Finally, as discussed with Dr. Haber on February 10, 2000, we will submit an amendment describing the change from a — count to a 24-count sample bottle as soon as one-month accelerated stability data are available on the new configuration. We expect this submission to be provided later this month.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

GelTex PHARMACEUTICALS, INC.

February 3, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141 and NDA 21-176
Cholestagel® (colesevelam hydrochloride)
Amendment 002
Replacement of Cholestagel® trade name with Welchol™

Dear Sir/Madam:

Reference is made to the NDAs cited above for Cholestagel® (colesevelam hydrochloride) and to a February 3 telephone conversation between Dean Alger of GelTex and Margaret Simoneau and Bill Koch of CDER. As discussed, **the purpose of this submission is to replace the Cholestagel® trade name with Welchol™.**

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

ORIGINAL

SU

GelTex PHARMACEUTICALS, INC.

BEST POSSIBLE COPY

November 29, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141 and NDA [redacted]
Cholestagel® (colesevelam hydrochloride)
Amendment 001
Four Month Safety Update Report

Dear Sir/Madam:

Reference is made to the NDAs cited above for Cholestagel® (colesevelam hydrochloride). The purpose of this submission is to provide this four month Safety Update Report.

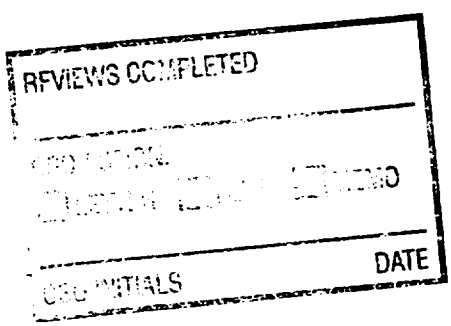
Please note that there is no new safety information to report for Cholestagel® at this time. There have been no ongoing or new clinical studies conducted with the drug since the submission was prepared. The Integrated Summary of Safety and the Risk-Benefit Discussion remain unchanged from the original submission.

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

Martha J. Carter
Vice President, Regulatory Affairs

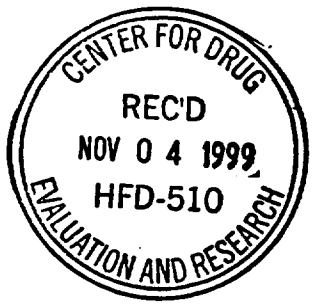


153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5800 Website: www.geltex.com

GelTex PHARMACEUTICALS, INC.

ORIGINAL

VC



November 3, 1999

Margaret Simoneau, R.Ph.
Regulatory Project Manager
Division of Metabolic & Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141 and 21-176
Cholestagel® (colesevelam hydrochloride)
Additional Carcinogenicity Datasets

Dear Margaret:

As discussed, I have enclosed the duplicate diskettes containing datasets from the mouse and rat carcinogenicity studies (Study Nos. GT-02-TX-24 and -25, respectively) conducted with colesevelam hydrochloride. Included is an additional complete copy of one set (three diskettes), as follows:

Disk 1 – Tumor data from GT-02-TX-24 [Project 87966 (mouse)]
Disk 2 – Food consumption and body weights from GT-02-TX-24 and -25 [Projects 87966 (mouse) and 87989 (rat)]
Disk 3 – Tumor data from GT-02-TX-25 [Project 87989 (rat)]

Also included is one additional copy of disk 3. Please note that these diskettes are exact copies of those sent to you on September 7th.

As always, please feel free to call me if you have any questions or require additional information.

Best regards,

Dean F. Alger
Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

GelTex
PHARMACEUTICALS, INC.

ORIGINAL

October 14, 1999

NEW CORRESP
NC

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Document Room 14B-04
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Noted
/S/

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT 15 1999
HFD-510

RE: NDA 21-141
Cholestagel® (colesevelam hydrochloride)
Change of Address

Dear Dr. Sobel:

We are pleased to inform you that GelTex Pharmaceuticals Inc., has recently moved to a new facility. The new official address for all correspondence is:

GelTex Pharmaceuticals, Inc.
153 Second Avenue
Waltham, MA 02451

Noted
/S/ 10-28-99

The main fax number to be used for all regulatory correspondence is (781) 895-4981.

Although the main phone number for the facility remains (781) 290-5888, the direct phone lines for the official contacts for this NDA at GelTex Pharmaceuticals, Inc., 153 Second Ave, Waltham, MA 02451 are:

Noted
/S/ 10/28/99

Dean F. Alger
Director, Regulatory Affairs
Tel: (781) 434-3421

Martha J. Carter
Vice President, Regulatory Affairs
Tel: (781) 434-3443

Debra Sojka
Senior Associate, Regulatory Affairs
Tel: (781) 434-3513

APPEARS THIS WAY
ON ORIGINAL

Please do not hesitate to contact us if you have questions or require additional information.

Sincerely yours,

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED
CSO ACTION:
LETTER MEMO
10-29-99
DATE
CSO INITIALS

GelTex PHARMACEUTICALS, INC.

SUPPL NEW CORRESP
SNC

ORIGINAL

October 5, 1999

Margaret Simoneau, R.Ph.
Regulatory Project Manager
Division of Metabolic & Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

/S/ 12/2/99

RE: NDA 21-141 and 21-176 (cover letter only)
Cholestagel® (colesevelam hydrochloride)
Response to FDA Request for Information
Word Files of Draft Labeling

Where is diskette?
/S/
1-4-00

Dear Margaret:

As discussed, I have enclosed one diskette containing the Word files of the draft labeling from the NDAs cited above. Please note that these are the exact files from which the pdf versions were created for the submission.

Please feel free to call me if you have any questions or require additional information. Again, my new phone number is (781) 434-3421.

Best regards,

/S/ 12/15/99

Dean F. Alger
Director, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
DATE
INITIALS

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5800 Website: www.geltex.com

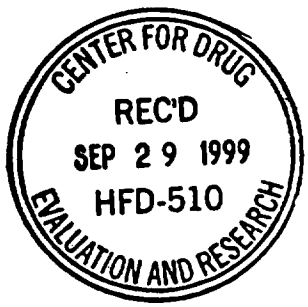
GelTex PHARMACEUTICALS, INC.

ORIGINAL

ORIG AMENDMENT
SMC

September 28, 1999

Martin T. Haber, Ph.D.
Chemistry Reviewer
Division of Metabolic & Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-141 and NDA 21-176
Cholestagel® (colesevelam hydrochloride)
Response to Request for Information

Dear Dr. Haber:

As requested during your telephone conversation with Martha Carter today, enclosed is a table of volumes listing the specific information included in each of the twelve volumes (volumes 2 through 13) of the CMC section of the NDA cited above.

Also enclosed is an additional copy of the Environmental Assessment with its appendices, from the CMC section. Please note that this is an exact copy from the original submission.

Please feel free to call me at (781) 434-3421 with any further questions or if you require additional information.

Best regards,

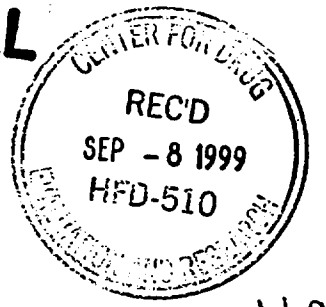
Dean F. Alger
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

SUPPL NEW CORRESP

GelTex PHARMACEUTICALS, INC.

