CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-487/S-022

Name: Imodium A-D (Loperamide HCl) Liquid

Sponsor: McNeil Consumer & Specialty Pharmaceuticals

Approval Date: July 8, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-487/S-022

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-487/S-022

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-022

McNeil Consumer & Specialty Pharmaceuticals
Attention: Victoria Wagner-Weber
Associate Director, Regulatory Affairs
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms.Wagner-Weber:

Please refer to your supplemental new drug applications submitted March 5, 2004, received March 8, 2004, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for: Imodium® A-D (loperamide HCL) Liquid.

We also acknowledge receipt of your submissions dated June 9, June 30, July 1, and July 7, 2004.

This supplemental application proposes a reformulation of Imodium A-D liquid to an opaque, green liquid with a mint flavor.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

The final printed labeling (FPL) must be identical to the approved draft labeling (carton label principal display panel submitted March 5, 2004, and Drug Facts panel submitted July 1, 2004) and must be formatted in accordance with the requirements of 21 CFR 201.66.

We remind you to remove the phrase "NEW FORMULA" from the product labels after 180 days of OTC marketing.

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely yours,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Deputy Director
Division of Over the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brian Harvey
7/8/04 01:13:40 PM
Signed for Dr. Curtis Rosebraugh.

CENTER FOR DRUG EVALUATION AND RESEARCH

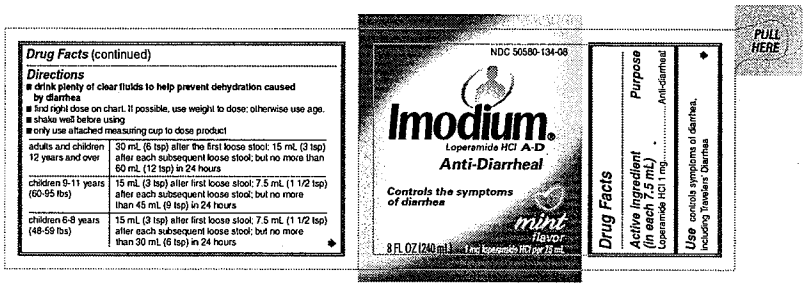
APPLICATION NUMBER:

NDA 19-487/S-022

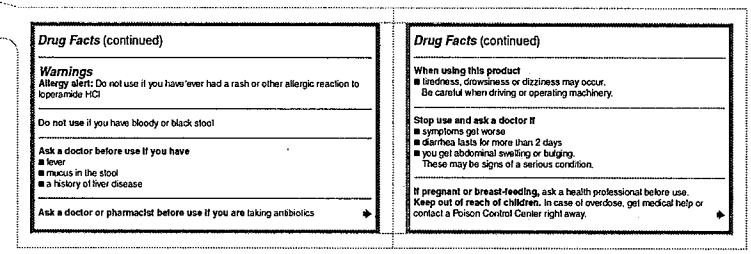
LABELING

NOTES:
1) DRAWING SHOWN PRINT SIDE UP.
2) TOLERANCES UNLESS SPECIFIED +/- 1/64.
3) BASED ON NATIONAL LABEL DRAWING NO. 1-04-4

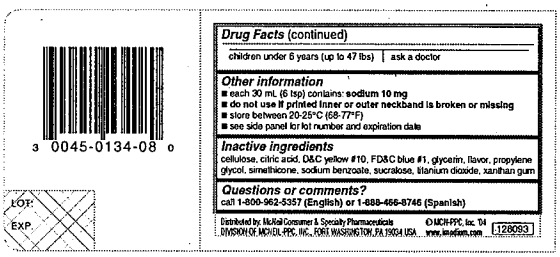
INIT.	NO.	DATE	REVISIONS	SVG NO. LB-PS-1057	McNeil Consumer & Specialty Pharmaceuticals, 7050 Camp Hill Road, Fort Washington, PA 19034
				DRAWN SKH	
				SCALE NONE	TITLE: LABEL
				DATE 1-26-04	IMODIUM 8OZ. BOTTLE
				APPROVED	



PAGE 4 COVER PAGE 1



PAGE 2 PAGE 3



BASE PAGE 5

Labeling Format Information:

Fonts: Helvetica regular, bold, and bold oblique.

Drug Facts:	8.5 pt	**Leading:**	6.5 pt
Header:	8 pt	**Bullets:**	5 pt
Subheader:	6 pt	**Barlines:**	2.5 pt
Body Text:	6 pt	**Hairlines:**	.5 pt
Drug Facts (continued):	8 pt		

Horizontal Scale: 80-85 % Average Kerning: -5

INFORMATION BLOCK

OUR DEPTH IS ODD STRENGTH

DESCRIPTION LBL BKLT IMODIUM A-D 8 OZ

FILE # 3005155 VERSION B-2

DATE JULY 1, 2004 CONT

PS IMAGE(S) NEW ART

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

DOMESTIC McN GAG 6/17/03 REV 2

THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL

NATIONAL PRINT BUYER INFORMATION BLOCK

NATIONAL PRINT BUYER:

PUT-UP NUMBER:

PART NUMBER:

DIE VINYL NUMBER:

NPA / PCN NUMBER:

FCC NUMBER:

PACKAGING LOCATION:

DOMESTIC COPY CLEARANCE APPROVAL BLOCK

McNeil Johnson & Johnson • MERCK

ARTWORK APPROVAL INITIAL BLOCK

	INITIALS	DATE
REGULATORY		
MEDICAL		

NOTES:

1) DRAWING SHOWN PRINT SIDE UP
2) ALL DIMENSIONS IN INCHES
3) TOLERANCE UNLESS SPECIFIED FRACTIONS ±1/32, ANGLES ±1°
4) [hatched box] LOT & EXP. DATE

				DWG. NO. LB-PS-1017	McNeil Consumer & Specialty Pharmaceuticals 7050 Camp Hill Road, Fort Washington, PA 19034
				DRAWN SKH	TITLE: LABEL, PS 1 X 3 1/2
				SCALE NONE	
SKH/JL	1	3/27/03	ADDED LOT & EXP. DATE AREA	DATE 3/14/03	
INIT.	NO.	DATE	REVISIONS	APPROVED	

Important: Read all product information before using. Keep the box for important information. *Use:* controls symptoms of diarrhea, including Travelers' Diarrhea *Warnings:* Allergy alert: Do not use if you have ever had a rash or other allergic reaction to loperamide HCl. Do not use if you have bloody or black stool. *Directions* • drink plenty of clear fluids to help prevent dehydration caused by diarrhea • find right dose on chart. If possible, use weight to dose; otherwise use age. • shake well before using • only use attached measuring cup to dose product. Adults and children 12 years and over: 30 mL (6 tsp) after the first loose stool; 15 mL (3 tsp) after each subsequent loose stool; but no more than 60 mL (12 tsp) in 24 hours. Children 9-11 years (60-95 lbs): 15 mL (3 tsp) after first loose stool; 7.5 mL (1 1/2 tsp) after each subsequent loose stool; but no more than 45 mL (9 tsp) in 24 hours. Children 6-8 years (48-59 lbs): 15 mL (3 tsp) after first loose stool; 7.5 mL (1 1/2 tsp) after each subsequent loose stool; but no more than 30 mL (6 tsp) in 24 hours. Children under 6 years (up to 47 lbs): ask a doctor. *Other information* • each 30 mL (6 tsp) contains: sodium 10 mg • do not use if printed inner or outer neckband is broken or missing • store between 20-25°C (68-77°F)

LOT:

EXP.

