

Number of Pages
Redacted 14



Draft Labeling
(not releasable)

21-DEC-2001



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-292

GenPharm Inc.
Attention: Eugene M. Pfeifer
US Agent for GenPharm Incorporated
King and Spalding
1730 Pennsylvania Ave. N.W.
Washington, D.D. 20006

Dear Mr. Pfeifer:

We acknowledge receipt on December 3, 2001, of your December 3, 2001, resubmission to your new drug application (NDA) for _____ (levothyroxine sodium) Tablets.

This resubmission contains additional chemistry, biopharmacology, nomenclature and labeling information submitted in response to our May 4, 2001, action letter.

With this amendment, we have received a complete response to our May 4, 2001, action letter.

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
12/21/01 03:04:47 PM

**APPEARS THIS WAY
ON ORIGINAL**

REQUEST FOR CONSULTATION

(Division/Office):

DMAC - Margie Kober, HFD-42
Room 17B-17

FROM: Steve McCort, Project Manager, HFD-510
Division of Metabolic and Endocrine Drug Products
Rm 14B-19

| | | | | |
|--|---------|-----------------------------|------------------------------|---|
| DATE May 4, 2001 | IND NO. | NDA NO. 21-292 | TYPE OF DOCUMENT Labeling | DATE OF DOCUMENT May 4, 2000 |
| NAME OF DRUG Class labeling for L-thyroxine | | PRIORITY CONSIDERATION S | CLASSIFICATION OF DRUG 5S | DESIRED COMPLETION DATE June 1, 2001 |

NAME OF FIRM: Genpharm Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Enclosed is a copy of the template (class Labeling) that we are sending to the Sponsor in our Approvable letter dated May 4, 2001. Enclosed is the draft labeling that the Sponsor sent in with the original submission. Please review the labeling and comment where necessary. If you have any questions, feel free to contact me at 827-6415. Thanks.

Steve McCort, HFD-510

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Stephen McCort
5/7/01 10:06:43 AM

**APPEARS THIS WAY
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04.06.01

MEMORANDUM

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

DATE: April 20, 2001
TO: File for NDA 21-292
FROM: Steve McCort, Project Manager, HFD-510
SUBJECT: Proprietary Name Change Drug Product

The firm originally submitted the name " _____ " dated June 27, 2000, with their original application for NDA 21-292.

The proprietary name was reviewed by both OPDRA and the Division of Metabolic and Endocrine Drug Products, HFD-510 and found to be unacceptable. On September 1, 2000, the Firm was called by Steve McCort of FDA to inform Trithro Uppal of GenPharm that a new name would have to be submitted to the Agency.

On November 27, 2000, the firm submitted a new name " _____ " for review (FAX).

On January 17, 2001, the firm was called by Steve McCort to inform Trithro Uppal, of GenPharm that this name was also unacceptable. The name was judged to be promotional and a third name would have to be proposed.

On January 29, 2001 the Firm in a FAX submission, proposed a new name " _____ " for review.

The new name was forwarded for consult to OPDRA for review. In their review, OPDRA found the name " _____ " unacceptable for the following reasons:

1. The proprietary name " _____ " has strong sound-alike qualities between that name and "Unithroid". The proposed name would pose a high risk for name confusion.
2. The name " _____ " is still listed as a live thyroid preparation in a patent assigned to " _____ " even though the product is not currently marketed.

For the above reasons, the Division recommended the proprietary name, " _____ " was unacceptable and that a new name would have to be submitted to the Agency.

15/ 20-APR-01

Meeting Minutes

Page 1

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Date: February 21, 2001

Time: 9:30 am

Location: Parklawn 14B-03

Drug: Levothyroxine Sodium

Firm: Genpharm INC.

NDA: 21-292

Type of Meeting: T/Con -Advice Biopharm Issues

Meeting Chair: Steve Johnson, Biopharmaceutics Reviewer

Meeting Recorder: Steve McCort, Project Manager

FDA Attendees:

Steven Johnson, Pharm D, Biopharm. Reviewer, OCPB, HFD-870
H. Malinowski, Director, Division of Pharmaceutical Evaluation I
Steve McCort, Project Manager, DMEDP, HFD-510

GenPharm Inc. Attendees:

Donna Hillier, Supervisor Regulatory Affairs
Tirtho Uppal, Director Regulatory Affairs
Ard Karnatz, Ph.D., Analytical Development, Pharmaceutical Development
Sven Alexander Schreder, Ph.D., Head of Laboratory Team Formulation, E. Merck

Background: This was a follow-up to a telephone conversation dated January 17, 2001, with Steve McCort of FDA advising the Agency that the Firm plans to submit an amendment to the pending NDA for an alternate source for the active drug substance, L-Thyroxine. The objective in this telephone conversation was to discuss what if any pharmacokinetic data would be needed to support this alternate supplier.

