CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-140

CHEMISTRY REVIEW(S)

Levine

JUL 11 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA 21-140 **CMC REVIEW #1** **REVIEW DATE:** 07/06/00

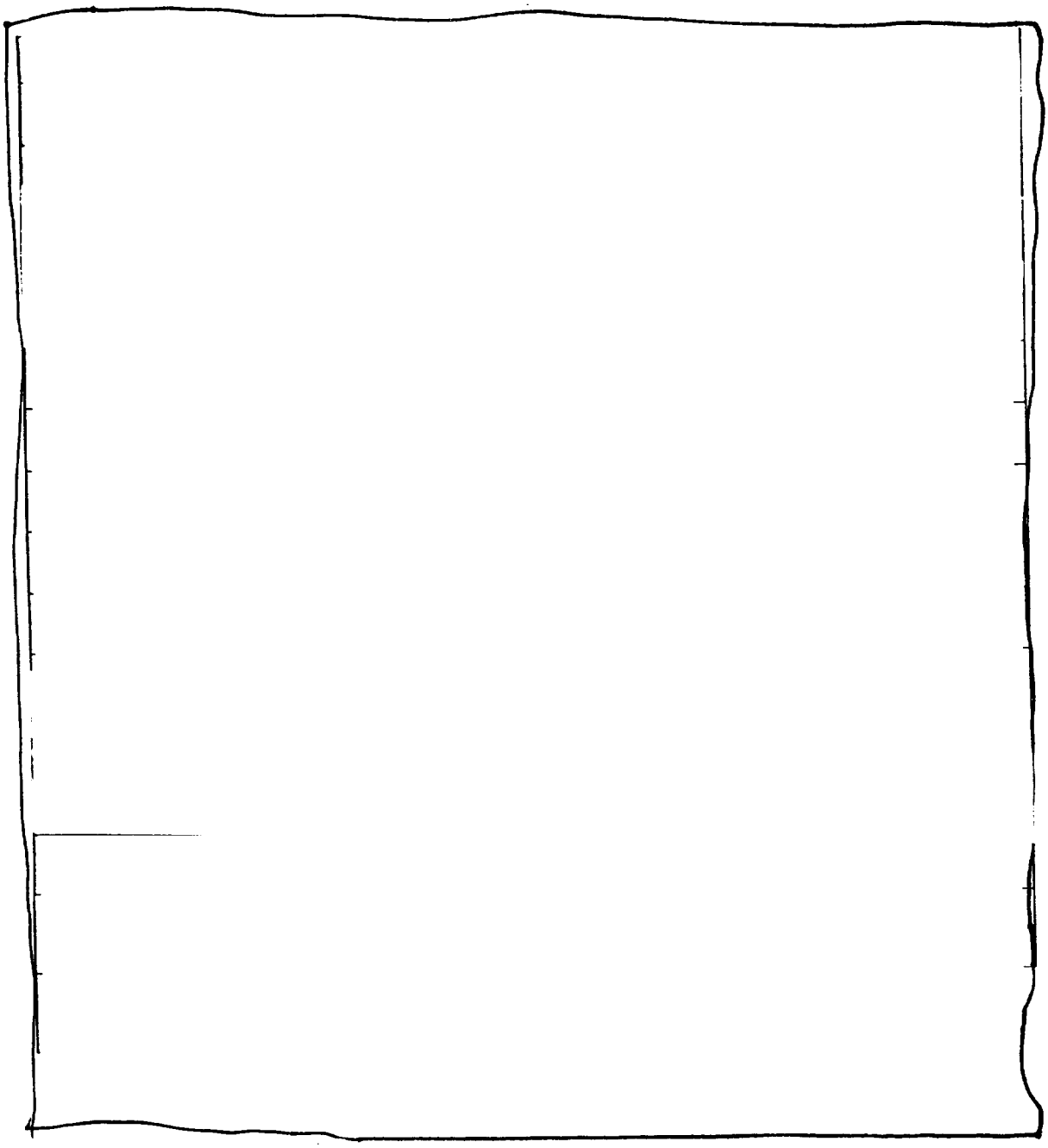
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	10/29/99	11/01/99	11/05/99
BC Amendment	05/05/00	05/08/00	05/12/00

NAME & ADDRESS OF APPLICANT:
McNeil Consumer Healthcare
Camp Hill Road
Fort Washington, PA 19034