NDC 50580-134-01

Imodium®

Loperamide HCl A-D

Anti-Diarrheal

Controls the symptoms of diarrhea

1 FL OZ (30 mL)

mint flavor

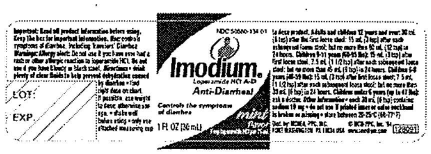
1 mg loperamide HCl per 7.5 mL

Dist. by: MCNEIL-PPC, INC. FORT WASHINGTON, PA 19034 USA

© MCN-PPC, Inc. '04 www.imodium.com

128091

200 % OF ACTUAL SIZE



Labeling Format Information:

Fonts: Helvetica condensed black oblique, condensed black, condensed bold.

Drug Facts:	NA pt	**Leading:**	4.9 pt
Header:	4.5 pt	**Bullets:**	4.5 pt
Subheader:	4.5 pt	**Barlines:**	NA pt
Body Text:	4.5 pt	**Hairlines:**	.5 pt
Drug Facts (continued):	NA pt		

Horizontal Scale: 75-77 %   Average Kerning: 0

INFORMATION BLOCK

OUR DEPTH IS OUR STRENGTH

DESCRIPTION LBL IMODIUM A-D 1 OZ

FILE # 3005150   **VERSION** D-1

DATE JULY 2, 2004   **CONT.**

PS IMAGE(S) NEW ART

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL.

NATIONAL PRINT BUYER INFORMATION BLOCK

NATIONAL PRINT BUYER:

PUT-UP NUMBER:

PART NUMBER:

DIE VINYL NUMBER:

NPA / PCN NUMBER:

FCC NUMBER:

PACKAGING LOCATION:

DOMESTIC COPY CLEARANCE APPROVAL BLOCK

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ARTWORK APPROVAL INITIAL BLOCK

INITIALS   **DATE**

REGULATORY

MEDICAL

Adhesive

Lot & Exp. Date

INIT.	NO.	DATE	REVISIONS

DWG. NO. LB-PS-1019

DRAWN SKH

SCALE NONE

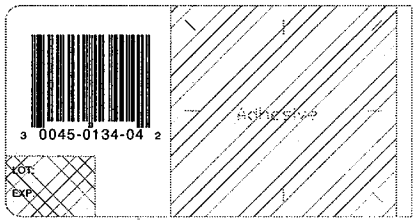
DATE

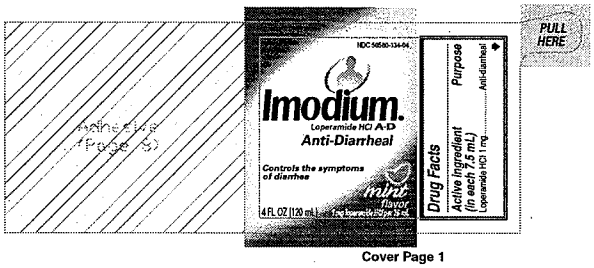
APPROVED

McNeil

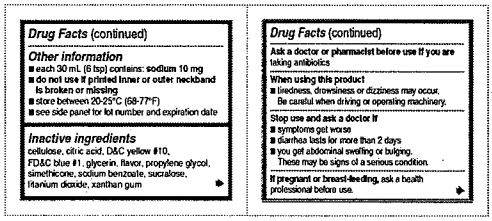
Consumer & Specialty Pharmaceuticals
7050 Camp Hill Road, Fort Washington, PA 19034

TITLE:
BOOKLET
IMODIUM 4 OZ.

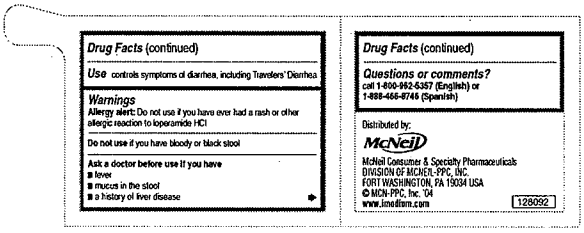




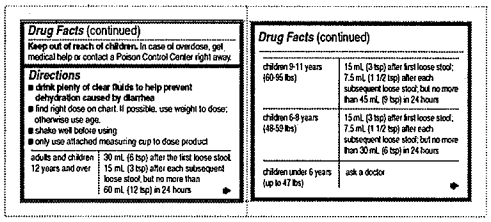
Cover Page 1



Page 6 Page 3



Page 2 Page 7



Page 4 Page 5

Labeling Format Information:

Fonts: Helvetica regular, bold, and bold oblique.

Drug Facts:	10 pt	Leading:	6.5 pt
Header:	8 pt	Bullets:	5 pt
Subheader:	6 pt	Barlines:	2.5 pt
Body Text:	6 pt	Hairlines:	.5 pt
Drug Facts (continued):	8 pt		

Horizontal Scale: 72-80 % Average Kerning: -10

INFORMATION BLOCK

OUR DEPTH IS OUR STRENGTH

DESCRIPTION LBL BKLT IMODIUM A-D 4 OZ

FILE # 3005156 VERSION A-2

DATE JULY 1, 2004 COI

PS IMAGE(S) NEW ART

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

DOMESTIC MKN GAG 041703 REV 2

THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL.

NATIONAL PRINT BUYER INFORMATION BLOCK

NATIONAL PRINT BUYER:

PUT-UP NUMBER:

PART NUMBER:

DIE VINYL NUMBER:

NPA / PCN NUMBER:

PCC NUMBER:

PACKAGING LOCATION:

DOMESTIC COPY CLEARANCE APPROVAL BLOCK

McNeil Johnson & Johnson • MERCK

ARTWORK APPROVAL INITIAL BLOCK

INITIALS DATE

REGULATORY

MEDICAL

NOTES:

