD-20-448
HFD-180/Division File
HFD-180/SFredd
HFD-181/CSO
HFD-180/GChen
R/D Init: JGibbs/3-6-95
GC/dob DRAFT 3-6-95\F/T 3-8-95\WP: c:\wpfiles\chem\N\20448501.2GC

McNEIL

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

ORIG AMENDMENT
ORIGINAL

MAY 20 1994

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 23 1994
HFD-180

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IMODIUM® A-D (loperamide HCl) Chewable Tablet, 2 mg
NDA 20-448
Amendment to New Drug Application

Dear Dr. Fredd:

We are submitting this amendment in follow up to a telephone discussion between Kati Johnson and Paula Oliver on May 9, 1994. Each item requested and discussed will be separately addressed.

1. Package Interchangeability Protocol.

2. Submit a completed batch record for one of the primary stability batches.

   A copy of the completed batch record for Batch C-130-9H (the biobatch) is provided as Attachment 1.

3. Bio Comments
   a. Provide detailed methodology of grinding procedure for dissolution.

5/31/94

c. Conduct a dissolution study using whole, unchewed tablets.

Data are provided as Attachment 2. Two different lots of finished product were tested.

4. Issuance of FD-483 Round Rock, TX plant during the last inspection.

As provided via FAX on 5/9/94, Round Rock was inspected in October, 1992 and an FD-483 was issued. A copy of the FD-483 was included with our 5/9/94 FAX to the division. Duplicate copy is provided as Attachment 3.

Additional Information

As discussed between Kati Johnson and Paula Oliver on 5/17/94, we are also providing updated hard copy stability data for all packages included in the application (Attachment 4).

If you have any questions on the attached, please contact Paula J. Oliver at (215) 233-7878.

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester

Vivian A. Chester
Executive Director, Regulatory Affairs

cc: (letter only) Kati Johnson

F:\fredd3.ltr

McNEIL

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

MAY 13 1994

ORIG AMENDMENT

ORIGINAL

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IMODIUM® A-D (Loperamide HCl) Chewable Tablet, 2mg
NDA 20-448
Amendment to New Drug Application

Dear Dr. Fredd:

As requested in a telephone conversation with Kati Johnson, CSO, on April 29, 1994, we are providing the following:

- Statistical analysis for loperamide in the finished product and SAS data sets.
- Statistical analysis covering 18 month stability data of product packaged in vials at our Round Rock, TX plant and SAS data sets.

If there are any questions, please contact Paula J. Oliver at (215) 233-7878.

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester

Vivian A. Chester
Executive Director, Regulatory Affairs

PJO:dtg
Attachments

cc: Kati Johnson (letter only)

5/18/94

5/18/94

McNEIL

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

ORIGINAL

APR 21 1994

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IMODIUM® A-D (Loperamide HCl) Chewable Tablet, 2 mg
NDA 20-448
Amendment to New Drug Application

Dear Dr. Fredd:

As requested in a telephone conversation with Kati Johnson, CSO, we are providing a statistical analysis summary of stability data and PC-SAS data sets for our 2 mg chewable tablet.

If there are any questions on the attached, please give me a call at (215) 233-7878.

Very truly yours,

Paula J. Oliver

Paula J. Oliver
Director, Regulatory Affairs

PJO:dtg

Attachment

cc: (letter only) Kati Johnson, CSO

F:\fredd6.ltr

4/26/94

Cpe 1/1

NDA 20-448

MAR 22 1994

McNeil Consumer Products Company
Attention: Ms. Vivian A. Chester
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Chester:

We have received your new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Imodium A-D (Loperamide) Chewable Tablets

Date of Application: March 14, 1994

Date of Receipt: March 15, 1994

Our Reference Number: NDA 20-448

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)(1) of the Act on May 14, 1994 in accordance with 21 CFR 314.101(a).

If the application is filed, the regulatory due date is September 10, 1994.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact me at (301) 443-0487.

Sincerely yours,

kj 3/22/94

Kati Johnson
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA 20-448
HFD-180
HFD-181/CSO
DISTRICT OFFICE
kj/March 22, 1994/c:\wp51\cso\n\20448403.0kj
ACKNOWLEDGEMENT

0-8 54-71

McNEIL

ORIG AMENDMENT

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

DEC 14 1994

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D DEC 14 1994 HFD-180

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IMODIUM® A-D (Loperamide HCl) Chewable Tablets
NDA 20-448
Amendment #6

Dear Dr. Fredd:

In response to your letter of September 27, 1994 (copy attached), we are submitting the enclosed amendment to our pending NDA for IMODIUM® Chewable Tablets. This amendment provides responses to the drug substance and drug product items. For ease of review, each request is reiterated in bold type followed by our response.