DRUG PRODUCT NAME:
PROPRIETARY: Imodium Advanced Caplet
NONPROPRIETARY: Loperamide HCL/Simethicone caplet
CODE NAME: none
CHEMICAL TYPE/THERAPEUTIC CLASS: 4NS

INDICATION: control of symptoms of diarrhea plus bloating, pressure, and cramps commonly asscciated with gas
DOSAGE FORM: capsule-shaped, uncoated tablet (caplet)
STRENGTH: 2 mg Loperamide HCL/125 mg Simethicone
ROUTE OF ADMINISTRATION: oral
HOW DISPENSED: OTC
CHEMICAL NAME/STRUCTURE, MOLECULAR FORMULA/WEIGHT: USP 24

SUPPORTING DOCUMENTS:



DOCUMENTS SUPPORTED BY THIS FILE: None

RELATED DOCUMENTS:

NDA 20-606 Imodium Advanced Chewable tablets

SPECIAL COMPOUND: No

CONSULTS:

Biopharm: pending review completion
EER: filed; pending conclusions for each firm
Trademark: OTC consult

REMARKS/COMMENTS:

The application was filed under 505(b)(1) for an alternative to the currently marketed IMODIUM Advanced chewable tablets [NDA 20-606]; the proposed product is to be swallowed without chewing. Both drug products contain the same active ingredients and the same doses.

CONCLUSIONS & RECOMMENDATIONS:

The proposed application is APPROVABLE (AE) for CMC issues pending resolution of the comments listed in the draft in section H of this review, completion of the Biopharm review and action on the EES submission.

/S/ 07/11/00

Mike Adams
Review Chemist, HFD-820

/S/ 07/13/00

/S/ 7/11/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:
NDA 21-140
HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 07/ /00

Levine

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

Title: [redacted] Simethicone Compounds and Emulsions

1. CHEM REVIEW #2 **2. REVIEW DATE:** 07/11/00

3. DMF INFORMATION REVIEWED:

Submission Type	Submission Date	Location of Information
Amendment	07/08/99	volume 2.1

4. PREVIOUS DOCUMENTS:

IR letter	07/02/97	volume 1.1

5. DMF HOLDER: [redacted]

REPRESENTATIVE
Barbara H. Rather, Food & Drug Counsel
mail #CO1242
John T. Woodard, Food & Drug Regulatory Specialist
mail #CO3101

6. ITEM REVIEWED: [redacted]
7. DMF REFERENCED FOR:
APPLICATION: NDA 21-140
APPLICANT: McNeil Consumer Healthcare
LOA DATE: 03/02/99
DRUG PRODUCT: Loperamide HCL/Simethicone caplets (OTC)
DOSE: 2 mg/125 mg, solid oral
8. SUPPORTING DOCUMENTS: none
9. CURRENT STATUS OF DMF:
DATE OF LAST DMF UPDATE: 07/08/99
DATE OF MOST RECENT LIST OF COMPANIES WITH LOA: 07/08/99
10. CONSULTS: none

11. REMARKS/COMMENTS

This amendment (06/99 version) is stated to be a complete and updated submission of the entire file which includes all previously submitted information, thus previous submissions are not reviewed. The last IR letter was a request for an annual report.

[redacted] is proposed for use as an active ingredient in a finished dosage form.

7/14/00

12. CONCLUSIONS & RECOMMENDATIONS:

The CMC information re [redacted] in the 07/08/99 submission is considered NOT ADEQUATE to support approval for its use as an active ingredient in the proposed new drug application.

/S/ 07/13/00

Mike Adams
Review Chemist, HFD-820

/S/ 7/13/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:
[redacted]
HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 07/ /00

N 21-140

JUL 13 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

[redacted]

Title: Section 79

1. CHEM REVIEW #1 **2. REVIEW DATE:** 07/13/00

3. DMF INFORMATION REVIEWED:

Submission Type	Submission Date	Location of Information
Amendment	January 29, 1999	volume 4.1

4. PREVIOUS DOCUMENTS: none

5. DMF HOLDER:

[redacted]

6. ITEM REVIEWED: section 79

7. DMF REFERENCED FOR:
APPLICATION: NDA 21-140
APPLICANT: McNeil Consumer Healthcare
LOA DATE: 06/14/99
DRUG PRODUCT: Loperamide HCL/Simethicone caplets
DOSE: 2 mg/125 mg; oral, uncoated caplet

8. SUPPORTING DOCUMENTS: none
9. CURRENT STATUS OF DMF:
DATE OF LAST DMF UPDATE: 01/29/99
DATE OF MOST RECENT LIST OF COMPANIES WITH LOA: unknown
10. CONSULTS: none

11. REMARKS/COMMENTS:

[redacted]

12. CONCLUSIONS & RECOMMENDATIONS:

The file is considered NOT ADEQUATE to support the use of the proposed [redacted] in the proposed new drug application.