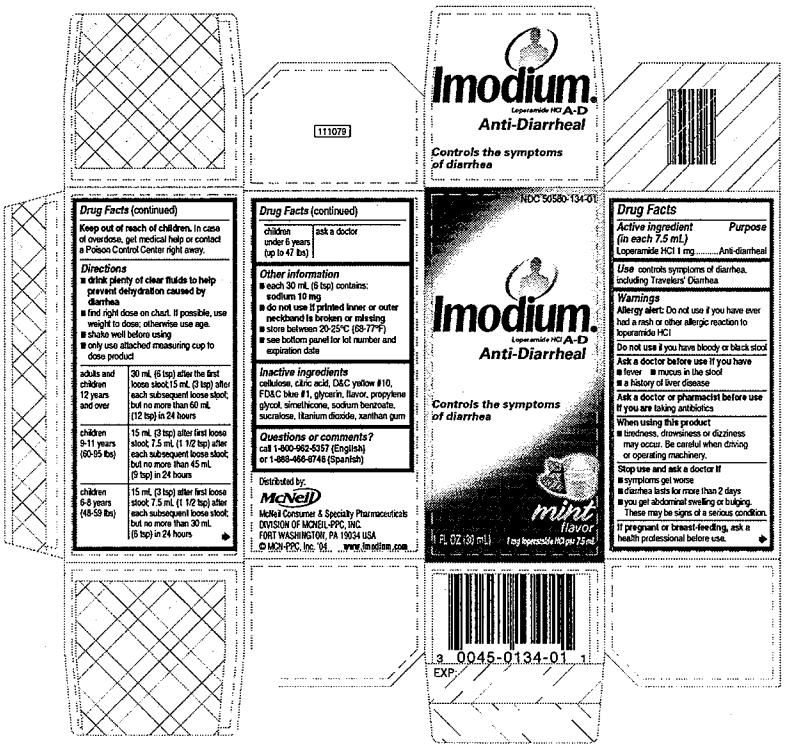
1) DRAWING SHOWN PRINT SIDE UP
2) ALL DIMENSIONS IN INCHES
3) TOLERANCES UNLESS SPECIFIED:
   FRACTIONS ±1/32
   ANGLES ±1°
4) --- NO PRINT
5) KNOCK OUT AREA
6) VISIONS BARCODE AREA.
7) EXP DATE AREA
8) LOT AREA

INIT.	NO.	DATE	REVISIONS
DM/SH	14	3/25/04	REMOVED KNOCKOUT AREAS / UPDATED NOTES.
ARS/TH	13	4/12/00	REVERSE BACK TO REV 10 LEV.
ARS/TH	12	4/10/00	REMOVED MANUF. AREA
ARS/HX	11	2/21/00	SPLIT LOT, EXP, MANUF
ARS/JG	10	12/1/99	ADDED NO VARNISH TO MIN FLAP
ARS/CM	9	8/12/98	SPLIT LOT & EXP AREA
ARS	8	6/25/97	ADDED DV INFO
EMP	7	7-6-93	ADDED VISION BARCODE AREA
EMP	6	7-23-92	ADDED LOT/EXP. DATE AREA
EMP	5	1-2-92	REDRAWN ON NEW FORMAT
WBC	4	8-28-89	FLAP ANGLE AND RADII CORRECTED
TMW	3	6-13-89	DIE VINYL DIMENSIONS CORRECTED
WBC	2	6-6-88	DEPTH DIMENSION CORRECTED
WBC	1	3-21-88	NOTE ADDED: PRINT SIDE UP

DWG. NO. FC-C-252
DRAWN CGD/WBC
PLOT SCALE NONE
DATE 10-26-87

McNEIL
CONSUMER PRODUCTS CO.
CAMP HILL ROAD, FORT WASHINGTON, PA. 19034

TITLE:
CARTON, SEAL END
1.50 L X 1.50 W
X 3.06 D



Labeling Format Information:

Fonts: Helvetica regular, bold, and bold oblique.

Drug Facts:	8.5 pt	**Leading:**	6.5 pt
Header:	7 pt	**Bullets:**	5 pt
Subheader:	6 pt	**Barlines:**	2.5 pt
Body Text:	6 pt	**Hairlines:**	.5 pt
Drug Facts (continued):	7 pt		

Horizontal Scale: 78-80 % Average Kerning: -15

INFORMATION BLOCK

OUR DEPTH IS OUR STRENGTH

DESCRIPTION CTN IMODIUM A-D 1 OZ
FILE # 3005194 VERSION A-1
DATE JULY 30, 2004 CON
PS IMAGE(S) NEW ART

TEAL	GREEN	LT BLUE	DK BLUE
YELLOW	BLACK		

DOMESTIC MCM CLNS 6/7/02 REV 7

THIS DESIGN BLOCK MUST BE SAVED WITH FILE AND PRINTED ON THERMAL.

NATIONAL PRINT BUYER INFORMATION BLOCK

NATIONAL PRINT BUYER:
PUT-UP NUMBER:
PART NUMBER:
DIE VINYL NUMBER:
NPA / PCN NUMBER:
FCC NUMBER:
PACKAGING LOCATION:

DOMESTIC COPY CLEARANCE APPROVAL BLOCK

McNeil Johnson & Johnson • MERCK

ARTWORK APPROVAL INITIAL BLOCK

INITIALS DATE

REGULATORY

MEDICAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-487/S-022

LABELING REVIEWS

Division of OTC Drug Products Labeling Review for an NDA Supplement

NDA 19-487 / SCF-022

Submission Date:	March 5, 2004
Received Date:	March 8, 2004
Drug product:	IMODIUM A-D Liquid
Active ingredient:	Loperamide HCl
Pharmacological category:	anti-diarrheal
Sponsor/Contact:	Cynthia Gulian Assistant Director, CMC Regulatory Affairs McNeil Consumer & Specialty Pharmaceuticals 7050 Camp Hill Road Fort Washington, PA 19034 (215)273-8464
Labeling submitted:	1 oz carton label, 1 oz bottle label, 4 oz booklet label, 8 oz booklet label
Reviewer:	Reynold Tan
Review date:	June 25, 2004
Project manager:	Laura Shay

Background: The sponsor submitted this supplemental new drug application (NDA 19-487 / SCF-022) on March 5, 2004 to provide for a reformulation to a mint flavor liquid of the Imodium A-D Liquid product. This application included draft labeling for the reformulated product. For the 1 oz size product, the sponsor submitted the carton and bottle labels. For the 4 oz and 8 oz size products, the sponsor submitted the booklet-style labels, which affix to the bottles.

Reviewer's Comments:
The following differences were noted between the submitted labels and previously approved labels:

(principal display panels):

1) The phrase "NEW FORMULA" appears in red upon a yellow banner. (For the 1 oz size, this NEW FORMULA banner also appears on the end flap of the carton label.)
Comment: This change is acceptable. The phrase "NEW FORMULA" must be removed after 180 days of OTC marketing.

2) The statement "contains 0.5% Alcohol" is removed.
Comment: This change is acceptable.

3) The description "Mint Flavor Liquid" replaces "Cherry Mint Flavor Liquid."
Comment: This change is acceptable.

4) The strength of the drug, described as "1 mg loperamide HCl per 7.5 mL," replaces the previous description, "Each tsp (5 mL) contains 1 mg loperamide HCl."
Comment: This change is acceptable

5) (For the 4 oz and 8 oz size products only) A peel back tab which states, "To read all Warnings and Directions before purchase PEEL BACK HERE," is added.
Comment: This change is acceptable.

(Drug Facts labeling): *Unless otherwise noted, the reviewer's comments refer to the 1, 4, and 8 oz size products.*

1) Under "Active ingredient," the amount of drug is stated as "(in each 7.5 mL) Loperamide HCl 1 mg." For the original Imodium A-D Liquid formulation, the amount of drug is stated as "(in each teaspoonful = 5 mL) Loperamide HCl 1 mg."
Comment: The "Directions" section instructs the consumer to use only the attached measuring cup to dose the product. The unit dose marked on this measuring cup should reflect both the units of dosage stated in the "Directions" and "Active ingredient" sections. The measuring cup was not submitted for review. This cup should be marked at 7.5 mL (1½ tsp), 15 mL (3 tsp), and 30 mL (6 tsp) to correspond to the dosages recommended under "Directions."