In addition to the responses provided in this amendment, we have requested a meeting with the Division to discuss the comments pertaining to the environmental assessment (meeting request submitted 10/31/94). Also, the comparative dissolution information requested by the biopharmaceutics reviewer was submitted on 11/16/94.

Should there be any questions on the material provided in this submission, please contact Paula J. Oliver at (215) 233-7878.

Sincerely,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester

Vivian A. Chester
Executive Director, Regulatory Affairs

JAU:dtg

cc: (Field Copy) Debra Pagano, Philadelphia District Office
(Letter only) Kati Johnson, CSO (HFD-180)

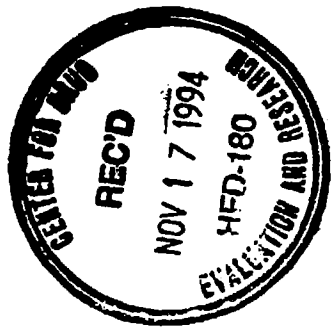
12/22/94

V DIV 21

McNEIL

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

NOV 16 1994



Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IMODIUM® A-D (Loperamide HCl) Chewable Tablets
NDA 20-448
Amendment No. 5

Dear Dr. Fredd:

In response to the biopharmaceutics items listed in your letter of September 27, 1994 (copy attached), we are submitting the enclosed amendment to our pending NDA for IMODIUM® Chewable Tablets. This amendment provides the comparative dissolution information requested by the biopharmaceutics reviewer. For ease of review, each request is reiterated in bold type followed by our response.

We are responding to the drug substance, drug product and environmental assessment items contained in your letter of September 27, 1994 separately.

If there are any questions on the material provided in this submission, please contact Paula J. Oliver at (215) 233-7878.

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Paula J Oliver for

Vivian A. Chester
Executive Director, Regulatory Affairs

JAU:dtg

cc: Biopharmaceutics Reviewer
(Letter only) Kati Johnson, CSO (HFD-180)

11/22/94

11/14/94

0 54

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 15, 1995

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Loperamide Chewable Tablets, Biopharmaceutics Review dated 3/13/95.

TO: NDA 20-448

In the 3/13/95 Biopharmaceutics review several comments are brought to my attention for resolution.

First, the directions for use in the approvable labeling will not prohibit water or state the chewable tablet can be taken without water.

Second, the recommended product release specifications have been sent to the sponsor.

Third, since the chewable formulation is bioequivalent to the reference Imodium capsules, I am not sure why greater systemic exposure is postulated or why chewable tablets would be less effective in the presence of diarrhea. Based on the bioequivalence study we expect the same clinical profile with the new formulation compared to previously approved formulations.

Stephen Fredd, M.D.

cc:
HFD-180
HFD-426/Dr. Pradhan
HFD-181/CSO/KJohnson
HFD-180/SFredd: 3/15/95
f/t deg: 3/15/95
MEMO\NDA20448.0SF

ORIG AMENDMENT

McNEIL ORIGINAL

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

MAR 15 1995

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IMODIUM® A-D (Loperamide HCl) Chewable Tablets, 2 mg
Correspondence to NDA 20-448
Revised Draft Labeling

Dear Dr. Fredd:

Attached is revised draft labeling for our 2 mg chewable tablet. A representative carton (12 tablets) is being provided for review. The labeling for other package sizes (6's, 18's, 24's, pouch 2) would be consistent with the attached labeling.

This revised "draft" labeling differs slightly from the labeling in our original NDA submission dated March 14, 1994. The minor changes we have made include the following:

PRINCIPAL DISPLAY PANEL

- "Chewable Tablets" has been changed to:

  "ChewTab Tablets"

- "NEW! Chewable Tablets only from Imodium A-D" has been changed to:

  "NEW! ChewTab Tablets only from the makers of Imodium A-D"

BACK PANEL

- Only from Imodium A-D, new Chewable Tablets for effective diarrhea relief often in one dose. Imodium A-D Chewables are:

  - The original prescription strength power of Imodium A-D in a uniquely formulated tablet.