Discussion Points/Conclusions:

1. FDA requested additional data using a modified USP 24 method.
2. In response to Dr. Karatz' concerns that using the USP 24 method at _____ would lead to fast dissolution rates, the FDA responded as follows:
 - a. Test one strength with and without surfactant using _____ media. On the basis of the result, the firm should decide which media needs to be used for their dissolution studies.
 - b. In addition the firm should test one lot using _____
 - c. On the basis of these results the Firm should perform dissolution profiles on one lot of each strength to be marketed.

Minutes Preparer: _____
Steve McCort, Project Manager

Chair Concurrence: _____
Steve Johnson, Pharm. D.
Biopharm. Reviewer

MEETING MINUTES TELECON

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/s/

Stephen McCort

4/20/01 06:05:54 PM

**APPEARS THIS WAY
ON ORIGINAL**

C O V E R
S H E E T



FAX

To: Steve McCort, Project Manager,
Fax #: 301-443-9282
Subject: NDA 21-292, Levothyroxine Sodium Tablets from Genpharm Inc.
Date: January 29, 2001
Pages: 1, including this cover sheet.

Further to the telephone conversation of Wednesday, January 17, 2001 in which you advised that the name "_____ " was also not acceptable to the FDA Nomenclature Committee, we would like to propose a new name. We propose the use of the name '_____ '.

We are faxing to determine if the new name is acceptable to the Nomenclature Committee. If it is, we will formally file an amendment to the NDA to change the name and will send all required labeling information and all appropriate copies for filing.

We would greatly appreciate your reply with regard to the acceptability of the proposed name.

Regards,

A handwritten signature in cursive script that reads "Donna Hillier".

Donna Hillier
Supervisor, Regulatory Affairs

c.c Tirtho Uppal, Director, Regulatory Affairs, Genpharm Inc.

From the desk of...

Donna Hillier
Regulatory Affairs Supervisor
Genpharm Inc.
85 Advance Road
Etobicoke, ON M8Z 2S9

416-236-2631, Ext 245, Direct 207-1210
Fax: 416-236-4363

MEMORANDUM

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

DATE: 18 December, 2000

FROM: Dr. David G. Orloff
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

SUBJECT: Analytical Site Audits for NDAs: 21-292 and 21-301
(Levothyroxine Sodium Tablets)

TO: Dr. C.T. Viswanathan
Branch Chief, Good Practice and Bioequivalence Branch
Division of Scientific Investigations (DSI)
HFD-48

The Division of Metabolic and Endocrine Drug Products (DMEDP) is formally requesting that analytical site audits be made for two new levothyroxine sodium NDAs, which are currently under review. Because DMEDP expects further levothyroxine sodium applications in the coming year, additional foreign and domestic analytical site audits may be requested in the near future.

Presently, levothyroxine sodium is an unapproved marketed drug product. In a Federal Register Notice, dated 14 August, 1997, "Prescription Drug Products: Levothyroxine Sodium," it was declared that manufacturers of levothyroxine sodium would be required to submit a NDA by 14 August, 2000, in order to continue marketing said product. This compliance date was subsequently extended until 14 August, 2001. Nevertheless, the notice established that NDA approval for levothyroxine sodium tablets would be based upon the evidence derived from the bioavailability and dosage form equivalence studies and that no additional clinical studies would be required.

The current levothyroxine sodium NDA submissions are as follows:

| | |
|---------------------------------|---|
| NDA: | 21-292 - / levothyroxine sodium tablets |
| Sponsor: | Genpharm Incorporated |
| Analytical Site: | _____ |
| Desired Completion Date: | _____ |
| NDA: | 21-301 - Levoxyl / levothyroxine sodium tablets |
| Sponsor: | _____ |
| Analytical Site: | _____ |
| Desired Completion Date: | 28 March, 2001 |

As there are no clinical studies required for these applications, final regulatory action will be primarily based on PK and chemistry reviews, and results of the analytical site audits, both foreign and domestic, are critical.

Thank you for your time and consideration. If there are any further questions regarding this request, please feel free to contact Stephen McCort, Project Manager, at (301) 827-6415.