2) *Comment:* The "Directions" section for the 1 oz product only gives recommended doses in teaspoons, whereas the amount of drug in the "Active ingredient" section is given in milliliters ("in each 7.5 mL"). Under "Active ingredient," the amount of drug must be stated in terms of the dosage unit provided under "Directions" (see 21 CFR 201.66(c)(2)). Therefore, the amount of drug under "Active ingredient" must also be given in teaspoons. Note that the "Active ingredient" and "Directions" sections for the 1 oz product would conform to the regulation, 21 CFR 201.66(c)(2), if the recommended dosages in the "Directions" section for the 1 oz product appeared in both milliliters and teaspoons, as they do for the 4 oz and 8 oz products.

3) Under "Directions," two additional bulleted statements are added: "shake well before using" and "only use attached measuring cup to dose product."
Comment: This change is acceptable.

4) Under "Directions," recommended doses are adjusted to account for the lower concentration of loperamide HCl in the reformulated product compared to the original product.
Comment: This change is acceptable. However, for the 1 oz product, the recommended doses should be provided in both units of milliliters and teaspoons. (see above, *Comment 2* under "(Drug Facts labeling)").

5) Under "Other information," the tamper-evident statement "do not use if printed inner or outer neckband is broken or missing" replaces "do not use if carton is opened or if printed plastic neck wrap is broken or missing."
Comment: This change is acceptable.

6) Under "Other information," the statement "see bottom panel for expiration date and lot number" is removed.
Comment: This change is acceptable.

7) *Comment:* The reformulated product contains — mg sodium benzoate per 7.5 mL. At this concentration, the recommended 30 mL (6 tsp) dose for adults or children 12 years and over contains more than 5 mg of sodium. If the sodium content of a single recommended dose of an OTC drug product intended for oral ingestion is 5 mg or more, the labeling of the product must contain the sodium content per dosage unit (see 21 CFR 201.64(a)). The sodium content information should appear immediately following the "Other information" heading as follows (see 21 CFR 201.64(b) and 201.66(c)(7)(i)):

- each 30 mL (6 tsp) contains: **sodium 10 mg**

8) Under "Inactive ingredients," the list of ingredients reflects the reformulation of the product.
Comment: This change is acceptable.

9) *Comment:* The labeling conforms to the format requirements in 21 CFR 201.66(d). Type sizes for the title, headings, and subheadings conform to the format requirements in 21 CFR 201.66(d)(10).

Reviewer's recommendations: The following comments can be conveyed to the sponsor:

1) The sponsor must verify that the measuring cup used to dose the product is marked at the 7.5 mL (1½ tsp), 15 mL (3 tsp), and 30 mL (6 tsp) marks, thereby providing both units of milliliters and teaspoons for the recommended doses.

2) For the dosing table that appears in the "Directions" section of the 1 oz size product, the recommended dosages must appear in both milliliters and teaspoons, as they do for the 4 oz and 8 oz products.

3) Immediately following the "Other information" heading, the sponsor must include the sodium content information as follows (see 21 CFR 201.64(b) and 201.66(c)(7)(i)):

- each 30 mL (6 tsp) contains: **sodium 10 mg**

4) The sponsor must remove the phrase "NEW FORMULA" from the product labels after 180 days of OTC marketing.

5) The sponsor is reminded of their submission on December 15, 2003 (NDA 19-487/SLR-021) proposing added warnings alerting consumers to the possibility of the adverse effects of toxic megacolon and sedation that may be associated with the use of loperamide HCl. The sponsor

should include these warnings using the language recommended by FDA in the June 16, 2004 approval letter.

The sponsor must incorporate these changes in labeling before this supplement is approved.

Reynold Tan, Ph.D.
IDS/Biologist, HFD-560

Helen Cothran, B.S.
Team Leader, HFD-560

APPEARS THIS WAY
ON ORIGINAL

4 pages of draft labeling were removed from this portion of the review

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Reynold Tan
6/25/04 03:17:46 PM
INTERDISCIPLINARY

Helen Cothran
6/25/04 03:30:42 PM
INTERDISCIPLINARY

Division of OTC Drug Products Labeling Review for an NDA Supplement

NDA 19-487 / SCF-022 / July 1, 2004 submission

Submission Date:	July 1, 2004
Received Date:	July 1, 2004
Drug product:	IMODIUM A-D Liquid
Active ingredient:	Loperamide HCl
Pharmacological category:	anti-diarrheal
Sponsor/Contact:	Victoria Wagner-Weber Associate Director, Regulatory Affairs McNeil Consumer & Specialty Pharmaceuticals 7050 Camp Hill Road Fort Washington, PA 19034 (215)273-8278
Labeling submitted:	Drug Facts labeling (WORD version) label
Reviewer:	Reynold Tan
Review date:	July 6, 2004
Project manager:	Laura Shay

Background: The sponsor sent a fax communication on July 1, 2004 which included the Drug Facts labeling in Microsoft Word format for the reformulated mint-flavor Imodium A-D Liquid (NDA 19-487 / SCF-022). This new Drug Facts labeling was submitted in response to FDA's June 28, 2004 fax containing labeling recommendations for this product. These recommendations included: 1) Provide the recommended dosages in both milliliters and teaspoons in the dosing table under "**Directions**" for the 1 oz size product 2) include the sodium content information in "**Other information**" according to 21 CFR 201.64(b) and 201.66(c)(7)(i), and 3) add the proposed warnings alerting consumers to the adverse effects of toxic megacolon and sedation that may be associated with the use of loperamide HCl. The sponsor also sent representative containers for the 1 oz, 4 oz, and 8 oz packages on June 28, 2004 and stated that final printed labeling would be submitted for all three sizes within 30 days of final approval of SCF-022.

Reviewer's Comments:
1) The phrase "NEW FORMULA" appears in red upon a yellow banner. (For the 1 oz size, this NEW FORMULA banner also appears on the end flap of the carton label.)
Comment: This change is acceptable. However, the phrase "NEW FORMULA" must be removed after 180 days of OTC marketing.

2) The dosing cup for the 1 oz size product is marked in units of milliliters only, whereas the dosing cups for the 4 oz and 8 oz size products are marked in units of both milliliters and

teaspoons. The sponsor revised the dosing table under "Directions" for the 1 oz size product to provide doses in both units of milliliters and teaspoons, consistent with the "Directions" sections for the 4 oz and 8 oz packages.
Comment: The markings on the dosing cups are acceptable. While the dosing cup for the 1 oz size product provides markings in milliliter units only, the revised dosing table under "Directions" now provides doses in both units of milliliters and teaspoons.

3) The first bulleted statement in the "Other information" section reads:
"each 30 mL (6 tsp) contains: **sodium 10 mg**".
Comment: This change is acceptable.

4) To alert consumers to the possibility of sedative effects associated with the use of loperamide HCl, the sponsor added a warning statement. This warning statement reads:
"**When using this product**
• tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery."
Comment: This change is acceptable.