3/24/95

- Convenient and easy to take without water.
- Labeled effective for Travelers' Diarrhea.
- Available in great tasting mint tablets.

The above has changed to:

- "Only from the makers of Imodium A-D, new ChewTab Tablets are uniquely formulated chewable tablets that provide effective diarrhea relief often in one dose.
    - Imodium A-D ChewTabs offer the convenience of a chewable so they are easy to take without water.
    - ChewTabs contain the original prescription strength of Imodium A-D for effective diarrhea relief you can count on.
    - Imodium A-D ChewTabs are available in a great tasting mint flavor.

The remainder of the labeling is consistent with our originally submitted labeling of 3/14/94.

Should there be any questions or comments on the attached, please contact Paula J. Oliver at (215) 233-7878.

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester
Executive Director, Regulatory Affairs

PJO:dtg
Attachments

cc: Kati Johnson, CSO (HFD-180)
\fredd11.ltr

CN 3-1

NDA 20-448

MAR 15 1995

McNeil Consumer Products Company
Attention: Paula Oliver
Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Oliver:

Please refer to your pending March 14, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imodium A-D (Loperamide HCL) Chewable Tablets.

We also refer to your amendments dated April 21 and 26, May 13 and 20, November 16, December 13, 1994 and January 27, 1995.

We have completed our review of the chemistry, manufacturing and controls section of your submissions and have the following comments and requests:

A. Specifications

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

We would appreciate your prompt written response so we can continue our evaluation of your application.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

KJ 3/15/95
SBF 3/15/95

cc:
Original NDA 20-448
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
HFD-180/GChen
R/D init: KJohnson 3/14/95
GChen 3/14/95
JGibbs 3/14/95
SFredd 3/14/95
DISTRICT OFFICE

drafted: kj/March 10, 1995/c:\wpfiles\cso\n\20448503.0kj

INFORMATION REQUEST (IR)

(with disk)

McNEIL ORIG AMENDMENT

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

JAN 27 1995

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

CENTER FOR DRUG
REC'D
JAN 30 1995
HFD-180
EVALUATION AND RESEARCH

RE: IMODIUM® A-D (Loperamide HCl) Chewable Tablets
NDA 20-448
Amendment No. 7

Dear Dr. Fredd:

In response to a discussion with Kati Johnson regarding updated stability data on this product, we are providing the attached data. It covers product that has been packaged in vials, blisters and pouches, and includes results through 34-35 months under 15°C - 30°C storage conditions. An evaluation of the data demonstrates a stable formulation in all packages.

In addition, we have provided the SAS dataset files on disk as requested.

If there are any questions, please contact Paula Oliver at 215/233-7878.

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester

Vivian A. Chester
Executive Director, Regulatory Affairs

cc: Kati Johnson, CSO (HFD-180) (letter only)
Debra Pagano (Philadelphia District Office) (without disk)

fredd.ltr

2/6/95

5.1

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-448

MAY 14 1996

Name of Drug: Imodium A-D (loperamide HCL) Chewable Tablets

Sponsor: McNeil Consumer Products

Material Reviewed

Content: Revised Draft Labeling

Submission Date(s): March 21, 1996

Receipt Date(s): March 22, 1996

Background and Summary Description: This application was submitted March 14, 1994 to market a chewable tablet formulation of Imodium A-D, currently approved in liquid (NDA 19-487) and caplet (NDA 19-860) formulations. The application was AE March 15, 1995 pending a satisfactory response to a chemistry, manufacturing and controls information request (IR) letter dated March 15, 1995 and final printed labeling identical in content to marked-up draft enclosed with the AE letter. The firm responded to the IR letter in a submission dated December 21, 1995, and the new user fee due date is June 22, 1996.

On March 21, 1996 the firm submitted revised draft labeling reformatted in accordance with the Nonprescription Drug Manufacturers Association comments submitted in response to an FDA Federal Register notice dated August 16, 1995 relating to improving communication of information in nonprescription drug labeling. The changes include the use of a bullet point format, rephrasing certain text using simpler language, and placing information in a different order. The Division of Over-the-Counter Drug Products reviewed the labeling for format and content and compared it to the currently approved labeling for Imodium A-D Caplets. Their review is attached, and the comments are reflected herein.