Dr. David G. Orloff
Director, DMEDP
HFD-510

/s/

Steve Johnson
12/18/00 05:25:49 PM
BIOPHARMACEUTICS

Hae-Young Ahn
12/22/00 02:13:53 PM
BIOPHARMACEUTICS

David Orloff
12/22/00 03:18:03 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

C O V E R

 S H E E T



FAX

To: Mr. Steve McCort, FDA Project Manager
Fax #: 301-443-9282
Subject: NDA 21-292 (Levothyroxine Sodium Tablets, USP) Name Change for NDA
Date: November 27, 2000
Pages: 1, including this cover sheet.

Dear Mr. McCort:

Further to a recent telephone conversation that you had with Ms Tirho Uppal, Director of Regulatory Affairs at Genpharm Inc., please be advised that we would like your input on a name change for the product Levothyroxine Sodium Tablets, USP submitted under NDA 21-292.

As a result of being advised that the name _____ is not acceptable to the FDA Nomenclature Committee, we would like to propose the use of the name _____.

We are faxing to determine if the new name would be acceptable to the Nomenclature Committee. If it is, we will formally file an amendment to the NDA to change the name and will send all required labelling information and all appropriate copies for filing purposes.

We would greatly appreciate your reply with regard to the acceptability of the proposed name..

Sincerely,

Donna Hillier
 Donna Hillier
 Supervisor, Regulatory Affairs

Resent January 4, 2001
 to Fax # 1 301 443 0072
DH

From the desk of...

Donna Hillier
 Regulatory Affairs Supervisor
 Genpharm Inc.
 85 Advance Road
 Etobicoke, ON M8Z 2S9

416-236-2631, Ext 245, Direct 207-1210
 Fax: 416-236-4363

/s/ 27-APR-2001

MEMORANDUM OF T/CON

Meeting Date: November 17, 2000
Time: 9:00 am

Drug: Levothyroxine Sodium

Firm: Genpharm INC.

NDA: 21-292

Type of Meeting: Advice NDA

Meeting Recorder: Steve McCort, Project Manager

FDA Attendees:

Steven Johnson, Pharm D, Biopharm. Reviewer, OCPB, HFD-870
Steve McCort, Project Manager, DMEDP, HFD-510

GenPharm Inc. Attendees:

Donna Hillier, Regulatory Affairs
Tirtho Uppal, Director Regulatory Affairs
Arnd Karntz, Head Stability Studies, E. Merck
Sven Alexander Schreder, Ph.D., Head of Laboratory Team Formulation, E. Merck

Background: In a letter dated November 9, 2000, the firm requested a teleconference to discuss a biowaiver request for the nine strengths of _____ on which the bioequivalence studies were not performed. The meeting was requested to further discuss the issue of needing dissolution profiles for three batches of each strength and the need to adopt the USP 24 method for dissolution testing.

**APPEARS THIS WAY
ON ORIGINAL**

Discussion:

The following comments from the Agency are in response to the August 11, 2000 telephone conversation between Genpharm and the Agency:

1. **The use of the dissolution method as described in USP 23 monograph for levothyroxine sodium tablets is not current nor is it acceptable to the Agency. Please refer to the current USP 24 monograph for levothyroxine sodium tablets for the revised dissolution method.**

Genpharm's Response:

In order that the comparison can be made with the data previously submitted, the method based on the dissolution medium of the USP 23 (phosphate buffer pH 7.4) and an in-house HPLC method was used to generate the data submitted in this response.

FDA Response:

The test speed of _____ is unacceptable to the Agency for USP testing.

2. **In order to grant a biowaiver for the intermediate strength tablets not evaluated in the PK studies, dissolution data must be submitted for at least three lots of each to-be-marketed strength tablets (3 x 12 strengths = 36 tests): which is to include those lots used in the PK studies, using the revised dissolution method.**

FDA Response:

The request that the Agency made was in accordance with the "Guidance" given previously to the Sponsor. In order to meet the goal date of March, 2001 the firm can submit data on three lots of the each of to-be marketed strengths using their current revised dissolution method. However, the designation of USP cannot be given if the data do not conform to the current USP method which includes the lower paddle speed of 50 RPM.

**APPEARS THIS WAY
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3. **Similarity (f_2) calculations will be based on the following criteria:
300 mcg tablets will serve as the reference for the 122 mcg through 200 mcg strengths**

Meeting Minutes

Page 3

100 mcg tablets will serve as the reference for the 75 mcg and 88 mcg strengths; and the 50 mcg tablets will serve as the reference for the 25 mcg strength.

Genpharm's Response:

Genpharm agreed with the f_2 criteria.

Minutes Preparer: _____
Steve McCort
Project Manager, HFD-510

Chair Concurrence: _____
Steve Johnson, HFD-510
Bipharmaeutics Reviewer

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/s/

Steve Johnson

4/27/01 09:49:44 AM

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15/25-APR-2001

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Date: October 12, 2000

Time: 9:00 AM

Location: Parklawn 14B-03

Drug: Levothyroxine Sodium

Firm: Genpharm INC.