/S/ 07/13/00

Mike Adams
Review Chemist, HFD-820

/S/ 7/13/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:
[redacted]
HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 07/ /00

Levme

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

[redacted]

Title: Loperamide Hydrochloride

1. CHEM REVIEW #8 **2. REVIEW DATE:** 07/17/00

3. DMF INFORMATION REVIEWED:

Submission Type	Submission Date	Location of Information
Amendment	12/02/99	volume 2.1

4. PREVIOUS DOCUMENTS: none

CMC Review #7	10/08/99	volume 2.1

5. DMF HOLDER:

[redacted]

6. ITEM REVIEWED: Loperamide HCL bulk drug substance
7. DMF REFERENCED FOR:
APPLICATION: NDA 21-140
APPLICANT: McNeil Consumer Healthcare
LOA DATE: 03/15/99
DRUG PRODUCT: Loperamide HCL/Simethicone caplets (OTC)
DOSE: 2 mg/125 mg, oral, uncoated caplet
8. SUPPORTING DOCUMENTS: none
9. CURRENT STATUS OF DMF:
DATE OF LAST DMF UPDATE: 12/02/99
DATE OF MOST RECENT LIST OF COMPANIES WITH LOA: 07/09/99
10. CONSULTS: none
11. REMARKS/COMMENTS

The amendment, submission dated 12/02/99 by the US agent, is a complete update (dated 11/26/99) of the file. They state that no major changes have been introduced.

CMC Review #7 covered the submission up to the current submissions and concluded that the CMC information was ADEQUATE. This CMC review covers only the current revisions.

12. CONCLUSIONS & RECOMMENDATIONS:

The file is considered ADEQUATE to support approval of the new drug application.

/S/ 07/17/00

Mike Adams
Review Chemist, HFD-820

/S/ 7/17/0

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:

HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 07/ /00

ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

Title: [redacted]

1. CHEM REVIEW #1 **2. REVIEW DATE:** 07/25/00

3. DMF INFORMATION REVIEWED:

Submission Type	Submission Date	Location of Information
Annual Report	09/15/99	volume 1.1
Annual Report	08/02/99	volume 1.1
Amendment	06/26/91	volume 1.1
Original	09/17/90	volume 1.1

4. PREVIOUS DOCUMENTS: none

5. DMF HOLDER:

[redacted]

6. ITEM REVIEWED: [redacted]

7. DMF REFERENCED FOR:

APPLICATION: NDA 21-140
APPLICANT: McNeil Consumer Healthcare
LOA DATE: 02/08/99
DRUG PRODUCT: Loperamide HCL/Simethicone caplets
DOSE: 2 mg/125 mg, oral, uncoated caplet

8. SUPPORTING DOCUMENTS: none

9. CURRENT STATUS OF DMF:

DATE OF LAST DMF UPDATE: 09/15/99
DATE OF MOST RECENT LIST OF COMPANIES WITH LOA: 09/15/99

10. CONSULTS: none

11. REMARKS/COMMENTS:

The material is a single compound used as a [redacted] in an oral, uncoated caplet.

12. CONCLUSIONS & RECOMMENDATIONS:

The file is considered ADEQUATE to support approval of the proposed new drug application.

/S/ 07/25/00

Mike Adams
Review Chemist, HFD-820

/S/ 7/25/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:

[redacted]

HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 07/ /00

Levine

JUL 28 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

Title: [redacted]

1. CHEM REVIEW #4 **2. REVIEW DATE:** 07/28 00

3. DMF INFORMATION REVIEWED:

Submission Type	Submission Date	Location of Information
Annual Report	05/02/00	volume 2.1

4. PREVIOUS DOCUMENTS:

CMC Review #3	11/02/98	volume 1.1

5. DMF HOLDER:

[redacted]

6. ITEM REVIEWED: Intermediate T001001

7. DMF REFERENCED FOR:

APPLICATION: NDA 21-140
APPLICANT: McNeil Consumer Healthcare
LOA DATE: 05/12/99
DRUG PRODUCT: Loperamide HCl/Simethicone caplets
DOSE: 2 mg/125 mg, oral, uncoated caplet

8. SUPPORTING DOCUMENTS:

[redacted]

9. CURRENT STATUS OF DMF:

DATE OF LAST DMF UPDATE: 05/02/00
DATE OF MOST RECENT LIST OF COMPANIES WITH LOA: 05/02/00

10. CONSULTS: none
11. REMARKS/COMMENTS: none

2. CONCLUSIONS & RECOMMENDATIONS:

The file is considered ADEQUATE to support approval of the proposed new drug application.