ORIGINAL



NC /S/ 3/28/00

Noted /S/ 4/4/00

September 7, 1999

Margaret Simoneau, R.Ph.
Regulatory Project Manager
Division of Metabolic & Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-141 and 21-176
Cholestagel® (colesevelam hydrochloride)
Carcinogenicity Datasets

Stat Reviews complete dated 3/17/00
/S/ 3/24/00

Dear Margaret:

As discussed, I have enclosed the diskettes containing datasets from the mouse and rat carcinogenicity studies (Study Nos. GT-02-TX-24 and -25, respectively) conducted with colesevelam hydrochloride. Included are the requested two copies (one each for Drs. Steigerwalt and Sahlroot) of three diskettes, as follows:

Disk 1 – Tumor data from GT-02-TX-24 [Project 87966 (mouse)]
Disk 2 – Food consumption and body weights from GT-02-TX-24 and -25 [Projects 87966 (mouse) and 87989 (rat)]
Disk 3 – Tumor data from GT-02-TX-25 [Project 87989 (rat)]

Noted /S/ 4/20/00

Please note that these diskettes contain the data that would be located in the folder named "pharmtox/datasets" in the electronic copy of the NDAs cited above.

I look forward to hearing from you after your filing meeting next week. Please feel free to call me if you have any questions or require additional information.

Best regards,

Dean

Dean F. Alger
Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

/S/ 04/18/00
CSO INITIALS DATE

Nine Fourth Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

Meeting Date: April 25, 2000 Time: 1:30 PM Location: PKLN Room #1456

NDA 21-141 & 21-176 Welchol (colesevelam hydrochloride)

Type of Meeting: Industry Labeling

External Participant: GelTex Pharmaceutical, Inc.

Meeting Chair: Ronald W. Steigerwalt, Ph.D.; Pharmacology Team Leader

External Participant Lead: Martha Carter, Vice President, Regulatory Affairs

Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

Ronald W. Steigerwalt, Ph.D.; Pharmacology Team Leader
Gemma Kuijpers, Ph.D., Pharmacology Reviewer
William C. Koch. R.Ph.; Regulatory Project Manager

External participant Attendees (by phone) and titles:

Dean Alger, Director, Regulatory Affairs
Martha Carter, Vice President, Regulatory Affairs
Judith Marquis, Ph.D., Senior Director, Preclinical Development
Edmund Sybertz, Ph.D., Senior Vice President, Research & Development

Meeting Objectives:

To discuss changes in the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section of the labeling with the applicant.

Discussion Points:

The Division initiated the discussion by asking for an explanation of the rationale for examining only part of the low and mid-dose rat tissues from the 104 week carcinogenicity study.

The remainder of the meeting was focused upon the revisions to the two paragraphs pertaining to the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section in particular with regard to the significance of the rat study tumor findings, and the results from the chromosomal aberration assay.

Decisions (agreements) reached:

The Division agreed to suggestions made by the applicant contingent upon pharm/tox team approval of a draft label to be e-mailed to the project manager.

Action Items:

The Division pharm/tox team will review the draft label resulting from this telephone discussion, and either approve the suggestions or submit further revisions to the applicant.

Prepared by: /S/ 04/26/00, Regulatory Project Manager
William C. Koch, R.Ph. date

Concurrence: /S/ 4/26/00, Meeting Chair
Ronald Steigerwalt, Ph.D. date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA 21-141
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-510/CSO
HFD-510/reviewers & attendees

Drafted by: WKoch/04.25.00
Initialed by: GKuijpers04.26.00/RSteigerwalt04.26.00
final: WKoch/04.26.00
filename: ———————————————————

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: April 19, 2000 Time: 3:00 PM Location: PKLN Room #1456

NDA 21-141 & 21-176 Welchol (colesevelam hydrochloride)

Type of Meeting: Industry Labeling

External Participant: GelTex Pharmaceutical, Inc.

Meeting Chair: David Orloff, M.D., Deputy Director

External Participant Lead: Dean Alger, Director, Regulatory Affairs

Meeting Recorder: Mr. William C. Koch, Regulatory Project Manager

FDA Attendees and titles:

David G. Orloff, M.D., Deputy Director
Shiao-Wei Shen, M.D., Medical Officer
Ronald Steigerwalt, Ph.D.; Pharmacology Team Leader
Gemma Kuijpers, Ph.D., Pharmacology Reviewer
Robert Shore, Pharm.D., Biopharmaceutics Reviewer
Andrew Haffer, Pharm.D., Regulatory Review Officer
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees (by phone) and titles:

GelTex Pharmaceuticals, Inc.

Dean Alger, Director, Regulatory Affairs
Steven Burke, M.D., Vice President, Clinical Research
Martha Carter, Vice President, Regulatory Affairs
Joanne Donovan, M.D., Ph.D., Medical Director
Daniel Lundberg, Welchol Project Director
Judith Marquis, Ph.D., Senior Director, Preclinical Development
Edmund Sybertz, Ph.D., Senior Vice President, Research & Development

Sankyo Parke Davis

William Bailey, Pharm.D., Director, Medical & Scientific Affairs
John Gargiulo, Vice President, Marketing

Meeting Objectives:

To discuss with the applicant and their marketing associates the revisions made to submitted draft labeling at the April 13, 2000, internal meeting.

Discussion Points:

The labeling revisions and the reasons for the revisions were discussed by each individual reviewer with industry representatives.

Decisions (agreements) reached:

The Division and the applicant agreed upon revisions to be submitted by the applicant.

The applicant requested more time to evaluate the recommendations made by the Pharm/tox team.

Unresolved or issues requiring further discussion:

The **Carcinogenesis, Mutagenesis, Impairment of Fertility** section of the labeling needs to be discussed further after the pharm/tox team has consulted with the statisticians.

Action Items:

The project manager will arrange a telephone conference between the applicant and the pharm/tox review team to further discuss the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section of the label.

Prepared by. /S/ 04/25/00, Regulatory Project Manager
William C. Koch, R.Ph. date

Concurrence: /S/ 4-25-00, Meeting Chair
David G. Orloff, M.D. date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA 21-141
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-510/CSO
HFD-510/reviewers & attendees

Drafted by: WKoch/04.19.00
Initialed by: RShore04.24.00/GKuijpers.04.24.00/RSteigerwalt04.25.00/SShen/
DOrloff04.25.00.
final: WKoch/04.25.00
filename:

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: April 13, 2000 Time: 02:30 PM Location: PKLN Room #1456

NDA 21-141 & 21-176 Welchol (colesevelam HCl)

Type of Meeting: Internal Labeling

Meeting Chair: David Orloff, M.D., DMEDP Deputy Director

Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

David Orloff, M.D., DMEDP Deputy Director
Shiao-Wei Shen, M.D., Medical Officer
Ronald Steigerwalt, Ph.D.; Pharmacology Team Leader
Robert Shore, Pharm.D., Biopharmaceutics Reviewer
Andrew Haffer, Pharm.D., Regulatory Review Officer
William C. Koch, R.Ph., Regulatory Project Manager

Meeting Objectives:

To review the labeling for these new drug applications.

Discussion Points:

Changes to the draft labeling were proposed by each reviewer.

Action Items:

Medical reviewer and project manager will meet on April 14, 2000, prior to the industry labeling teleconference, to discuss proposed changes.

Prepared by: /S/ 04/20/00, Regulatory Project Manager
William C. Koch, R.Ph. date

Concurrence: /S/ 4/24/00, Meeting Chair
David Orloff, M.D. date

cc: Original NDA 21-141
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-510/CSO
HFD-510/reviewers & attendees

Drafted by: WKoch/04.13.00
Initialed by: DOrloff/04.24.00
final: WKoch04.24.00
filename:

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION OR MEETING	DATE: 04/13/00 Time: 1000 hrs Location: PKLWN#14B04 68
FDA Attendees: W. Koch **Objectives:** Discuss acceptability of Submitted proprietary name, Welchol. **Discussion:** Division assessed March 27, 2000 submission. **Conclusion(s):** Division finds the Welchol Name acceptable. /S/ 04/13/00 William C. Koch, R.Ph. Date Regulatory Project Manager	**Telecon initiated by:** FDA **NDA:** 21-141 & 21-176 **Product name:** (colesevelam HCl) **Firm name:** GelTex Pharma **Name and title of person with whom conversation was held:** Dean Alger, Director, Regulatory Affairs **Telephone:** (781) 434-3421

Cc: Original NDA 's 21-176 & 21-141
Division File

Filename:

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION OR MEETING	DATE:01/14/00 Time:1330-1400 Location: PKLWN#1456
FDA Attendees: D. Orloff, MD S. Shen M. Simoneau W. Koch **Objectives:** Safety concerns with Proposed proprietary name raised by OPDRA will be discussed With sponsor. **Discussion:** Safety concerns re: proprietary name Presented by Dr. Orloff. Geltex: [redacted] **Conclusion(s):** Sponsor will submit new Proprietary name for review. /S/ 01/18/00 William C. Koch,R.Ph. Regulatory Project Manager	**Telecon initiated by:** Sponsor: ~~Geltex Pharmaceuticals~~ FDA **NDA: 21-176** **Product name:** Cholestagel **Firm name:** Geltex Pharmaceuticals **Name and title of person with whom conversation was held:** Dean Alger Director, Regulatory Affairs **Telephone:** (781) 434-3421

Cc: Original NDA 's 21-176 & 21-141
Division File

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** April 20, 2000
Date: September 16, 1999 Location: 14B74 Format: Teleconference FDA Attendee: Margaret Simoneau GelTex Attendee (by phone): Dean Alger, Director Regulatory Affairs 1. This telephone call was initiated by the Agency to notify the sponsor of the results of the filing meeting. This filing meeting took place on Wednesday, September 15, 1999 at 12:30 PM. 2. The sponsor was informed of the following: • The submission was filed and that it would be a standard review. • The electronic submission for the statistical section of the NDA was unacceptable but since the sponsor provided a hard copy the application was fileable. • Biopharm had further comments and I would be faxing those to the sponsor. cc: NDA 21-141 NDA 21-176 DivFile Margaret Simoneau /S/	**IND/NDA#:** NDA 21-141 Cholestagel 375 mg Caps and NDA 21-176 Cholestagel 625 mg Tablets **Telecon/Meeting initiated by:** O Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** **Firm Name:** GelTex Pharmaceuticals, Inc. **Phone:** (781) 290-5888 Ext 721

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Division of Metabolic and Endocrine Drug Products
NDA 21-141 Cholestagel 375 mg caps
NDA 21-176 Cholestagel 625 mg tablets

Date: Wednesday, September 15, 1999
Location: Parklawn 1456
Time: 12:30-1:30 PM

FDA Attendees:
Dr. Orloff
Dr. Shen
H. Ahn
R. Shore
R. Steigerwalt
G. Kuijpers
T. Sahlroot
J. Mele
D. Wu
M. Haber
M. Simoneau

This was a **Filing Meeting** for Cholestagel (colesevelam hydrochloride) capsules and tablets. The indication is for the reduction of elevated LDL cholesterol, alone or in combination with HMG-CoA reductase inhibitors.

Discussion:

- Clinical- no filing issues and the financial disclosure form was submitted.
- Pharmacology-Gemma Kuijpers said that there were no pharm/ tox issues.
- Chemistry-Martin Haber said that there were no chemistry issues.
- Biopharm- There were no filing issues according to Rob Shore. Reference to the Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDAs, Section 6 will be information requested for the sponsor to submit.
- Biostatistics- See enclosure 1. According to Joy Mele, the statistical section of the electronic submission was unacceptable. Since the sponsor provided a hard copy, the application was filable.
- DSI- Roy Blay was not present at the meeting so an e-mail will be sent to him with all the information necessary to conduct clinical audits.
- This submission will be a standard review. MAPP 6020.3 Priority Review Policy and comments regarding granting priority status from Biometrics were discussed.

- Advisory Committee- not needed.
- Review Goal Date with labeling- May 30, 2000 (User Fee at 10 months). Reviews are to be done by April 1, 1999.

Minutes preparer: M. Simoneau /S/ 9/23/99

Concurrence Chairman: Dr. Orloff /S/ 7/27/99

cc:Original NDA 21-141
NDA 21-176
DivFile

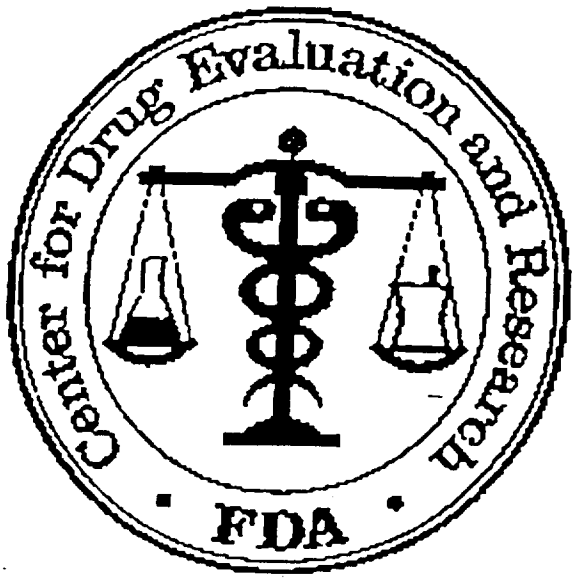
APPEARS THIS WAY
ON ORIGINAL

NO ADVISORY COMMITTEE MEETING

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE : September 16, 1999



TO:

Name: Dean Alger

Fax No.: 781-895-4960

Phone No.: 781-290-5888 x 721

Location: 62 TEX

Pages: 3 (including cover)

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6418

Location: FDA

Comments:

Biopharm request

APPEARS THIS WAY
ON ORIGINAL

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — NDAs

Section 6 only

APPEARS THIS WAY
ON ORIGINAL

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

IT 3
January 1999

a. Proposed labeling text

The proposed labeling text would be the draft labeling with an initial application or subsequent supplements, labeling provided with changes being effected submissions, or labeling changes submitted with the annual report. You should provide the proposed labeling text as a PDF file named *proposed.pdf*. Fill in the Document Information fields as described above.

In addition to the PDF file, you should provide all draft labeling text with an initial application or subsequent supplements in a word processing format as a review aid for editing purposes. You should consult the review division for the word processing format and version currently being used in the center.

b. Current labeling text

The current labeling text refers to the labeling text that is being used at the time of the submission. This labeling can be approved labeling as well as labeling that has not been approved such as changes being effected or changes with the annual report. You should provide the current labeling text as a PDF file named *current.pdf* and fill in the Document Information fields as described above.

c. Last approved labeling text

The last approved labeling text is the labeling most recently approved. You should provide the last approved labeling text as a PDF file named *approved.pdf*. Fill in the Document Information fields as described for labeling text.

5. Package insert

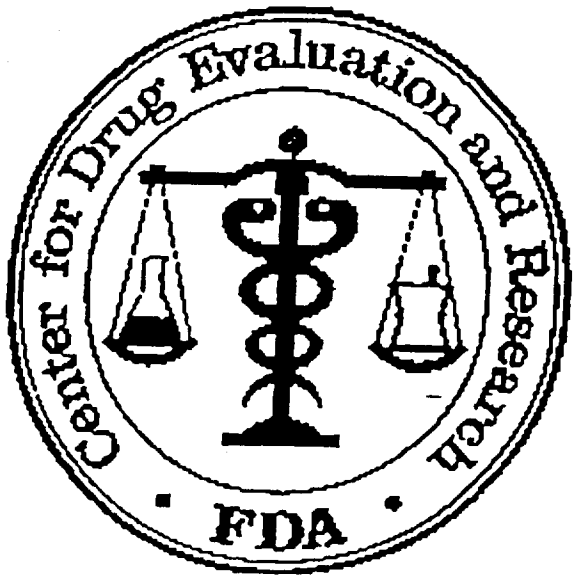
You should provide the final printed package insert as a single PDF file named *pi.pdf*. Fill in the Document Information fields as described with the labeling text.

6. Carton labeling

You should provide the carton labeling (all panels) as a PDF file(s). Fill in the Document Information fields as described with the labeling text.