5) To alert consumers to the possibility of the adverse effects of toxic megacolon that may be associated with the use of loperamide HCl, the sponsor added a warning statement. This warning statement reads:
"Stop use and ask a doctor if
• you get abdominal swelling or bulging. These may be signs of a serious condition."
Comment: This change is acceptable.

Reviewer's recommendation: The following comment can be conveyed to the sponsor:

1) The sponsor must remove the phrase "NEW FORMULA" from the product labels after 180 days of OTC marketing.

Reynold Tan, Ph.D.
IDS/Biologist, HFD-560

Helen Cothran, B.S.
Team Leader, HFD-560

2 pages of draft labeling were removed from this portion of the review

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Reynold Tan
7/7/04 05:25:41 PM
INTERDISCIPLINARY

Helen Cothran
7/8/04 08:46:01 AM
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Division of OTC Drug Products Labeling Review for an NDA Supplement

NDA 19-487 / SLR-021(FA) / SCF-022(FA)

Submission Date:	October 5, 2004
Received Date:	October 15, 2004
Drug product:	IMODIUM A-D Liquid, 1 mg/ 7.5 mL (reformulated)
Active ingredient:	loperamide HCl
Pharmacological category:	anti-diarrheal
Sponsor/Contact:	Victoria Wagner-Weber Director, Marketed Products McNeil Consumer & Specialty Pharmaceuticals 7050 Camp Hill Road Fort Washington, PA 19034 (215) 273-8278
Labeling submitted:	1 oz (30 mL) carton label, 1 oz bottle label, 4 oz (120 mL) booklet label, 8 oz (240 mL) booklet label
Reviewer:	Reynold Tan
Review date:	November 9, 2004
Project manager:	Laura Shay

Background: In a supplemental new drug application (NDA 19-487 / SLR-021) submitted on December 15, 2003, the sponsor proposed adding label warnings alerting consumers to the possibility of the adverse effects of toxic megacolon and sedation that may be associated with the use of loperamide HCl. FDA recommended warning language in the June 16, 2004 approval letter for this application. The sponsor submitted another supplemental new drug application (NDA 19-487 / SCF-022) on March 5, 2004 to provide for a reformulation to a mint flavor liquid of the Imodium A-D Liquid product. This submission (NDA 19-487 / SLR-021(FA) / SCF-022(FA)) includes the final printed labeling that incorporates several labeling changes recommended by FDA following the review of submitted draft labeling.

Reviewer's Comments:

The following changes are noted between the sponsor's draft labeling submitted on March 5, 2004 and the final printed labeling in this submission:

1) The sponsor adds a new section under the subheading "**When using this product**." The warning under this subheading reads "tiredness, drowsiness or dizziness may occur. Be careful when driving or operating machinery."
Comment: This change is acceptable.

2) The sponsor adds a third bulleted statement under the subheading "**Stop use and ask a doctor if**" that reads "you get abdominal swelling or bulging. These may be signs of a serious condition."
Comment: This change is acceptable.

3) The sponsor provides doses in both units of milliliters and teaspoons in the "**Directions**" sections of labels.
Comment: This change is acceptable.

4) The sponsor adds the bulleted statement "each 30 mL (6 tsp) contains: **sodium 10 mg**" as the first bulleted statement under "**Other information**".
Comment: This change is acceptable.

5) *Comment:* In all of the labeling, position the tradename "Imodium A-D" and the statement of identity (SOI) "Loperamide HCl/Anti-Diarrheal" such that the letters "A-D" do not appear to be part of the SOI.

Reviewer's recommendations: The following comments can be conveyed to the sponsor:

The final printed labels submitted for the 1 oz (30 mL) carton label, 1 oz bottle label, 4 oz (120 mL) booklet label, and the 8 oz (240mL) booklet label are acceptable. An ACKNOWLEDGED AND RETAINED letter can be issued to the sponsor. However, at the next printing for all labeling, position the tradename "Imodium A-D" and the statement of identity (SOI) "Loperamide HCl/Anti-Diarrheal" such that the letters "A-D" do not appear to be part of the SOI. Submit this change in the next annual report.

Reynold Tan, Ph.D.
IDS/Biologist, HFD-560

Helen Cothran, B.S.
Team Leader, HFD-560

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/s/

Reynold Tan
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Helen Cothran
11/10/04 01:47:28 PM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

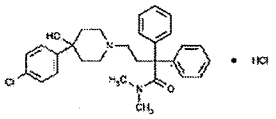
APPLICATION NUMBER:

NDA 19-487/S-022

CHEMISTRY REVIEW

Chemistry Review # 1	1. Division HFD-560	2. NDA Number 19-487
3. Name and Address of Applicant McNeil Consumer & Specialty Pharmaceuticals Attention: Lynn Pawelski, Director, Regulatory Affairs 750 Camp Hill Road Fort Washington, PA 19034 Phone: 215-273-7731		4. Supplement **Number:** SCF-022 **Letter Date:** 3/05/04 **Stamp Date:** 3/08/04 **PDUFA Due Date:** 7/08/04
5.Name of Drug Immodium ® A-D Liquid	6. Nonproprietary Name Loperamide HCl, USP	
7. Supplement Provides for: Changes in formulation, manufacturing process, drug product manufacturing and testing sites, container resin, label adhesive, and regulatory and alternative analytical procedures		8. Amendment(s) BC, dated 6/30/04 BC, dated 7/07/07 (fax)
9.Pharmacological Category Controls the symptoms of diarrhea, including Traveler's Diarrhea	10. How Dispensed OTC	11. Related Documents N/A
12. Dosage Form Solution	13. Potency(ies) 1 mg/7.5 mL	

14. Chemical Name and Structure see USAN
4-(p-Chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinebutyramide monohydrochloride, $C_{29}H_{33}ClN_2O_2$. HCl, Mol. wt. 513.50



15. Comment **Prior Approval Supplement**

This supplement provides for changes in formulation, manufacturing process, drug product manufacturing and testing sites, container resin, label adhesive, and regulatory and alternative analytical procedures.

The proposed resins and label adhesive were stated to comply with 21 CFR § 177.1520 and § 175.105 respectively for suitability. The supplement included test results of Physicochemical Tests-Plastics <USP 661> and Containers-Permeation Test <USP 671> for compatibility of the proposed container material. The supplement also included up to 12 months of long-term (25°C/60%RH) and 6 months accelerated (40°C) stability data on one production scale batch each in 1 oz, 4 oz and 8 oz bottles in support of the proposed changes. The submitted stability data did not indicate any adverse effect on the drug product because of the proposed changes.

16. Conclusions and Recommendations
This supplement is recommended for approval.
This supplement contains labeling. Action letter will be issued by HFD-560.