/S/ 07/28/00

Mike Adams
Review Chemist, HFD-820

/S/ 7/28/0

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:

[redacted]

HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 07/ /00

LEJME

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

JUL 28 2000

Title: [redacted]

1. **CHEM REVIEW #3** 2. **REVIEW DATE:** 07/28/00

3. **DMF INFORMATION REVIEWED:**

Submission Type	Submission Date	Location of Information
Annual Report	08/05/98	volume 3.1
Annual Report	03/22/00	volume 3.1

4. **PREVIOUS DOCUMENTS:**

CMC Review	07/24/98	volume 3.1
CMC Review	06/16/98	volume 3.1

5. **DMF HOLDER:**

[redacted]

6. **ITEM REVIEWED:** Loperamide bulk drug substance

7. **DMF REFERENCED FOR:**

APPLICATION: NDA 21-140
APPLICANT: McNeil Consumer Healthcare
LOA DATE: 05/12/99
DRUG PRODUCT: Loperamide HCL/Simethicone caplets
DOSE: 2 mg/125 mg, oral, uncoated caplet

8. **SUPPORTING DOCUMENTS:**

[redacted]

9. **CURRENT STATUS OF DMF:**

DATE OF LAST DMF UPDATE: 03/22/00
DATE OF MOST RECENT LIST OF COMPANIES WITH LOA: 03/22/00

10. **CONSULTS:** none

11. REMARKS/COMMENTS:

Each AR states that no mfg and control changes have been made and the 03/22/00 AR also included updated stability reports for the [redacted] mfg sites; and the DMF CMC tracking log.

12. CONCLUSIONS & RECOMMENDATIONS:

The file is considered ADEQUATE to support approval of the proposed new drug application.

/S/ 07/28/00

Mike Adams
Review Chemist, HFD-820

/S/ 7/28/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:
[redacted]
HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 07/ /00

Louise

AUG 10 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA 21-140 **CMC REVIEW #1** **REVIEW DATE:** 08/10/00
AMENDMENT

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	10/29/99	11/01/99	11/05/99
BC Amendment	05/05/00	05/08/00	05/12/00

NAME & ADDRESS OF APPLICANT:
McNeil Consumer Healthcare
Camp Hill Road
Fort Washington, PA 19034

DRUG PRODUCT NAME: Imodium Advanced Caplet
INDICATION: control of symptoms of diarrhea plus bloating, pressure, and cramps commonly associated with gas
DOSAGE FORM: capsule-shaped, uncoated tablet (caplet)
STRENGTH: 2 mg Loperamide HCl/125 mg Simethicone
ROUTE OF ADMINISTRATION: oral
HOW DISPENSED: OTC
CHEMICAL NAME/STRUCTURE, MOLECULAR FORMULA/WEIGHT: USP 24
SUPPORTING DOCUMENTS: See CMC Review #1
DOCUMENTS SUPPORTED BY THIS FILE: None
RELATED DOCUMENTS: See CMC Review #1
SPECIAL COMPOUND: No
CONSULTS:

Biopharm: completed by D.Udo (no date stamp)
EER: filed; pending conclusions for each firm
Trademark: OTC consult

REMARKS/COMMENTS:

This amendment is to address the EER and Biopharm issues left unresolved in CMC Review #1. The AE conclusion has not changed.

CONCLUSIONS & RECOMMENDATIONS:

The proposed application is APPROVABLE (AE) for CMC issues pending resolution of the comments listed in the draft in section H of this review, completion of the Biopharm review and action on the EES submission.