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: August 26, 1999



TO:

Name: Dean Alger

Fax No.: 781-895-4980

Phone No.: 781-290-5888 x 721

Location: GELTEX

Pages: 2 (including cover)

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6418

Location: FDA

Comments:

NDA 21-141 + NDA 21-176 Amend Ack Ltr

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-141
NDA 21-176

GelTex Pharmaceuticals, Inc.
Attention: Martha J. Carter
Vice President, Regulatory Affairs
Nine Fourth Avenue
Waltham, MA 02451

AUG 26 1999

Dear Ms. Carter:

We refer to your new drug applications for Cholestagel (colesevelam hydrochloride) 375 mg Capsules (NDA 21-141) and for Cholestagel (colesevelam hydrochloride) 625 mg Tablets (NDA 21-176) and also to our August 2, 1999, acknowledgement letters.

This letter corrects the filing date stated on our acknowledgment letters. We apologize for any inconvenience this may have caused.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, the applications will be filed under 505(b) of the Act on September 28, 1999, in accordance with 21 CFR 314.101(a).

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely yours,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Reseacch

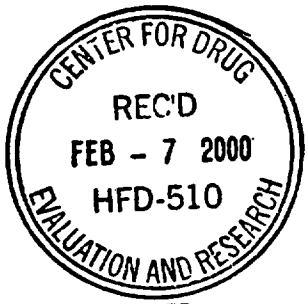
APPEARS THIS WAY
ON ORIGINAL

GelTex PHARMACEUTICALS, INC.

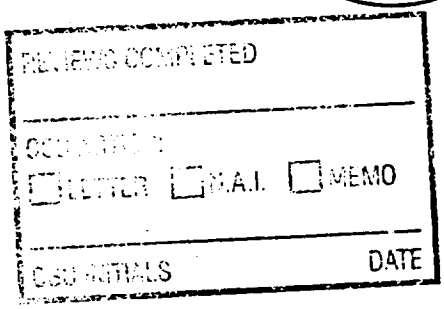
NC

ORIGINAL

February 4, 2000



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-141 and NDA 21-176
Cholestagel® (colesevelam hydrochloride)
Amendment 003
Response to January 14, 2000 Facsimile
Revised Environmental Assessment

Dear Sir/Madam:

Reference is made to the NDAs cited above for Cholestagel® (colesevelam hydrochloride), and to the Agency's facsimile of January 14, 2000 containing comments on the environmental assessment in section 4.4.

The purpose of this submission is to respond to your comments, and to provide a revised environmental assessment (EA) in Attachment 1. For ease of review, the Agency's requests/comments are repeated in ***bold italics***, followed by our responses.

General comment: In July 1997 FDA's regulations regarding environmental assessments (21 CFR Part 25) were revised. A revised guidance entitled Environmental Assessment of Human Drug and Biologics Applications (July 1998) was issued. The environmental assessment (EA) submitted in support of NDA 21-141 is based on the previous regulations and guidance and provides information that is now not routinely needed such as information on manufacturing sites. You may retain this information while revising this EA if you choose. However you may wish to consider not providing this information in future EAs unless specifically needed because of an extraordinary circumstance.

We apologize for this oversight. In the interest of maintaining a complete file, the revised EA in Attachment 1 retains all information from the original document. The appropriate revisions are indicated with highlighted text, and are referenced in our individual responses to your comments. Please note that no changes were made to any of the appendices to the document. We will base any future EAs on the revised regulations and July 1998 guidance document, which we consulted when addressing these comments.

153 Second Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

The following deficiencies in the environmental assessment submitted for NDA 21-141 should be corrected and a revised EA submitted. The citations included at the end of the deficiency refer to the section number of the EA guidance (cited above) which should be consulted when addressing the deficiency.

1. ***4.4.1.4.1: The citation to the regulations is not correct (IV.A.4.a).***

Please see page 3 of the attached, revised EA for the correct citation to the regulations.

2. ***4.4.1.4.3: The expected locations of use should be specified (IV.A.4.c).***

It is expected that the drug will be used by patients in their homes (please see page 3 of the revised EA).

3. ***4.4.1.6: Information on the substances expected to enter the environment (i.e., parent compound, metabolites) from use of the drug and the rationale for studying the parent compound should be provided (IV.B.1.a.i).***

Colesevelam hydrochloride, the parent compound, is expected to be the only substance entering the environment. Colesevelam hydrochloride has been shown to be stable for a minimum of 12 months at controlled room temperature. Colesevelam hydrochloride is not photosensitive and is not sensitive to freeze-thaw cycling. Only a slight increase in the primary degradation products is noted over time. Stability testing indicates that colesevelam hydrochloride is stable under all tested storage conditions.

Although colesevelam hydrochloride is a highly cross-linked polymer that is insoluble in all tested aqueous and organic solvents, testing was conducted to determine if potential leachables (*i.e.*, impurities trapped in the polymeric matrix) could be extracted from colesevelam hydrochloride by solvents. Various solvents were used in order to solubilize and extract any and all potential leachables in colesevelam hydrochloride. The tested solvents include water, 0.1 N HCl, 0.1 N HCl/50 °C, 1 N ammonium hydroxide, methylene chloride, acetonitrile, and methanol. A minimal amount of material is extracted from colesevelam hydrochloride in all tested solvents except for 1N ammonium hydroxide where an ammonium chloride salt is formed. Water and 0.1 N HCl gave the greatest amount of extractable residue. Very little material was extracted with the three organic solvents.

In addition, the stability of colesevelam hydrochloride was investigated in acid, base, and hydrogen peroxide solution. The only condition where substantial degradation was obtained was exposure of colesevelam hydrochloride to 30% hydrogen peroxide at room temperature, where the pH had been adjusted to 11 with ammonium hydroxide. After 24 hours under these extreme conditions, the total degradants level was 4.3% by ion chromatography and 7.1% by gas chromatography. However, these very aggressive conditions would not typically be encountered in nature.

4. ***4.4.1.6.10: The highest quantity expected to be produced in any of the next 5 years should be used in the calculations (III.A.2).***

The highest quantity of product which is expected to be produced in any of the next 5 years is 2×10^5 kg/year, the number used in the original EA. Using the calculation from the current guidance,

EIC-Aquatic (ppb) = A x B x C x D where

A = kg/year produced for direct use (as active moiety)
B = $1/1.214 \times 10^{11}$ liters per day entering publicly owned treatment works (POTWs)
C = year/365 days
D = 10^9 µg/kg (conversion factor)

EIC-Aquatic (ppb) =
2×10^5 kg/year x $1/1.214 \times 10^{11}$ liter per day x 1 year/365 days x 10^9 µg/kg = 4.5 ppb

Colesevelam hydrochloride was tested in an activated sludge respiration inhibition test and colesevelam hydrochloride did not inhibit respiration rates for bacteria at concentrations up to 300 mg/L. [The tested concentration far exceeds the EIC concentration.]

Please see page 23 of the revised EA for the new calculation.

5. *4.4.1.7.2:*

   a. ***A brief description of the test method used to determine the physical/chemical characteristics of colesevelam hydrochloride should be provided (IV.D). If the statements about the characteristics were based on fundamental chemical principles (e.g., chemical structure of the compound) rather than actual testing then this should be included.***

Colesevelam hydrochloride is a highly cross-linked polymer that is insoluble in all tested aqueous and organic solvents (water, methanol, 0.1 N HCl, acetonitrile, methylene chloride, and 1 N ammonium hydroxide). Please see Section 4.1.7 of NDA 21-141 for a description of the solubility testing performed on the drug substance.

In order to determine what could be leached out of the polymer, colesevelam hydrochloride was extracted with all of the aforementioned solvents. Solid colesevelam hydrochloride (2.5 g) was extracted with solvent (40 mL) at room temperature for 16 hours. The slurry was then [redacted] and the solvent was evaporated. [redacted] (for Br, Cl and quaternary amine related substances) and by [redacted] (for ordinary impurities). The level of soluble oligomers was determined by a [redacted] which quantitates the levels of

soluble amines. All individual identified impurities were less than 0.1%. Please see Appendix 4.1-3 of NDA 21-141 for a detailed description of the leachability study.