17. Name	Date
Rao Puttagunta, Ph.D., Reviewer	7/01/04

18. Concurrence
John Smith, Ph.D., Chemistry Team Leader

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information from

CHEMISTRY REVIEW #1

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/s/

Rao Puttagunta
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CHEMIST

John Smith
7/7/04 05:03:42 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-487/S-022

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA #	19-487 (SCF-022)
Submission Date (s)	March 5th, 2004, June 9th, 2004, July 1st, 2004
Brand Name	Imodium ® A-D Liquid
Generic Name	Loperamide Hydrochloride
Reviewer	Abimbola Adebowale Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DPE-III
OND division	HFD-560
Sponsor	McNeil Consumer and Specialty Pharmaceuticals, Fort Washington, PA 19034
Submission Type; Code	Supplemental New Drug Application
Formulation; Strength(s)	Oral Solution; 1 mg/7.5 mL
Indication	Controls symptoms of diarrhea, including Traveler's Diarrhea

1 Executive Summary

In this sNDA, the applicant is seeking approval for a reformulation of the currently marketed Imodium ® (loperamide hydrochloride) A-D liquid, to improve the flavor and aesthetic qualities of the product. Reformulated Imodium ® A-D liquid is a green, opaque liquid with a mint flavor, while the currently marketed product is a clear, colorless, cherry flavored liquid. The reformulated Loperamide Liquid (1 mg/7.5 mL) is also less concentrated than the currently marketed Imodium A-D liquid, (1 mg/5 mL).

In this submission the applicant included a bioequivalence study (No. 15-001) to link the reformulated product and the currently marketed product, to support these changes. A review of the study is discussed in this document.

1.1 Recommendation

The results of the bioequivalence study demonstrated that the reformulated Imodium A-D liquid is bioequivalent to the currently marketed Imodium A-D liquid. Therefore the data provided has met the requirements of 21CFR 320 and, is acceptable from the clinical pharmacology and biopharmaceutics perspective.

1.2 Phase IV Commitments: No Phase IV commitments are requested.

Abimbola Adebowale, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Dennis Bashaw, Pharm.D.
Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

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3 Summary of CPB Findings

Loperamide was approved by the FDA in 1976 for the control of the symptoms of diarrhea. It is currently available OTC as single-ingredient caplets (2 mg) and clear liquid (1 mg/5mL). It is also available in combination with simethicone as chewable and conventional tablets. The current application is for a reformulation of the currently marketed liquid.

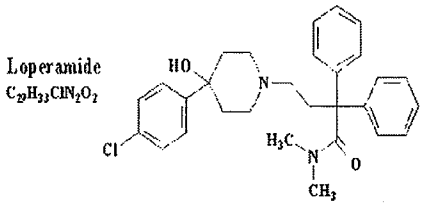
The bioequivalence study included in this submission indicated that the reformulated liquid is bioequivalent to the currently marketed liquid as demonstrated by the 90% CI of AUC and Cmax meeting the Agency criteria of 80-125 %.

The gender analysis of the data obtained in the BE study indicated that the exposure was higher in females than in males for both the currently marketed and reformulated liquid. However, weight normalization of the data resulted in comparable systemic exposure between the males and the females demonstrating that the observed difference in systemic exposure was due to the differences in body weight (i.e. volume). Loperamide was assayed in plasma by a validated LC/MS/MS method with acceptable reproducibility, accuracy and sensitivity. Overall, the CPB information provided in this supplement is acceptable to support the reformulation of the currently marketed Imodium A-D Liquid.

4 QBR

4.1 General Attributes:

The molecular weight of the hydrochloride salt is 513.50. It is a weak base with a pKa of 8.66 and it has the following structure:



Mechanism of Action:
Loperamide is believed to act locally on the intestine wall to decrease gastrointestinal (GI) transit time and motility by inhibiting peristalsis, and it also has anti-secretory properties. Specifically, loperamide inhibits peristalsis by direct action on cholinergic and non-cholinergic neuronal mechanisms involved in the peristaltic reflex. It alters fluid and electrolyte movement within the intestine.

Proposed Dosage and Route of Administration:

The OTC dosing for the oral administration of the reformulated liquid is reproduced in the chart below:

adults and children 12 years and over	30 mL (6 tsp) (after the first loose stool; 15 mL (3 tsp) after each subsequent loose stool; but no more than 60 mL (12 tsp) in 24 hours
children 9-11 years (60-95 lbs)	15 mL (3 tsp) after the first loose stool; and 7.5 mL (1½ tsp) after each subsequent loose stool; but no more than 45 mL (9 tsp) in 24 hours
children 6-8 years (48-59 lbs)	15 mL (3 tsp) after the first loose stool; and 7.5 mL (1½ tsp) after each subsequent loose stool but no more than 30 mL (6tsp) in 24 hours
children under 6 years (up to 47 lbs)	ask a doctor

4.2 General Clinical Pharmacology:

This submission is supported by a BE study and some CMC information. No new information on E-R for safety or efficacy was included in this application.

4.2.1. What are the PK characteristics of loperamide?

The applicant included a brief summary of the PK characteristics of loperamide as follows:

Absorption: Only a small fraction is actually absorbed into the systemic circulation after an oral dose. Loperamide is transported via the portal vein to the liver where it is extensively metabolized (first-pass effect), conjugated and excreted into the bile. The plasma concentrations obtained from previous formulations are usually low 1-10 ng/mL.

Excretion: Only 1% of orally administered loperamide is excreted unchanged in humans. The half-life is about 10.8 hrs (range 9 to 11 hours)

4.3 **Intrinsic Factors:** A gender analysis of the results obtained from the BE study was conducted by the applicant. This data indicated that the systemic exposure (AUCinf and Cmax) although comparable for both the reformulated and current liquid was higher in women than in men. However, the women (mean weight (SD) = 61.4 (5.0) kg) also weighed less than the men (mean (SD) weight was 79.0 (11.6). Weight normalization of the data for the reformulated liquid indicated that the systemic exposure and clearance was comparable in both the males and females as shown in the table reproduced below:

Gender	Pharmacokinetic Parameters (mean ± SD)				
	Raw Data		Weight Normalized Data		
	AUC inf (ng-h/mL)	Cmax (ng/mL)	AUC inf (ng-h/mL)	Cmax (ng/mL)	CL (L-kg/h)
Male (N=16)	12.46 ± 3.96	0.61 ± 0.24	13.99 ± 4.52	0.69 ± 0.29	4.47 ± 1.30
Female (N=19)	15.18 ± 4.70	0.85 ± 0.25	13.27 ± 4.07	0.74 ± 0.23	4.65 ± 1.22

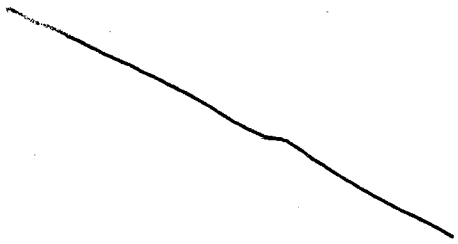
Therefore, the difference in systemic exposure for the reformulated liquid was due to differences in body weight between the males and the females and, is unlikely to be clinically relevant.