Review

1. The dosage form identification was changed from "Chewable Tablets", used in the draft labeling in the initial submission, to "ChewTab Tablets" in the current revised draft labeling. The Division of Over-the-Counter Drug Products recommended returning to the use of "Chewable Tablets" because they considered it less confusing. While this argument may be true, prohibiting use of the identification "ChewTabs" may be inconsistent with prior practice since non-USP dosage form titles have been included in the proprietary names for Imodium A-D Caplets (NDA 19-860) and Imodium A-D

Gelcaps (NDA 20-352).

To maintain consistency with prior practice, the firm will be permitted to use the dosage form identification "ChewTabs".

2. The heading, "INACTIVE INGREDIENTS" was moved to the bottom panel and changed to "ALSO CONTAINS".

The new heading fails to identify the listed ingredients as inactive and is therefore unacceptable. The heading "INACTIVE INGREDIENTS" should be retained.

3. The heading "ACTION" was added to the back panel to describe the statement of identity.

The heading "PURPOSE" is more clear and should be used in place of "ACTION".

4. In his review dated March 13, 1995, biopharmaceutics reviewer Rajendra Pradhan, Ph.D., noted that the protocol of bioequivalence Study 118 required the chewable tablets to be dosed with 200 ml of water. However, the proposed labeling includes the statement, "convenient to take anytime, anywhere", implying that water is not needed. Dr. Pradhan expressed concern about possible buccal absorption and toxicity when the chewable tablets are administered without water and stated that the bioavailability of the product when taken without water could not be evaluated from the data provided by Study 118. The Division of Over-the-Counter Drugs concurred with Dr. Pradhan's concerns.

The statement "convenient to take anytime, anywhere" should be deleted from the back panel, and the "DIRECTIONS" should instruct patients to take the tablets with water.

5. The term "Second Dose" is used in the "DOSAGE" section on the back panel to specify all doses after the first dose.

The term "Second Dose" is vague and possibly confusing. The term "Next Dose" should be substituted.

6. The "DIRECTIONS" headings reads:

   - Take the first dose after the first loose stool.
   - If needed, take the second dose after each subsequent loose stool.

- o Drink plenty of clear fluids to help prevent dehydration, which may occur with diarrhea.

This information could be stated more clearly and completely. The following revision is recommended:

See the chart below for the correct dose

- **o Chew the first dose and take with water after the first loose stool.**
- **o If needed, chew the next dose and take with water after the next loose stool.**
- **o Drink plenty of clear liquids to prevent dehydration.**

7. The pregnancy warning specified in 21 CFR 201.63 has been shortened to, "Do Not Use Without Asking a Doctor: If you are pregnant or nursing a baby."

Per the cited regulation, this is unacceptable. The text should be revised as specified in 21 CFR 201.63.

8. The general overdose warning specified in 21 CFR 330.1(g) has been shortened to, "Keep out of reach of children".

Per the cited regulation, this is unacceptable. The text should be revised as specified in 21 CFR 330.1(g).

9. It is stated on the back panel that the lot number and expiration date appear on the side panel. Their location is not clearly marked.

The location of the expiration date and lot number should be more clearly marked.

Conclusions

The recommendations stated above will be incorporated into the marked-up draft labeling to accompany the approvable letter.

Consumer Safety Officer

5/14/96
concur

cc:
Original
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Stephen B. Fredd, M.D.

draft: BS/May 8, 1996/c:\wpfiles\reviews|20448605.0
r/d Initials: M.Walsh/May 10, 1996
S.Fredd/May 10, 1996
final: BS/May 14, 1996

CSO REVIEW

5.1

NDA 20-448

JUN 14 1996

McNeil Consumer Products
Attention: Vivian Chester
7050 Camp Hill Road
Fort Washington, Pennsylvania 19034

Dear Ms. Chester:

Please refer to your pending March 14, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imodium® A-D (loperamide HCl) Chewable Tablets.

We also refer to your amendments dated September 22, and December 21, 1995 and March 11, 1996.

We have completed our review of the chemistry, manufacturing and controls section of your submission and have the following comments, recommendations, and requests concerning the drug product:

A. Method of Manufacture: In-process Controls & Tests

B. Regulatory Specifications

2. Your proposed dissolution specification is acceptable.

For your revised dissolution method, provide your standard method for preparation of the crushed tablet.