NDA: 21-292

Type of Meeting: NDA Review - Advice Biopharmaceutics Issues

Meeting Chair: Steve Johnson, Pharm D. Biopharmaceutics Reviewer

Meeting Recorder: Steve McCort, Project Manager

FDA Attendees:

Steve Johnson, Pharm D, Biopharm. Reviewer, OCPB, HFD-870

Steve McCort, Project Manager, DMEDP, HFD-510

GenPharm Inc. Attendees:

Richard Pike, Ph.D., Vice President, R&D and Regulatory Affairs

Tirtho Uppal, Director Regulatory Affairs

Donna Hellier, Supervisor Regulatory Affairs

Sven Alexander Schreder, Ph.D., Head of Laboratory Team Formulation, E. Merck

Bernd Overdiek, Ph.D., Chemistry Group Leader, E. Merck

Background: The phone call was requested by the Firm to discuss the phone call of August 11, 2000 from Dr. Steve Johnson Biopharm Reviewer FDA, 2000 and Genpharm's letter to the FDA dated August 25, 2000, with a proposal to respond to the telephone call of August 11, 2000.

Discussion Points:

1. The proposal in the letter of August 25, 2000, from the firm was not acceptable and the request for dissolution data on three batches of each to-be-marketed strengths and still applies. This data is required at least 2 to 3 months prior to the end of the review period.
2. The dissolution method should be updated to USP 24. Method for Levothyroxine. The USP 24, or other validated in-house method appropriate for your product, will be acceptable.
3. E. Merck currently has dissolution data on one batch of each strength of the product that has been generated using the USP 23 method.

Minutes Preparer: _____

Steve McCort, Project Manager

Chair Concurrence: _____

Steve Johnson, Pharm. D.
Bipharmaeutics Reviewer

MEETING MINUTES

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/s/

Steve Johnson
4/25/01 09:23:50 AM

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ON ORIGINAL**

NDA 21-292

SEP 15 2000

Genpharm Incorporated
Attention: Eugene M. Pfeifer
Agent for Genpharm
King & Spalding
1730 Pennsylvania Ave., N.W.
Washington, DC 20006

Dear Mr. Pfeifer:

Please refer to your new drug application (NDA), dated July 5, 2000, received July 6, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (levothyroxine sodium tablets).

After an internal review, our letters of August 3 and 22, 2000, are rescinded. The application is considered received on July 6, 2000.

This application was filed under section 505(b) of the Act on September 4, 2000, in accordance with 21 CFR 314.101(a). The primary user fee goal date will be May 6, 2001, and the secondary user fee goal date will be July 6, 2001.

If you have any questions, call me at (301) 827-6429.

Sincerely yours,


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

NDA 21-292

Page 2

cc:

Archival NDA 21-292

HFD-510/Div. Files

HFD-510/S.McCort

HFD-510/S.Johnson/D.Lewis/J.Temeck/J.El-Hage/D.Wu/H.Ahn/D.Orloff

HFD-5/M.Jones/B.Friedman

HFD-102/ADRA

DISTRICT OFFICE

HFD-094/F.Rowland

Drafted by: emg/September 8, 9, 11, 2000

Edited by: M. Jones/09.11.2000/

Initialed by: M.Jones/09.11.00/

final: emg/09.15.00/

filename: c:\data\wordfiles\21292CRX.DOC

ADVICE (AD)

DDR & Fran Rowland: Reset user fee receipt and clock information for this application.

The filing date is: 04-SEP-2000

The primary UF goal: 06-MAY-2001

The secondary goal: 06-JUL-2001

**APPEARS THIS WAY
ON ORIGINAL**

McCOST

NDA 21-292

AUG 22 2000

Genpharm Incorporated
Attention: Eugene M. Pfeifer
Agent for Genpharm
King & Spalding
1730 Pennsylvania Ave., N.W.
Washington, DC 20006

Dear Mr. Pfeifer:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for (levothyroxine sodium tablets, USP), 12 strengths.

You were notified in our letter dated August 3, 2000, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of August 14, 2000.

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 October 13, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 14, 2001, and the secondary user fee goal date will be August 14, 2001.