4.4 Extrinsic Factors: Not Applicable

4.5 General Biopharmaceutics:

Formulation: Reformulated Imodium A-D liquid is an Opaque mint colored liquid with a pH ranger of 3.4-4.6. A quantitative composition comparing the currently approved information and the proposed changes for Imodium ® (Loperamide hydrochloride) A-D liquid is inserted below:

	Currently Approved	Proposed
Drug Substance	No changes	
Drug Product		
Formulation		
Ingredient (mg per mL basis)	**mg/mL**	**mg/mL**
Loperamide HCl USP	0.2	0.133



4.5.1. What is the BCS classification?

Applicant did not propose any BCS classification neither did they provide adequate data for BCS classification of loperamide hydrochloride. The applicant did state that the solubility of loperamide HCL in water is 0.26g/L at the formulation target pH of ~ 4.0. Therefore the dose/solubility volume = 4mg/0.26mg/mL = 15.4 mLs. Since the highest dose-strength is soluble in ≤ 250 mL water at pH 4.0, loperamide HCL may be considered a highly soluble substance.

4.5.2. Is the new reformulated Liquid formulation bioequivalent to the currently marketed Liquid formulation?

Yes the new reformulated liquid formulation is bioequivalent to the currently marketed liquid formulation. This is because the data in the table inserted below indicates that the 90% CI for the Cmax and AUC meet the Agency criteria for bioequivalence of 80-125 %.

Table 9-2. Statistical Analysis of Primary Pharmacokinetic Parameters

Geometric Means	Reform Liquid [a]	Current Liquid [a]	Ratio[b] of Test to Reference	Intrasubject cv (%)	90% Confidence Intervals	Pr > |T|	Power (%)
AUCINF (ng·h/mL)	13.3	14.6	91.0	15.7	85.4 to 96.9	0.0162	>99.9
CMAX (ng/mL)	0.694	0.758	91.5	19.5	84.6 to 99.0	0.0648	99.5

a: geometric mean data
b: ratio of least squares means

4.6 Analytical:

4.6.1. What assay methods were used to quantitate loperamide in plasma? Were the methods adequately validated?

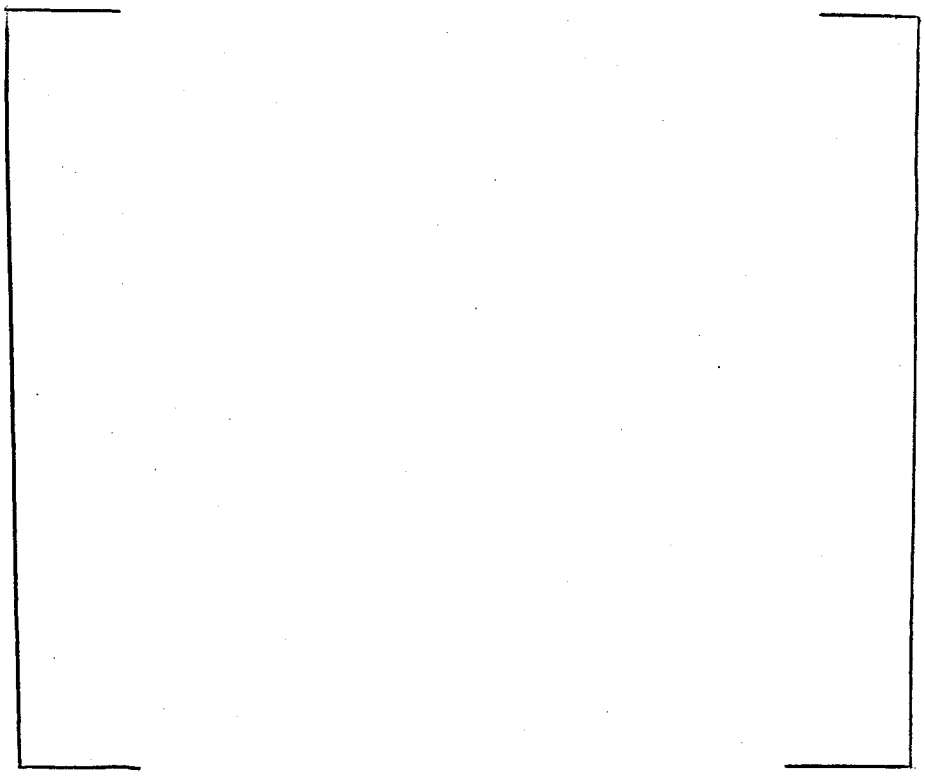
Loperamide was assayed in plasma by LC/MS/MS and this method was adequately validated with acceptable reproducibility, accuracy and sensitivity as shown in the table below:

Assay Validation:	
Precision Intra-day	1.2 to 2.6 %
Precision Inter-day	1.24 to 10.4 %
Accuracy Intra-day	94.7 to 100.5 %
Accuracy Inter-day	98.7 to 105.8 %
Linearity	0.01 to 10 ng/mL; Average r=0.9997 (n = 15)
Storage	Percent degradation following 3 freeze/thaw cycles was <3%.

5 Labeling Comments: In the proposed label under "directions", the applicant stated that only the attached measuring cup should be used to dose the product. Since the label indicates teaspoonful as well as mL, there was a concern that the measuring cup may not have the teaspoonful graduation on it, which could result in consumers using two types of measuring devices that may result in errors. Following discussions with the OTC reviewer for labeling (Mr. R.Tan) and also by visually looking at the measuring cup attached to a sample of the finished product, this reviewer confirmed that it was graduated in teaspoonful and mL.

6 Appendix

6.1 Proposed labeling



6.2 Individual Study Reviews:

5 STUDY ABSTRACT SHEETS FOR REVIEWERS

SNDA to NDA 19-487 SUBMISSION DATE: March 2004

Determination of Bioequivalence of Loperamide from a New Formulation of IMODIUM® A-D Liquid *vs* Currently marketed IMODIUM® A-D Liquid (Protocol 15-001)

DESIGN:
☒ Single Dose ☒ Crossover ☒ Washout = two weeks

DEMOGRAPHICS (completed): Total n = 38 Males = 18 Females = 20
☒ Normal Subjects ☒ Young

MALES	Range	Mean	FEMALES	Range	Mean
Age (yr)	18 to 60	31.6	Age (yr)	18 to 52	28.7
Weight (lb)	138 to 215	174.5	Weight (lb)	119 to 158	136.1
Height (in)	64 to 75	69.9	Height (in)	59 to 68	63.8

DRUG ADMINISTRATION:

Treatment	Dose	Strength	Formula/ Batch Number	Batch Size
A	Imodium® A-D Liquid	1 mg / 7.5 mL	C-918-1 TFDD	
B	Imodium® A-D Liquid	1 mg / 5 mL	C-129-31 HFM0000248	

☒ Fasted
☐ Non-Fasted ☐ Food Study ☐ High Fat Breakfast

SAMPLES: ☒ Plasma ☐ Serum
☐ Urine
Before (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 28, 32, 36, and 48 hours after dosing

ASSAY METHOD: LC/MS/MS Method for Loperamide
Method P557.00 (February 2001)

ASSAY SENSITIVITY: Loperamide Quantification Limit 0.010 ng/mL; Range 0.010 to 10.00 ng/mL

ASSAY ACCURACY: Loperamide Mean Recovery 80.4% (6 determinations)

Inserted below is this reviewer's additional information for the purpose of clarification of certain parts of the applicant's study abstract sheet:

Dose: Treatment A: 4-mg dose of loperamide as 30 mL of new Imodium A-D liquid, 1 mg/7.5 mL
Dose: Treatment B: 4-mg dose of loperamide as 20 mL of Imodium A-D liquid, 1 mg/5 mL
Administered orally using a dosing syringe followed with 240 mL of water after a 10-hour overnight fast.
Number of subjects: 38 enrolled, 35 completed
Demographics: Ethnicity Hispanic (12) and Non Hispanic (26), Race: White or Caucasian (34), Black or African American (2), Asian (1), American Indian or Alaskan Native (1)
Three subjects discontinued as follows: Two male subjects (9 and 19) elected to withdraw from the study before the second period. Subject 9 had a broken leg. One female subject (36) was discontinued from the study before the second period because she tested positive at screening for drugs of abuse.