C. Stability

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
(301) 443-0483

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-448
HFD-180/Div. Files
HFD-181/SO/BStrongin
HFD-180/GChen GC 6/14/96
HFD-180/EDuffy
HFD-820/Yuan Yuan Chiu (only for CMC related issues)

drafted: BS/May 24, 1996/c:\wpfiles\n\20448605.0
r/d Initials: EDuffy/6-14-96 EDUFFY 6/14/96
BS/GC/dob **F/T 6-14-96**/WP: C:\wpfiles\chem\N\20448605.agc

BS 6-14-96

INFORMATION REQUEST (IR)

BP 6/14/96

APPEARS THIS WAY
ON ORIGINAL

McNEIL

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

DEC 21 1995

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
BC (EA)

DEC 22 1995
HFD-180

RE: IMODIUM® A-D Chewable Tablets, 2mg
NDA 20-448
Amendment No. 9

Dear Dr. Fredd:

This amendment to NDA 20-448 for IMODIUM® A-D Chewable Tablets provides responses to the chemistry review comments in your letter dated March 15, 1995. For ease of review, each item is reiterated in bold type followed by our response.

At this time, we are also submitting a revised environmental assessment. It addresses comments in your letters dated September 27,1994 and March 15, 1995. To aid in the review process, we are providing a guide at the beginning of this section. If there are any questions on the information provided in this submission, please contact Janet A. Uetz at (215) 233-8368 or me at (215) 233-7010.

Very truly yours,

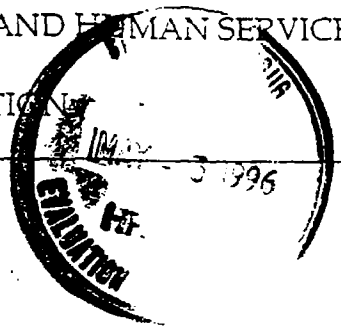
McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester
Executive Director, Regulatory Affairs

Attachment
cc: Brian Strongin, CSO (HFD-180) (letter only)
cc: Deborah Pagano (District Office)
\mmb130

12/22/95

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION



DATE: MAY 2 1996

FROM: Division of OTC Drug Products (HFD-560)

SUBJECT: Labeling Review for Imodium A-D Chewable Tablets (NDA 20-448)
And Imodium A-D Gelcap 2 mg (NDA 20-352)

TO: Director
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

We have reviewed the revised draft labeling for these products submitted by McNeil Consumer Products Company on March 21, 1996. We have no record of having reviewed draft labeling for either NDA previously. We have the following comments and suggestions:

1. In our view, "ChewTab" is more confusing than the word "Chewable." We recommend use of the word "Chewable" instead of "ChewTab." Your chemist should determine if "GELCAPS" is an acceptable term in place of capsules.

2. The heading "ALSO CONTAINS" is unacceptable. The heading "INACTIVE INGREDIENTS" should be retained.

3. We believe some better use could be made of the space at the top of the back panel to enable the print size of the back panel to be a little larger. There is a lot of duplicate information by having the words "anti-diarrheal," "ChewTab Tablets," and "only from the makers of Imodium A-D, ChewTab Tablets:" in this area. This section could use a more efficient design of the information conveyed. We prefer use of the word "Purpose" in place of the word "Action." Although the new labeling format is not in effect yet as a regulation, "action" has not been suggested yet as a term to use to describe the statement of identity.

4. In consideration of the Biopharm review, the directions should state to take the chewable tablets with water because this was one of the conditions under which the study protocol was performed. It is not clear to us whether the same labeling would be necessary for the gelcaps

5/15/96

dosage form. Also, the words about taking "anytime, anywhere" should be deleted because they infer that the product may be taken without water and may give the impression that the product is for unlimited use.

5. The term "second" dose is vague and differs from pre-existing draft labeling and labeling for the previously approved liquid product (NDA 19-487). Because more than one "second" dose could be taken, we recommend use of the term "next" dose. We believe the text part of the directions section could be more clearly stated. For the gelcaps, we recommend the following: "Adults and children 12 years and over: Take two gelcaps (with water?) after the first loose stool. If needed, take 1 gelcap (with water?) after the next loose stool. Drink plenty of clear liquids to prevent dehydration."

   For the chewable tablets, we recommend the following: "See chart below for correct dose. Chew the first dose and take with water after the first loose stool. If needed, chew the next dose and take with water after the next loose stool. Drink plenty of clear liquids to prevent dehydration."