/S/ 8/10/00

Mike Adams
Review Chemist, HFD-820

/S/ 8/10/00

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:
NDA 21-140
HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 08/ /00

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA 21-140 **CMC REVIEW #2** **REVIEW DATE:** 11/14/00

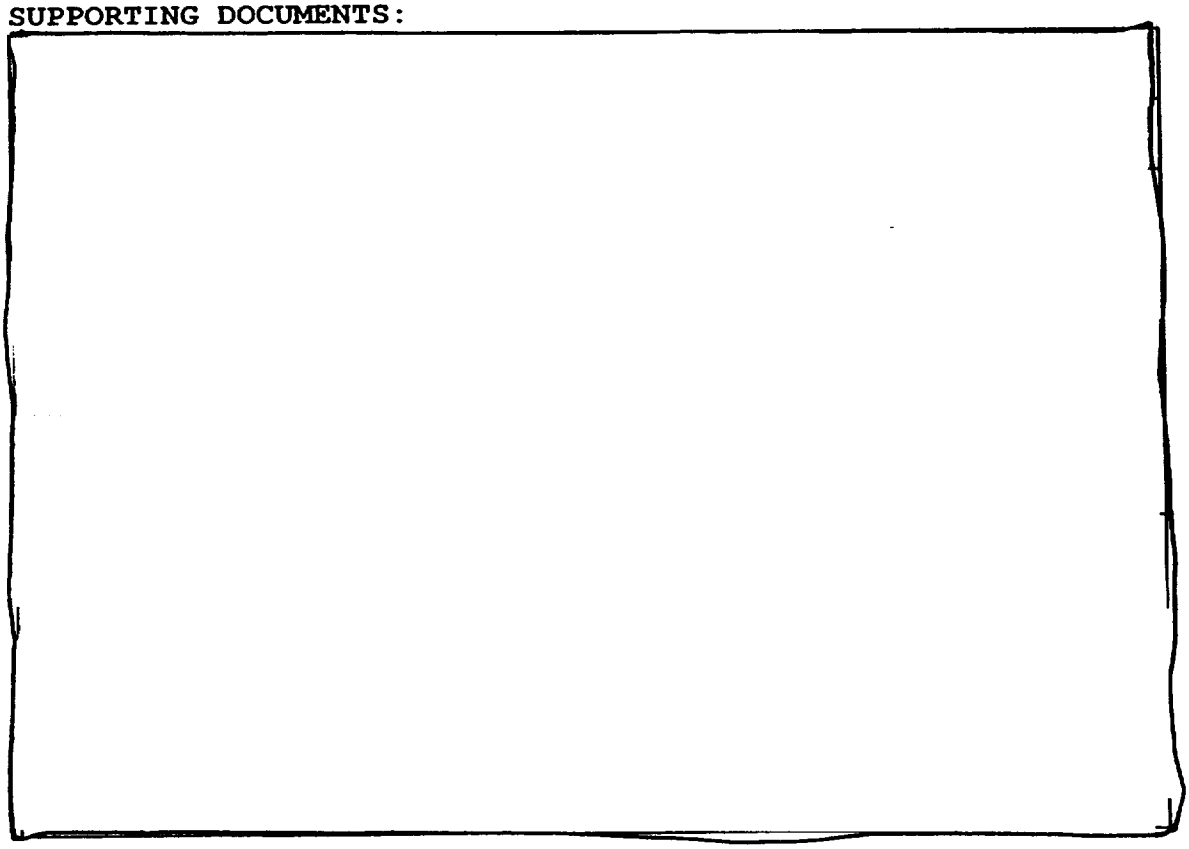
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC Amendment	08/29/00	05/30/00	08/30/00