Since colesevelam hydrochloride is not soluble in either water or octanol, the partition coefficient could not be determined.

Colesevelam hydrochloride is a polyelectrolyte and there is no discrete dissociation constant. Acid-base titration is used to quantitate both the primary and secondary titratable amines in colesevelam hydrochloride. The total titratable amines of colesevelam hydrochloride are from the poly(allylamine hydrochloride) starting material. The total titratable amines range from 4.4 to 4.8 mmoles of amine per gram of colesevelam hydrochloride, on an anhydrous basis. The total titratable amines for a representative lot of colesevelam hydrochloride, Lot TLMC005-1840, is 4.6 mmoles of amine per gram. The experimental value differs from the theoretical amine content of 5.0 mmoles of amine per gram of colesevelam hydrochloride. This difference is likely due to the broad titration curve associated with the titration of polyelectrolytes that results in a small percentage of the amines not being titrated. Please see Appendix 4.1-34 of NDA 21-141 for a detailed description of the titratable amine quantitation protocol.

b. The statement that colesevelam hydrochloride has "no" vapor pressure needs to be clarified. Substances with very low vapor pressure are typically reported, for example, as having a vapor pressure of $<10^{-5}$ Pa.

Because colesevelam hydrochloride is a cross-linked polymer, each particle is one molecule due to multiple covalent cross-links between polymer chains. [This is supported by the insolubility of the compound.] Therefore, the molecular weight of an individual particle is equal to the weight of the particle itself. The molecular weight of a particle can be calculated from the diameter of the particle, the pycnometric density of colesevelam hydrochloride and the conversion factor from grams to atomic mass units (amu). Since the pycnometric density of colesevelam hydrochloride is 1.11 g/cm ^{3}, the molecular weight of a 25 µm diameter particle of colesevelam hydrochloride is equal to 5.4×10^{15} amu. A substance with such high molecular weight has no vapor pressure, therefore, a vapor pressure test of colesevelam hydrochloride was not performed.

TGA-FT-IR data confirm that the only volatile compound detected in colesevelam hydrochloride during heating from ambient to 160°C is water. At higher temperatures the compound begins to decompose.

6. 4.4.1.7.3: Hydrolysis and photolysis as potential depletion mechanisms should be discussed (IV.B.1.a.iii).

The hydrolytic stability of colesevelam hydrochloride was investigated in acid and in base solution. Approximately 1 g of colesevelam hydrochloride was suspended in 10 mL of 1 N NaOH and 10 mL of 1 N HCl. The mixtures were stored at 60°C for 12 hours. After centrifugation, the supernatant was diluted 1:5 and analyzed by gas

chromatography and ion chromatography. Both the acid- and base-treated samples showed no detectable peaks by gas chromatography. By ion chromatography the total level of stability-indicating impurities was less than 0.1%. These results indicate that colesevelam hydrochloride is very stable in acid and base solution. Please see Section 4.1.10.10 of NDA 21-141 for a description of the degradation testing performed.

Photostability studies were conducted on colesevelam hydrochloride following ICH Guidelines using UV-b, daylight, and fluorescent bulbs (1.2 million-lux hours and 200 watt hours/m^2) with the sample placed in an open petri dish. Colesevelam hydrochloride was found to be stable under these conditions. In addition, photolysis as a potential depletion mechanism was discussed with Dr. Hofer, a toxicologist at Seiberdorf. In his opinion, photolysis is relevant mainly for gaseous materials in the atmosphere. Photolysis of a polymer suspended in water or deposited in sludge is predicted to have no significance for depletion.

In conclusion, neither hydrolysis nor photolysis is expected to be a potential depletion mechanism for colesevelam hydrochloride. Colesevelam hydrochloride is expected to remain intact.

7. ***4.4.1.7.5: A more detailed discussion of the expected fate of colesevelam hydrochloride, based on its physical/chemical properties, should be provided. For example, because of the insolubility of the compound, what would be expected to happen in the waste water treatment process or if it entered the aquatic environment (IV.B.1.a.v).***

Colesevelam hydrochloride, the parent compound, is expected to be the only substance entering the environment. If the entire amount of colesevelam hydrochloride produced were to enter the aquatic environment, the level calculated from the "EIC-Aquatic" equation is 4.5 ppb. This amount is 1000 - 10,000 times lower (in the effluent) than the toxicity level. [The EC_{50} in Daphia magna at 24h and 48h is higher than 100mg/L (loading rate). The LC50 in fish (Zebrafish) at 24h, 48h, 72h, and 96h was higher than 100mg/L (loading rate). For algae (Selenastrum capricornutum) the $NOEC_{0\text{-}72H}$ was 25.3 mg "loading" per liter and the $EC50_{0\text{-}72H}$ = 67.2 mg "loading" per liter.]

In addition, preclinical studies show that ^{14}C-colesevelam hydrochloride is essentially not absorbed in rats or dogs and clinical studies have confirmed the lack of absorption in humans. Because colesevelam hydrochloride is unabsorbed in mammals, it should be unabsorbed in aquatic species and, therefore, should not bio-accumulate. Colesevelam hydrochloride is not metabolized. The insolubility, molecular weight, and lack of absorption in mammals indicate that colesevelam hydrochloride is not bioavailable. In addition, all toxicity studies indicate a very low level of toxicity.

Lastly, colesevelam hydrochloride is predicted to adsorb completely and irreversibly to the biosolids in a wastewater treatment process and, as such, is expected to be land filled or incinerated. Indeed, compounds of a similar nature serve as flocculating agents.

8. ***4.4.1.8: In the text of the EA for the daphnia and fish studies it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These conflicting statements should be explained. The EA text should fully explain and justify why analysis was not performed for each occurrence.***

The statements "There is no method of analysis of the soluble components of the test substance available" and "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available" should be clarified. Colesevelam hydrochloride is not soluble in water and it is stable towards hydrolysis within the time incubated in aqueous solutions during the tests (24 to 72 hours).

The test solutions were prepared by grinding the test substance in a mortar, adding to water at the desired concentration, stirring for the required time, and filtering. The filtrate was then used for the testing. The recovered colesevelam hydrochloride was analyzed (IR, elemental analysis, volatile impurities, and titratable amines) and showed little or no change occurred during the extraction process.

Parameter	**Test substance before incubation TNBC 401**	**Test substance after incubation in *Daphnia*-water and drying**	**Test substance after incubation in fish-water and drying**	**Test substance after incubation in algae-water and drying**
dry substance (IR, 15 min, 120 °C)	98.12 %	97.40 %	99.22 %	97.98 %
elemental analysis	C = 54.40 % H = 11.17 % N = 8.60 % Cl = 20.56 % Br = 0.64 %	C = 54.67 % H = 11.20 % N = 8.86 % Cl = 20.44 % Br = 0.67 %	C = 54.88 % H = 11.10 % N = 8.92 % Cl = 20.26 % Br = 0.67 %	C = 55.50 % H = 11.18 % N = 8.73 % Cl = 20.11 % Br = 0.52 %
volatile impurities	< 0.1% (as specified)	< 0.1%	< 0.1%	< 0.1%
titratable amines	4.56 mmol/g	4.63 mmol/g	4.55 mmol/g	4.56 mmol/g

The filtrates were analyzed for chloride and bromide (see table below). Since the filtrates contained no organic material, they were not tested for stability.

	Acute Toxicity Study in *Daphnia magna*	Acute Toxicity Study in Fish	Algae (*Selenastrum capritornutum*) Growth Inhibition Test
Bromide	< 10 ppm	< 10 ppm	< 10 ppm
Chloride	230 ppm	215 ppm	90 ppm

The trial is representative of what is expected to occur in nature if colesevelam hydrochloride entered the aquatic environment, since colesevelam hydrochloride is not soluble in water.