   Please note that we suggest use of the word liquids in place of fluids although fluids has been used in the OTC labeling since the product was switched. We believe that liquids is more consumer friendly and the more appropriate word based on the dictionary definitions of these words. We also suggest shortening the dehydration statement as noted above.

6. There is no current provision in the regulations to shorten the general pregnancy warning (21 CFR 201.63) or the first part of the general overdose warning (21 CFR 330.1(g) or 21 CFR 369.9). Please follow the CFR language.

7. It is stated on the back panel that the expiration date appears on the side panel, but the location is not clearly marked. Also, the location of the lot number is not marked.

APPEARS THIS WAY
ON ORIGINAL

8. Compliance needs to review the blister labeling.

Debra Bowen, M.D.

Arthur Baker, M.D.

Helen Cothran

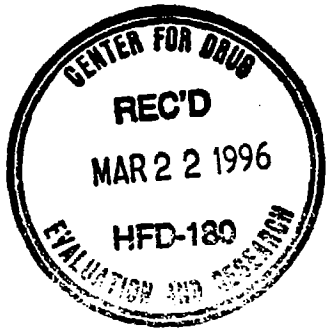
Gerald M. Rachanow, P.D., J.D.

McNEIL

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

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MAR 21 1996



ORIG AMENDMENT
BL

RE: IMODIUM® A-D Chewable Tablets
NDA 20-448
Amendment No. 11

Dear Dr. Fredd:

In response to your 3/15/95 approvable letter (copy attached), we are submitting revised draft labeling for your review. We have elected to reformat the labeling to make the information on the package more "user friendly" for consumers to read and understand. The front panel and the information on the back panel are consistent with the labeling submitted 3/14/94. The following changes have been made:

FRONT PANEL

1. The dosage form is identified as "ChewTab Tablets".

2. The flag on the principal display panel is now centered in the middle of the front panel and reads "NEW! Great Tasting Mint Chewable".

3. The phrase "Original Prescription Strength" has been moved from the flag to below the phrase "Controls the Symptoms of Diarrhea".

BACK PANEL

1. The back panel has been reformatted in accordance with the NDMA comments to FDA Docket No. 95N-0259 on OTC labeling dated 11/15/95. The recommended sequence of information and bullet point format have been applied. In some cases the language has been rephrased to use shorter words or to accomodate bullet point headings.

2. Inactive Ingredients, under the new heading "ALSO CONTAINS", have been moved to the bottom flap.

3/22/96

Included with this submission are the following labeling pieces: a representative carton for a 6 count package, an enlarged carton back panel, blister backing, blister carton tray and a 2 count pouch.

Submission of this reformatted labeling was discussed with Brian Strongin, CSO. We trust that you will find it acceptable. If you have any questions regarding this submission, please contact Janet A. Uetz at (215) 233-8368 or me at (215) 233-7010.

Sincerely,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester

Vivian A. Chester
Vice President, Regulatory Affairs

cc: B. Strongin, CSO

jau048e

APPEARS THIS WAY
ON ORIGINAL

5.1

McNEIL

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

MAR 11 1996

Stephen B. Fredd, MD, Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

RE: IMODIUM® A-D Chewable Tablets, 2mg
NDA 20-448
Amendment No. 10

Dear Dr. Fredd:

This submission contains an amended environmental assessment (EA) for NDA 20-448 for the IMODIUM® A-D Chewable Tablets, 2mg. The revised EA has been prepared in accordance with the recent EA Guidance Document issued by the Agency entitled "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" (Federal Register, Vol. 61, No. 8, dated January 11, 1996, pages 1031-1032).

According to Section III.D.7.c of the Guidance Document, if an application meets Tier 0 criteria, format items 7, 8, 9, 10, 11 and 15 are unnecessary and can be omitted. Appendix 1 provides information demonstrating the Tier 0 circumstances for this application. A revised EA in which items 7, 8, 9, 10, 11 and 15 are omitted is provided in Appendix 2. The remaining information provided in the revised EA is identical to what was previously submitted.

Please note that Appendix 1 contains information considered confidential by McNeil Consumer Products Company. Appendix 2 is considered nonconfidential, except for Attachments 5, 10 and 13. If you have any questions regarding this information, please contact Janet Uetz at (215) 233-8368 or me at (215) 233-7010.