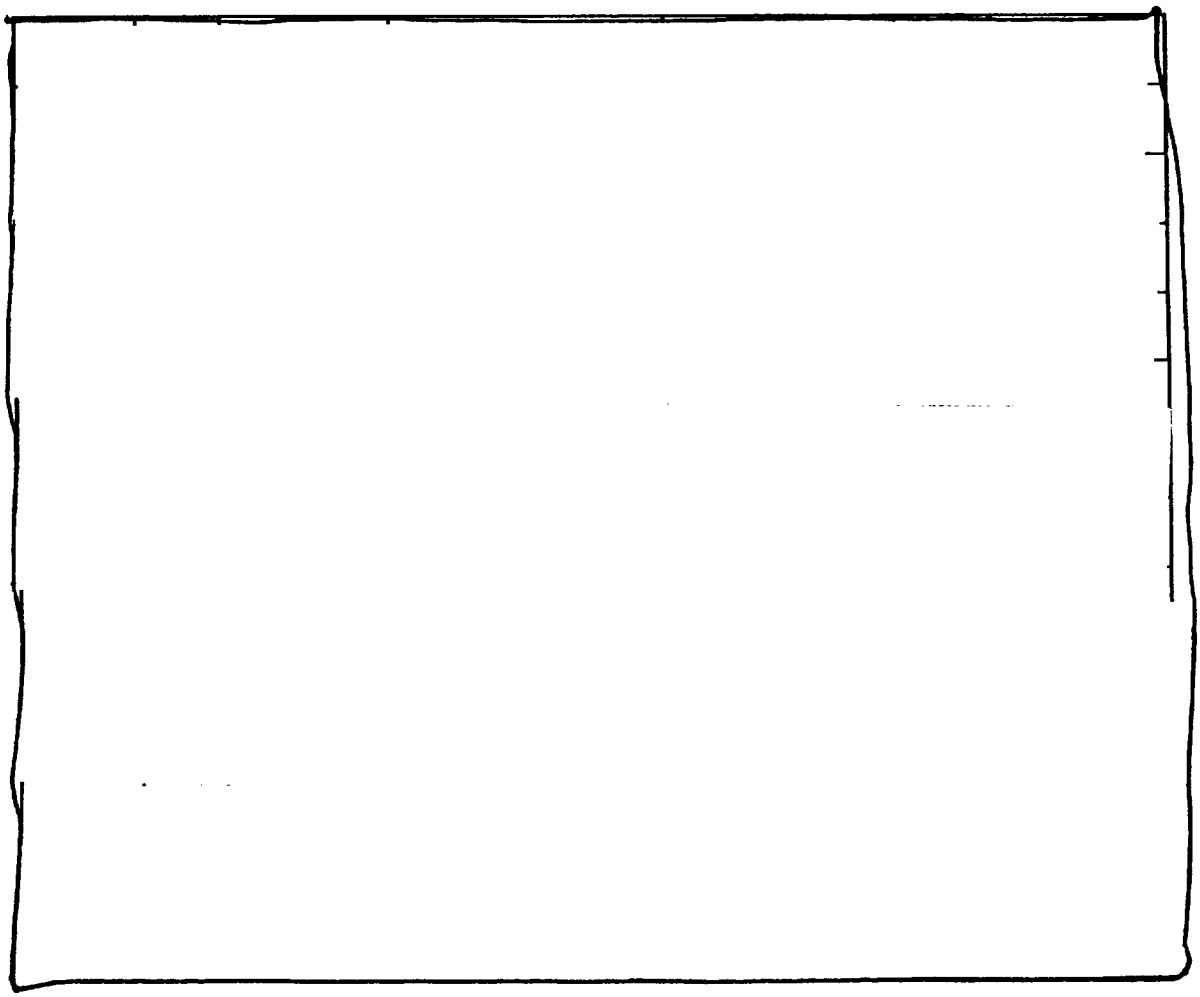
NAME & ADDRESS OF APPLICANT:
McNeil Consumer Healthcare
Camp Hill Road
Fort Washington, PA 19034

DRUG PRODUCT NAME:
PROPRIETARY: Imodium Advanced Caplet
NONPROPRIETARY: Loperamide HCl/Simethicone caplet
CHEMICAL TYPE/THERAPEUTIC CLASS: 4

INDICATION: control of symptons of diarrhea plus bloating, pressure, and cramps commonly associated with gas
DOSAGE FORM: capsule-shaped, uncoated tablet (caplet)
STRENGTH: 2 mg Loperamide HCl/125 mg Simethicone
ROUTE OF ADMINISTRATION: oral
HOW DISPENSED: OTC
CHEMICAL STRUCTURE: USP drug substances & non-USP drug product

SUPPORTING DOCUMENTS:





DOCUMENTS SUPPORTED BY THIS FILE: None
RELATED DOCUMENTS: See CMC Review #1
SPECIAL PRODUCT: No
CONSULTS:

Biopharm: see conclusion in CMC Review #1, Addendum
EER: all sites acceptable
Trademark: resolved by OTC division

REMARKS/COMMENTS:

This is a response to the AE letter dated 08/17/00 which was FAXed to the firm.

CONCLUSIONS & RECOMMENDATIONS:

The proposed application is APPROVABLE (AE) for CMC issues pending acceptance of the conclusions listed in the draft in section H of this review.

/S/ ; 11/14/00. /S/ 11/14/00 wrq

Mike Adams
Review Chemist, HFD-820

/S/

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-820

cc:
NDA 21-140
HFD-180/div file
HFD-181/CSO/P.Levine
HFD-820/M.Adams
R/D Initial: L.Zhou 11/ /00