9. ***4.4.3: Information on any mitigation measures necessary based on the use of the drug should be provided (IV.A.7).***

As stated in the July 1998 guidance document (Section IV.A.7), because no adverse environmental effects have been identified based on use of the drug, no mitigation measures, beyond those described in Section 4.4.3 of the attached EA (see page 31) are needed.

10. ***4.4.5: The name, job title, and qualifications of the people preparing the assessment should be provided (IV.A.9).***

This information is provided in the following table.

Company	Name	Job Title	Qualification
GelTex	Eugene Zhorov	Associate Director, Analytical Development	Ph.D. (Organic Chemistry)
GelTex	Joe Tyler	Vice President, Manufacturing	M. S. (Chemical Engineering)
GelTex	Toni Chancellor	Senior Director, Manufacturing	Ph.D. (Organic Chemistry)
DSM	Christian Ramaseder	Environmental Manager	Dr. Dipl.-Ing.*
DSM	Franz Thomas Schwarz	Safety Manager	Dr. Dipl.-Ing.
DSM	Erich Steinwender	Analytical Chemist	Dr. Mag.**
Seibersdorf***	Norbert Bornatowicz	Head of Toxicology Dept.	Dr.
Seibersdorf	Christine Fenzl	Study Director	Mag.
Seibersdorf	Heinz Hofer	Toxicologist	Dr.
Powdersize	Tom Moran	President	BS (Civil Engineering) and MBA
Global Pharm	Thomas Tassou	Project Manager Manufacturing	B.Sc., (Pharm. Tech., R&D)

* Doctorate degree in engineering. ** Doctorate and master's degree.
*** Austrian Research Center (contract testing laboratory)

Please do not hesitate to contact the undersigned at (781) 434-3443 or Dean F. Alger, Director, Regulatory Affairs at (781) 434-3421 if you have questions or require additional information.

Sincerely yours,

Martha J. Carter.

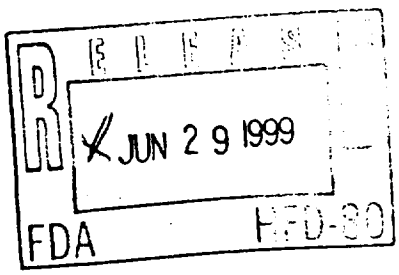
Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

GelTex PHARMACEUTICALS, INC.

July 30, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic & Endocrine Drug Products, HFD-510
Room 14B04
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-141
Cholestagel® (colesevelam hydrochloride)
ORIGINAL APPLICATION

Dear Dr. Sobel:

We are pleased to submit an original new drug application for Cholestagel® (colesevelam hydrochloride). Cholestagel is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia. Studies included in this application support the use of Cholestagel alone or in combination with an HMG-CoA reductase inhibitor. The studies were conducted under IND ——— We are seeking approval for Cholestagel capsules and tablets. ———

Cholestagel is a non-absorbed bile acid sequestrant. Because Cholestagel is a significant improvement over existing bile acid sequestrant therapies, we are requesting priority review status. Cholestagel, we believe, meets three of the four criteria for priority review described in MAPP 6020.3, namely: "(1) evidence of increased effectiveness in treatment, prevention or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; and (3) documented enhancement of patient compliance."

Regarding evidence of increased effectiveness, Cholestagel achieves a mean reduction of nearly 20% in LDL cholesterol at a dose of 4.5 grams per day, whereas cholestyramine and colestipol achieve similar effects at doses of 15 to 30 grams per day. While a comparative efficacy study was not done, it is apparent that Cholestagel is considerably more potent than the currently approved bile acid sequestrants. This directly contributes to Cholestagel's beneficial effects on side effects and on patient compliance.

Nine Fourth Avenue Waltham, MA 02451 Phone: (781) 290-5888 Fax: (781) 290-5890 Website: www.geltex.com

Regarding elimination or substantial reduction of a treatment limiting drug reaction, we point out the superior safety profile of Cholestagel. As reviewed in the Integrated Summary of Safety (ISS) "Discussion" section, compared with published trial data, Cholestagel has approximately one-quarter to one-fifth the risk of constipation and dyspepsia of the available bile acid sequestrants. In addition, other gastrointestinal adverse events associated with other bile acid sequestrants (abdominal pain, bloating, gas and nausea) do not appear to be associated with Cholestagel treatment.

Compared with published clinical trials of other bile acid sequestrants, the percentage of Cholestagel patients discontinuing well-controlled trials may be as little as one-third of that observed with other bile acid sequestrants. In addition, in the long term open label extension study, the Cholestagel discontinuation rate was approximately one-half what would be expected based on published trials of other bile acid sequestrants.

Importantly, Cholestagel did not interfere with the absorption of fat soluble vitamins. Cholestagel was without harmful effect in human drug-drug interaction studies. Cholestagel had no significant effect on the bioavailability of digoxin, metoprolol, quinidine, valproic acid or warfarin in human studies. In contradistinction, the labeling for cholestyramine indicates that it may delay or reduce the absorption of a number of drugs, including propranolol and warfarin. Notably, Cholestagel was administered simultaneously with three different HMG-CoA reductase inhibitors, and no interactions were observed. The ability to dose Cholestagel concurrently with a number of other commonly prescribed medications is a significant advantage over existing bile acid sequestrants.

All of the foregoing factors are likely to contribute to improved patient compliance. The ability to dose once per day; to take other medications, including lipid-lowering therapies, at the same time; and to avoid bothersome and frequent side effects are important elements in achieving a high level of patient compliance. Given the significant benefit on cardiovascular morbidity and mortality demonstrated with currently available bile acid sequestrants, and the alarming prevalence of coronary heart disease, the greater tolerability and convenience of Cholestagel may encourage the initiation of beneficial therapy in a substantial number of patients currently intolerant of bile acid sequestrants or systemic lipid-lowering agents.

Taken together, our data suggest that Cholestagel offers a number of significant advantages over existing bile acid sequestrants. Given the role of bile acid sequestrants in the physician's armamentarium to treat hypercholesterolemia, agents that are a significant improvement over existing marketed products should receive priority status. We respectfully request your consideration of priority status for Cholestagel.

In accordance with the guidance for industry entitled "Providing Regulatory Submissions in Electronic Format – NDAs (January 1999)," we are submitting this new drug application electronically. The following table describes which portions are presented only in paper, which portions are presented only in electronic format, and which portions

are presented in both paper and electronic format.

NDA Section	*Title*	*Paper*	*Electronic*
1.	Index	✓	✓
2.	Labeling	✓	✓
3.	Summary	✓	✓
4.	Chemistry	✓	✓
5.	Nonclinical Pharmacology/Toxicology	✓(partial)	✓
6.	Human Pk/Bioavailability	✓	✓
7.	Microbiology	Not applicable	Not applicable
8.	Clinical Data	✓ (partial)	✓
9.	Safety Update	Not applicable	Not applicable
10.	Statistical	See Section 8	See Section 8
11.	Case Report Tabulations		✓
12.	Case Report Forms		✓
13.	Patent Information	✓	✓
14.	Patent Certification	Not applicable	Not applicable
15.	Establishment Description	Not applicable	Not applicable
16.	Debarment Certification	✓	✓
17.	Field Copy Certification	✓	✓
18.	User Fee Cover Sheet	✓	✓
19.	Other (Financial Disclosure)	✓	✓

The electronic submission consists of one (1) DLT tape made with NT backup containing approximately 2.8 gigabytes of memory. Paper copies of selected sections are being provided at the request of the review team to aid in their review. Please note that the archival copy of this NDA is the electronic version. We certify that this electronic submission is virus free using Symantic Norton Anti Virus Version 5.01.01. Virus signatures updated as of July 19, 1999 were used to check the files for viruses.