Very truly yours,

McNEIL CONSUMER PRODUCT COMPANY

Vivian A. Chester
Vice President, Regulatory Affairs

cc: N. Sager (HFD-357)
B. Strongin, CSO (letter only)

p:\jau037

3/15/96

McNEIL

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

OCT 14 1996

Stephen B. Fredd, M.D., Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: IMODIUM® A-D (Loperamide HCl) Chewable Tablets
NDA 20-448
Amendment #12

Dear Dr. Fredd:

In response to your letter of June 14, 1996 (copy attached), we are submitting the enclosed amendment to our pending NDA 20-448 for IMODIUM® Chewable Tablets. This amendment provides responses to questions and includes a revised Stability Protocol for Coated Granulation Holding Time and an amended Stability Section, to support our request for a 24 month Expiry Date. For ease of review each request is reiterated in bold type followed by our response.

We trust that you will find this response acceptable. If there are any questions, however, please contact Janet A. Uetz at (215) 233-8368 or me at (215) 233-7010.

Sincerely,

Vivian A. Chester

Vivian A. Chester
Vice President, Regulatory Affairs

Attachment
cc: B. Strongin, CSO (HFD-180)

P:\nda\corresp\fred130.rsp

10/24/96

NDA 20-448

McNeil Consumer Products Company
Attention: Janet Uetz
7050 Camp Hill Road
Fort Washington, PA 19034

JAN - 4 1996

Dear Ms. Uetz:

We acknowledge receipt on December 22, 1995 of your December 21, 1995 amendment to your new drug application for Imodium A-D (loperamide) Chewable Tablets.

The amendment contains additional chemistry information submitted in response to our March 15, 1995 approvable letter.

We consider this amendment major under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is June 22, 1996.

Should you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
Telephone: (301) 443-0483

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

cc:
Original NDA 20-448
HFD-180/Div. Files
HFD-80
HFD-180/CSO/B.Strongin

1/3/96

drafted: BS/January 3, 1996/c:\wpfiles\n\20448601.0
Final:

1/4/96

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

NDA 20-448

FEB - 7 1997

McNeil Consumer Products Company
Attention: Vivian Chester
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Chester:

We acknowledge receipt on January 27, 1997 of your January 24, 1997 amendment to your new drug application (NDA) for Imodium A-D (loperamide hydrochloride) Chewable Tablets.

This amendment contains additional chemistry, manufacturing and controls information submitted in response to our June 14, 1996 approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is July 27, 1997.

Should you have any questions, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

cc:
Original NDA 20-448
HFD-180/Div. Files
HFD-180/CSO/B.Strongin
HFD-180/E.Duffy
HFD-180/G.Chen
DISTRICT OFFICE

drafted: BS/February 5, 1997/c:\wpfiles\n\20448702.0
Final: S.Fredd/February 5, 1997

2/5-5-97

ACKNOWLEDGEMENT (AC)

2/5/97

APPEARS THIS WAY
ON ORIGINAL

NEW CORRESP

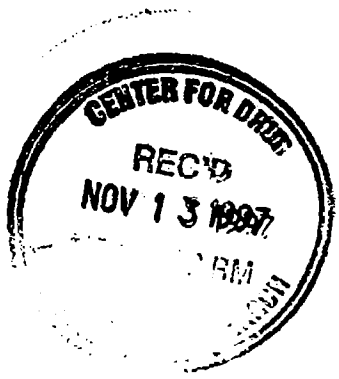
ORIGINAL

McNEIL

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

NOV 12 1997

Debra L. Bowen, MD
Director
Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Central Document Room N115
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850



RE: IMODIUM® A-D Chewable Tablets
NDA 20-448
Correspondence

Dear Dr. Bowen:

We are submitting updated patent information to NDA 20-448 for IMODIUM® A-D Chewable Tablets. US Patent No. 5,489,436 was issued on February 6, 1996. This patent covers coated loperamide HCl granules, which are used in the manufacture of IMODIUM® A-D Chewable Tablets. The full patent information and patent declaration are attached.

As requested in correspondence dated October 7, 1997, a copy of this submission is also being sent to the Division of Data Management and Services for use in publishing data in ***Approved Drug Products with Therapeutic Equivalence Evaluations*** (Orange Book).

If you have any futher questions, please call Janet A. Uetz at (215) 233-8368 or me at (215) 233-7010.