Results:

Figure 12-1. Spaghetti Plots for Reformulated IMODIUM® A-D Liquid (Treatment A)

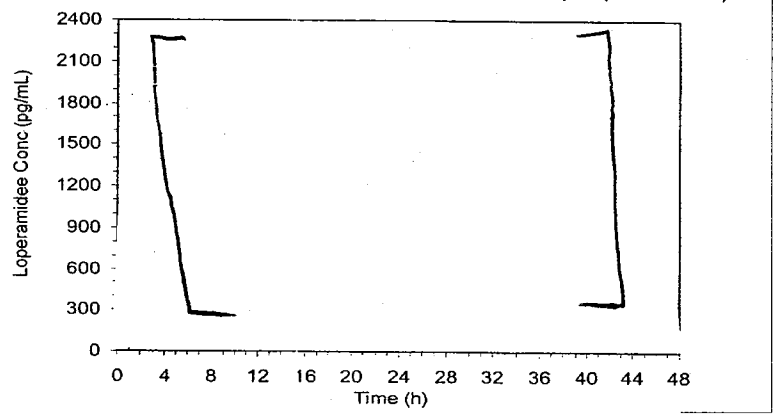


Figure 12-2. Spaghetti Plots for Current IMODIUM® A-D Liquid (Treatment B)

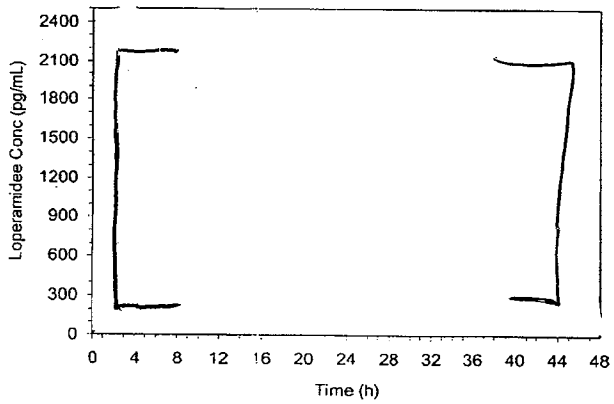


Table 9-1. Loperamide Pharmacokinetic Parameters (mean, sd, cv%)

Product	AUCT (ng·h/mL)	AUCINF (ng·h/mL)	CMAX (ng/mL)	TMAX (h)	KEL (1/h)	t½ (h)
Reformulated IMODIUM® A-D Liquid (Treatment A)	12.5 (4.05) 33%	13.9 (4.52) 33%	0.739 (0.270) 37%	4.5 (2.3) 50%	0.050 (0.006) 12%	14.0 (1.81) 13%
Currently Marketed IMODIUM® A-D Liquid (Treatment B)	13.9 (5.47) 39%	15.5 (5.77) 37%	0.859 (0.464) 54%	4.5 (2.3) 51%	0.049 (0.007) 14%	14.5 (2.16) 15%

Adverse Events: Ten of the 38 subjects reported a total of 21 adverse events (AE's). Of these seven AE's were considered possibly related to the study drug by the investigator.

Conclusions:
The 90% CI for Cmax and AUC met the Agency criteria of 80-125% for bioequivalence, therefore reformulated Imodium® A-D liquid and the currently marketed Imodium® A-D Liquid are bioequivalent.

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/s/

Abi Adebowale
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BIOPHARMACEUTICS

Dennis Bashaw
7/7/04 03:09:48 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-487/S-022

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PRIOR APPROVAL SUPPLEMENT

NDA 19-487/S-022

McNeil Consumer & Specialty Pharmaceuticals
Attention: Cynthia Gulian
Associate Director, CMC Regulatory Affairs
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Gulian:

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

Name of Drug Product: Imodium® A-D (loperamide HCl) Liquid
NDA Number: 19-487
Supplement number: 022

Date of supplements: March 5, 2004

Date of receipt: March 8, 2004

This supplemental application proposes a reformulation of Imodium A-D liquid to an opaque, green liquid with a mint flavor.

Unless we notify you within 60 days of the receipt date that this application is not sufficiently complete to permit a substantive review, we will file this application on May 7, 2004, in accordance with 21 CFR 314.101(a). If the applications are filed, the goal date will be July 8, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Over the Counter Drug Products, HFD-560
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over the Counter Drug Products, HFD-560
Attention: Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely yours,

{See appended electronic signature page}

David Hilfiker
Chief, Project Management Staff
Division of Over the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

David Hilfiker
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-022

McNeil Consumer & Specialty Pharmaceuticals
Attention: Victoria Wagner-Weber
Associate Director, Regulatory Affairs
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Wagner-Weber:

We have received your supplemental drug application submitted March 5, 2004, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for: Imodium® A-D (loperamide HCL) Liquid.

This supplemental application proposes a reformulation of Imodium A-D liquid to an opaque, green liquid with a mint flavor.

We have reviewed this supplemental application and have the following comments and recommendations:

Drug Facts Label:

1. The dosing table under ***Directions*** for the 1 oz. size product must appear in both milliliters and teaspoons, as it does for the 4 oz. and the 8 oz. products.

2. Immediately following ***Other information***, the sponsor must include the sodium content information in the following format (21 CFR 201.64(b) and 201.66(c)(7)(i)):
   - each 30 mL (6 tsp) contains: **sodium 10 mg**

3. Under ***Warnings***, add the warnings that alert consumers to the possibility of the adverse effects of toxic megacolon and sedation as written in the draft labeling for NDA 19-487/S-021, approved June 16, 2004.

In order to ensure a timely action for this supplemental new drug application, we request that you respond to the issues listed above as soon as possible. If you have any questions, you may call Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-487/S-022

McNeil Consumer & Specialty Pharmaceuticals
Attention: Victoria Wagner-Weber
Director, Regulatory Development
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Dear Ms. Wagner-Weber:

We acknowledge receipt of your October 5, 2004 submission containing final printed labeling in response to our July 8, 2004, letter approving your supplemental new drug application for Imodium A-D (loperamide HCl) Liquid.

We have reviewed the labeling that you submitted in accordance with our July 8, 2004, letter and we find it acceptable.

At next printing make the following changes and submit these changes in the next annual report:

1. Position the tradename "Imodium A-D" and the statement of identity (SOI) "Loperamide HCl/Anti-Diarrheal" so that the letters "A-D" do not appear to be part of the SOI.

2. Replace the hairline that divides the ***Directions*** section from the **Keep out of reach of children** section with a barline.

If you have any questions, call Laura Shay, Regulatory Project Manager, at 301-827-2274.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D.
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
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