We understand that the review team for the Cholestagel NDA will consist of the following individuals in the Division of Metabolic & Endocrine Drug Products. Noted in parentheses is the paper copy that each reviewer has requested and that is being provided:

Hae-Young Ahn, Ph.D., Team Leader, Biopharmaceutics
Martin Haber, Ph.D., Chemistry Reviewer (Section 4)
Gemma Kuijpers, Ph.D., Pharmacology Reviewer (Section 5)
Joy Mele, M.S., Statistical Reviewer (Section 8)
David Orloff, M.D., Team Leader, Medical
Shiao Wei Shen, M.D., Medical Reviewer (Section 8)
Margaret Simoneau, Project Manager
Ronald Steigerwalt, Ph.D., Team Leader, Pharmacology
Robert Shore, Pharm.D., Biopharmaceutics Reviewer (Section 6)
Duu-Gong Wu, Ph.D., Team Leader, Chemistry

In addition, each primary reviewer and the project manager is being provided a paper copy of Volume 1, which contains Sections 1-3, 13, and 16-19.

As discussed with Tod Sahlroot on July 20, 1999, SAS data sets for the mouse and rat carcinogenicity studies reported in Section 5 are not included with the NDA. They are being obtained and will be forwarded immediately upon receipt.

[redacted]

As required by the Prescription Drug User Fee Act, a check in the amount of [redacted] has been submitted. User fee I.D. number 3726 has been assigned to this new drug application.

The official contacts for this NDA at GelTex Pharmaceuticals, Inc., Nine Fourth Avenue, Waltham, MA 02451 are:

Dean F. Alger
Director, Regulatory Affairs
Tel: (781) 290-5888, ext. 721
Fax (781) 895-4980

Martha J. Carter
Vice President, Regulatory Affairs
Tel: (781) 290-5888, ext. 766
Fax (781) 895-4980

APPEARS THIS WAY
ON ORIGINAL

Debra Sojka
Senior Associate, Regulatory Affairs
Tel: (781) 290-5888, ext. 716
Fax (781) 895-4980

We look forward to your review of the Cholestagel NDA. Please do not hesitate to contact us if you have questions or require additional information.

Sincerely yours,

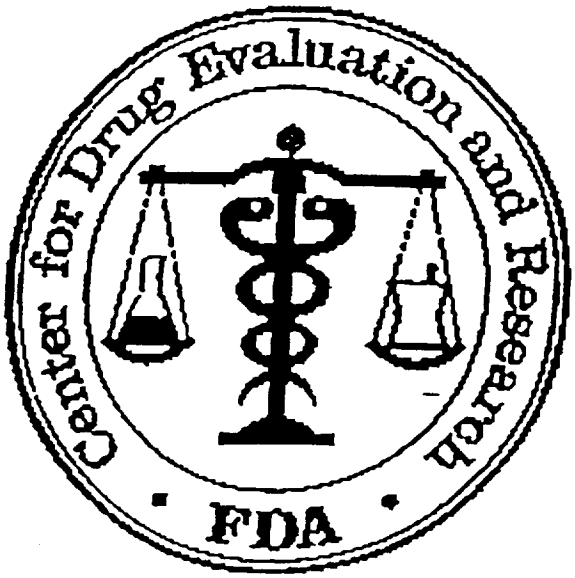
Martha J. Carter

Martha J. Carter
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: March 13, 2000



TO:

Name: Dian Allen

ax No.: 781-434-3603 ~~781-245-4481~~

Phone No.: 781-434-3421

Location: GGTEX

Pages: 3 (including cover)

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6418

Location: FDA

Comments:

NDA 21-141 Alesevelam HCl - EA Comments

NDA 21-141 Colesevelam hydrochloride
Gel Tex Pharmaceutical, Inc.

General comment: Environmental Assessments (EAs) are considered public documents and are available once an application is approved. You may want to obtain copies of recently approved EAs to guide you in the preparation of your EAs in the future.

The following deficiencies in the environmental assessment that was submitted on February 4, 2000 should be corrected and a revised EA submitted. The deficiency from the first review is listed followed by the recommended revision.

1. 4.4.1.6: Information on the substances expected to enter the environment (i.e., parent compound, metabolites) from use of the drug and the rationale for studying the parent compound should be provided (IV.B.1.a.i):

   The information you provided in the February 4, 2000 response is adequate, however, you need to incorporate it into the EA document.

2. 4.4.1.7.2 (deficiency a): A brief description of the test method used to determine the physical/chemical characteristics of colesevelam hydrochloride should be provided (IV.D). If the statements about the characteristics were based on fundamental chemical principles (e.g., chemical structure of the compound) rather than actual testing then this should be included:

   a. Solubility-Water: The response cross references a section of the NDA for this information. This needs to be summarized and included in the EA. Only a brief description of the test method (e.g., quantity, temperature, method (e.g., under/over saturation method)) used to determine the solubility in water needs to be provided in section 4.4.1.7.2.1 of the EA.

   b. Dissociation constant: The information is adequate but needs to be included in section 4.4.1.7.2.2 of the EA.

3. 4.4.1.7.2 (deficiency b): The statement that colesevelam hydrochloride has "no" vapor pressure needs to be clarified. Substances with very low vapor pressure are typically reported, for example, as having a vapor pressure of $<10^{-5}$ Pa:

   The information provided in the February 4, 2000 response is adequate but needs to be incorporated into section 4.4.1.7.2.4.

4. 4.4.1.7.3: Hydrolysis and photolysis as potential depletion mechanisms should be discussed (IV.B.1.a.iii):

The information provided in the February 4, 2000 response is adequate but needs to be included in section 4.4.1.7.3 of the EA.

5. 4.4.1.7.5: A more detailed discussion of the expected fate of colesevelam hydrochloride, based on its physical/chemical properties, should be provided. For example, because of the insolubility of the compound, what would be expected to happen in the waste water treatment process or if it entered the aquatic environment (IV.B.1.a.v):

   a. The first 2 paragraphs deal with a summary of the effects of the drug. The discussion is acceptable but is not included in the EA text. It should be included at the end of section 4.4.1.8.

   b. You have stated that that the drug is predicted to ——————— ——————— This statement should not be included because no formal adsorption/desorption test was performed. Based on the insolubility of the compound the potential to "settle out" in the waste water treatment process and the aquatic environment should be discussed and included in 4.4.1.7.5

6. 4.4.1.8: In the text of the EA for the daphnia and fish studies it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These conflicting statements should be explained. The EA text should fully explain and justify why analysis was not performed for each occurrence:

   The information provided is adequate. However, this information needs to be included in the EA and the EA needs to be revised to deleted the incorrect statements that indicate no testing was performed.

7. 4.4.3: Information on any mitigation measures necessary based on the use of the drug should be provided (IV.A.7):

   You added a statement to section 4.4.4 that ——————— —— This does not address the issue. An EA focuses on the potential environmental affects of the use of drug. The mitigation measures included in the EA only pertain to the manufacturing site. Mitigation measures necessary because of any environmental affects from the use of the drug need to be discussed. The information that was added to section 4.4.4 should be deleted.

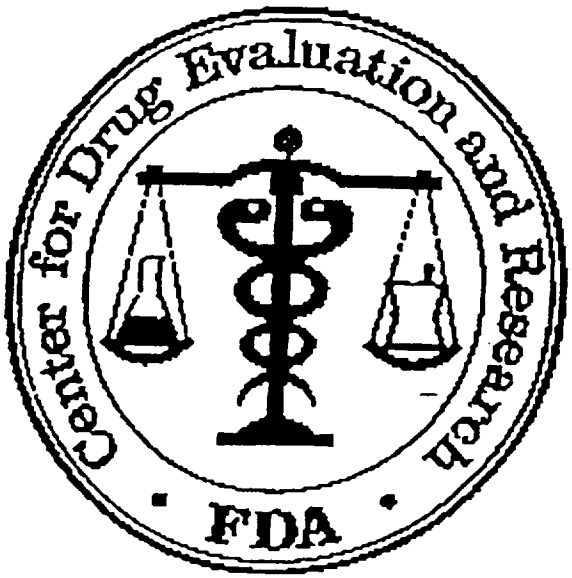
8. 4.4.5: The name, job title, and qualifications of the people preparing the assessment should be provided (IV.A.9):

   The information provided in the February 4, 2000 response is adequate but needs to be included in section 4.4.5 of the EA.