Very truly yours,

McNEIL CONSUMER PRODUCTS COMPANY

Vivian A. Chester

Vivian A. Chester
Vice President, Regulatory Affairs

cc: M.A. Holovac, R.Ph., Drug Information Services Branch, HFD-93
jau147

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-448

JUL 22 1997

Name of Drug: Imodium A-D (loperamide HCL) Chewable Tablets

Sponsor: McNeil Consumer Products Company

Material Reviewed

Submission Date(s): July 18, 1997

Receipt Date(s): July 22, 1997

Contents: Final Printed Labeling

Background and Summary Description

NDA 20-448 was submitted March 14, 1994 to market a chewable formulation of Imodium A-D, currently approved in liquid (NDA 19-487), caplet (NDA 19-860), and chewable tablets in combination with simethicone (NDA 20-606). The application was approvable March 15, 1995 and June 14, 1996 pending a satisfactory response to CMC information request letters and final printed labeling identical in content to marked-up draft attached to the letters. The firm submitted a complete response to the AE letter January 24, 1997 and FPL identical to the marked-up draft attached to the June 14, 1996 AE letter was included in the July 18, 1997 submission. This review will compare the FPL to the marked-up draft.

Review

The FPL was compared to the marked-up draft attached to the June 14, 1996 AE letter and found to be identical.

Conclusions

I recommend approval of this application.

Consumer Safety Officer

cc:
Original
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Lilia Talarico, M.D. 7-22-97

draft: BS/July 22, 1997/c:\wpfiles\reviews\n\20448707.0
final: BS/July 22, 1997

CSO REVIEW

McNEIL

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

Lilia Talarico, MD
Acting Director
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)
Document Control Room #6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

JUL 18 1997

RE: IMODIUM® A-D Chewable Tablets
NDA 20-448
Correspondence - Final Printed Labeling

Dear Dr. Talarico:

This submission forwards Final Printed Labeling for Imodium® A-D Chewable Tablets, which is consistent with the draft labeling submitted to NDA 20-448 on January 7, 1997 with the following exceptions:

- The phrase "Next Dose" has been revised to "Next Doses" under Directions,
- The word "also" has been deleted from the first bullet under Warnings and
- The word "corn starch" has been added to the list of inactive ingredients because it was previously inadvertently omitted.

Included in this submission are 20 press proofs of the 6 count carton and 20 press proofs of the 2 count pouches. Upon product launch, additional carton count sizes may be used. Any cartons with additional count sizes will be submitted in an Annual Report to this NDA.

If you have any further questions, please contact Janet A. Uetz at (215) 233-8368 or me at (215) 233-7010.

Very truly yours,

McNEIL CONSUMER PRODUCT COMPANY

Vivian A. Chester

Vivian A. Chester
Vice President, Regulatory Affairs

cc: B. Strongin, CSO
P:jau137

EXCLUSIVITY SUMMARY for NDA # 20-448 SUPPL # _____

Trade Name Imodium A-D Chewable Tablets Generic Name loperamide HCL
Applicant Name McNeil Consumer Products Company HFD-180

Approval Date July 25, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO /_X_/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   The sponsor submitted only Study 118, a bioequivalence study with the objective of determining bioequivalence between Imodium A-D Chewable Tablets and Imodium Capsules. This was a single dose, open-label, cross-over study without clinical endpoints.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-487 Imodium A-D Liquid

NDA # 19-860 Imodium A-D Caplets

NDA # 17-690 Imodium Capsules

NDA # 20-606 Imodium Advanced (loperamide/simethicone) Chewable Tablets

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /__/ NO /__/ Explain: _____

Investigation #2

IND # _____ YES /__/ NO /__/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

_____ 7/22/97
Signature Date
Title: Regulatory Health Project Manager

_____ 7-24-97
Signature of Division Director Date
Acting

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-448 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Imodium A-D Chewable Tablets (loperamide HCL) Action: (AP) AE NA

Applicant McNeil Consumer Prods. Therapeutic Class 3S

Indication(s) previously approved None. New Approval
Pediatric information in labeling of approved indication(s) is adequate X inadequate ___

Indication in this application Diarrhea including Traveler's Diarrhea (For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Brian Strongin — 7/22/97

Signature of Preparer and Title — Date

cc: Orig NDA/PLA/PMA # 20-448
HFD-180 /Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

APPEARS THIS WAY
ON ORIGINAL