Cleared for faxing by: /S/ 3/13/00

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: February 14, 2000



TO:

Name: Lisa Allgire

Fax No.: 781-434-3603

Phone No.: 781-434-3421

Location: GELTEX

Pages: 2 (including cover)

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6418

Location: FDA

Comments:

NDA 21-141 / 21-176 Colesevelam Chemistry Review Comments

APPEARS THIS WAY
ON ORIGINAL

NDA 21-141/21-176
Colesevelam HCL
GelTex
Chemistry Review Comments:

With regard to the drug substance (colesevelam HCl):

[

With regard to the Drug Products (Welchol Capsules and Tablets):

[ ]

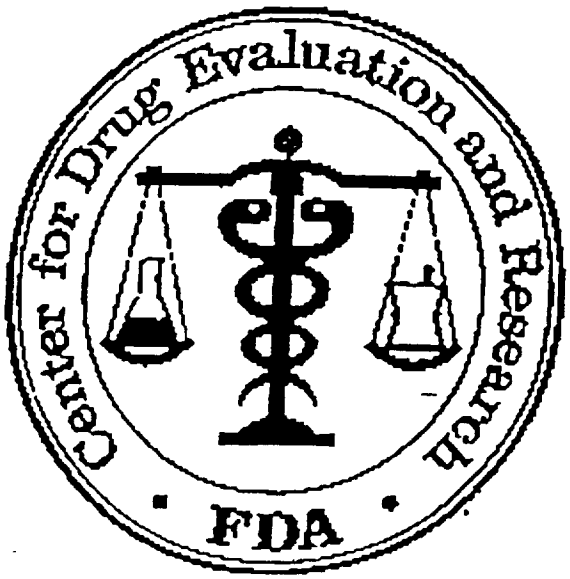
With regard to the Labeling: The description section is too long and detailed. Please delete the second paragraph and try to simplify the other text.

Cleared for faxing by: /S/ , 2-14-00

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: January 14, 2000



TO:

Name: Dean Algar

Fax No.: 781-895-4981

Phone No.: 781-434-3421

Location: GELTEX

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6418

Location: FDA

Pages: 3 (including cover)

Comments:

NDA 21-141 Cholestagel Caps EA comments
21-176 Cholestagel Tabs

NDA 21-141 Cholestagel Capsules and Cholestagel Tablets
(colesevelam hydrochloride)
Gel Tex Pharmaceutical,Inc.

General comment: In July 1997 FDA's regulations regarding environmental assessments (21 CFR Part 25) were revised. A revised guidance entitled *Environmental Assessment of Human Drug and Biologics Applications* (July 1998) was issued. The environmental assessment (EA) submitted in support of NDA 21-141 is based on the previous regulations and guidance and provides information that is now not routinely needed such as information on manufacturing sites. You may retain this information while revising this EA if you choose. However you may wish to consider not providing this information in future EAs unless specifically needed because of an extraordinary circumstance.

The following deficiencies in the environmental assessment submitted for NDA 21-141 should be corrected and a revised EA submitted. The citations included at the end of the deficiency refer to the section number of the EA guidance (cited above) which should be consulted when addressing the deficiency.

1. 4.4.1.4.1: The citation to the regulations in not correct (IV.A.4.a).

2. 4.4.1.4.3: The expected locations of use should be specified (IV.A.4.c).

3. 4.4.1.6: Information on the substances expected to enter the environment (i.e., parent compound, metabolites) from use of the drug and the rationale for studying the parent compound should be provided (IV.B.1.a.i).

4. 4.4.1.6.10: The highest quantity expected to be produced in any of the next 5 years should be used in the calculations (III.A.2).

5. 4.4.1.7.2:

   a. A brief description of the test method used to determine the physical/chemical characteristics of colesevelam hydrochloride should be provided (IV.D). If the statements about the characteristics were based on fundamental chemical principles (e.g., chemical structure of the compound) rather than actual testing then this should be included.

   b. The statement that colesevelam hydrochloride has "no" vapor pressure needs to be clarified. Substances with very low vapor pressure are typically reported, for example, as having a vapor pressure of $<10^{-5}$ Pa.

6. 4.4.1.7.3: Hydrolysis and photolysis as potential depletion mechanisms should be discussed (IV.B.1.a.iii).

7. 4.4.1.7.5: A more detailed discussion of the expected fate of colesevelam hydrochloride, based on its physical/chemical properties, should be provided. For example, because of the insolubility of the compound, what would be expected to happen in the waste water treatment process or if it entered the aquatic environment (IV.B.1.a.v).

8. 4.4.1.8: In the text of the EA for the daphnia and fish studies it is stated that "There is no method of analysis of the soluble components of the test substance available." For the algae test further explanation is included that "Because the soluble components of the test substance are not known, there is no appropriate method of analysis available. Therefore no determination of the actual concentration was performed." In the test reports it is stated that the solutions of the test substance were analyzed for stability of the test substance by the sponsor. These conflicting statements should be explained. The EA text should fully explain and justify why analysis was not performed for each occurrence.

9. 4.4.3: Information on any mitigation measures necessary based on the use of the drug should be provided (IV.A.7).

10. 4.4.5: The name, job title, and qualifications of the people preparing the assessment should be provided (IV.A.9)

APPEARS THIS WAY
ON ORIGINAL

Cleared for faxing by: /S/ 1-14-2000

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: September 17, 1999

TO:

Name: Dean Alger

Fax No.: 781-895-4980

Phone No.: 781-290-5888 x721

Location: GELTEX

Pages: 2 (including cover)

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6418

Location: FDA

Comments:

NDA 21-141 and 21-176
Cholestagel
Clin Pharm + Biopharm Comments

cc: Original NDA
Divfile
RSheet

NDA 21-141 and NDA 21-176
Cholestagel (colesevelam)
Geltex Pharmaceuticals, Inc.

Clinical Pharmacology and Biopharmaceutics Comments:

1. As per the 'Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs', page 16, the sponsor should provide proposed draft labeling in a word processing format (The FDA standard is currently Word).

2. The release specs for CholestaGel include bile acid binding and disintegration. The actual data used to set the proposed specs could not be located in the submission. If they are included, the sponsor should indicate where they are; if not included, the sponsor should submit these data for evaluation.

3. A 14C-labeled colesevelam ADME study in humans is referred to as study GTC-48-803 and GTC-37-803. The sponsor should clarify if this is the same study or if two studies were done.

4. It is indicated that the lots used in the in vitro bioequivalence study are: caps - EC75M, EC76M, EC78M; and tablets - EJ54M, EK12MB, UPM9901. The production size and formulation of most these lots could not be located in the submission. If this information is included, the sponsor should indicate where it is; if not included, the sponsor should submit this information.

Cleared for faxing by: /S/

APPEARS THIS WAY
ON ORIGINAL

5101 Amendment

AUG - 2 1999

GelTex Pharmaceuticals, Inc.
Attention: Martha J. Carter
Vice President, Regulatory Affairs
Nine Fourth Avenue
Waltham, MA 02451

Dear Ms. Carter:

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

Name of Drug Product:	Cholestagel® (colesevelam hydrochloride) 375mg Capsules
Therapeutic Classification:	To be determined at filing meeting
Date of Application:	July 30, 1999
Date of Receipt:	July 30, 1999
Our Reference Number:	21-141

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) of the Act on August 10, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 30, 2000, and the secondary user fee goal date will be July 30, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6418.

Sincerely,

/S/ 8.2.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-141
HFD-510/Div. Files
HFD-510/M. Simoneau
HFD-510/Reviewers and Team Leaders

Drafted by: ddk/June 15, 1999
Initialed by: EGalliers 8.2.99
final: EG 8.2.99
filename:

ACKNOWLEDGEMENT (AC)