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 approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver 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 make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. 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" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

/s/

for

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

NDA 21-292

Page 3

cc:

Archival NDA 21-292

HFD-510/Div. Files

HFD-510/S.McCort

HFD-510/Reviewers and Team Leaders

DISTRICT OFFICE

Drafted by: ddk/August 17, 2000

Initialed by:

final: ddk/August 17, 2000

filename: 21292AC.WPD

ACKNOWLEDGEMENT (AC)

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

TO: STEPHEN MCCOIRT, PROJECT MANAGER
FROM: STEVEN B. JOHNSON, CPB REVIEWER
SUBJECT: NDA 21-292 - GENPHARM, INC. - TELEPHONE CONFERENCE (11-AUGUST-2000)
DATE: 08/14/00
CC: ~~MAUREEN HESS, PROJECT MANAGER~~ & HAE-YOUNG AHN, CPB TEAM LEADER

Steve,

I would like to send a formal memo to the sponsor that conveys the following discussion items so that my requests are properly documented in the Division files. The first three items listed below were discussed in a telephone conference with Tirtho Uppal, Director of Regulatory Affairs for Genpharm, on Friday, August 11, 2000, and the last item on Monday, August 14, 2000. She was made aware that these items should be addressed in an amendment to the application. Thank you.

Friday, August 11, 2000 Discussion Items:

- The use of the dissolution method as described in the USP 23 monograph for levothyroxine sodium tablets is not current nor is it acceptable to the Agency. Please refer to the current USP 24 monograph for levothyroxine sodium tablets for the revised compendial dissolution method.
- In order to grant a biowaiver for the intermediate strength tablets not evaluated in the PK studies, dissolution data must be submitted for at least three lots of each to-be-marketed strength tablet (3 x 12 strengths = 36 tests); which is to include those lots used in the PK studies, using the revised dissolution method.
- Similarity (f_2) calculations will be based on the following criteria: 300 mcg tablets will serve as the reference for the 112 mcg through 200 mcg strengths; 100 mcg tablets will serve as the reference for the 75 mcg and 88 mcg strengths; and the 50 mcg tablets will serve as the reference for the 25 mcg strength.

Monday, August 14, 2000 Discussion Item:

- Please submit the individual concentration/time data from each of the PK studies in Excel® (97 or earlier version) format:


Steven B. Johnson, Pharm.D.
CPB Reviewer


Hae-Young Ahn, Ph.D.
CPB Team Leader

NDA 21-292

AUG - 3 2000

Genpharm Incorporated
Attention: Eugene M. Pfeifer
Agent for Genpharm
King & Spalding
1730 Pennsylvania Ave., N.W.
Washington, DC 20006

Dear Mr. Pfeifer:

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: _____ (levothyroxine sodium tablets, USP), 12 strengths

Date of Application: June 27, 2000

Date of Receipt: July 6, 2000

Our Reference Number: NDA 21-292

We have not received the appropriate user fee for this application. An application is considered incomplete and can not be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NDA 21-292

Page 2

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment was received by the bank.

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, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

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

NDA 21-292
Page 3

cc:
Archival NDA 21-292
HFD-510/Div. Files
HFD-510/S.McCort
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: ddk/August 3, 2000
Initialed by: Galliers 8.3.00
final: ddk/August 3, 2000
filename: 21292UN

UNACCEPTABLE FOR FILING (UN)

**APPEARS THIS WAY
ON ORIGINAL**

MCCort

NDA 21-292

JUL 17 2000

Genpharm Incorporated
Attention: Eugene M. Pfeifer
Agent for Genpharm
King & Spalding
1730 Pennsylvania Ave., NW
Washington, DC 20006

Dear Mr. Pfeifer:

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: Tablets (levothyroxine sodium tablets, USP), 12 strengths

Therapeutic Classification: Standard (S)

Date of Application: June 27, 2000

Date of Receipt: July 6, 2000

Our Reference Number: NDA 21-292

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 September 4, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 6, 2001, and the secondary user fee goal date will be July 6, 2001.

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 approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver 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 make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. 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" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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:

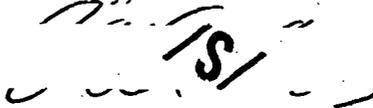
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-292

Page 3

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Sincerely,


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**

NDA 21-292

Page 4

cc:

Archival NDA 21-292

HFD-510/Div. Files

HFD-510/S.McCort

HFD-510/Reviewers and Team Leaders

DISTRICT OFFICE

Drafted by: ddk/July 10, 2000

Initialed by: McCort 7.10.00/Galliers 7.11.00

final: ddk/July 13, 2000

filename: 21292AC

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 8, 1999

Time: 11:00 am

Location: Parklawn Potomac Rm

Drug: Levothyroxine Sodium

Firm: Genpharm INC.

Type of Meeting: Pre-IND

Meeting Chair: Solomon Sobel, M.D., Division Director

Meeting Recorder: Steve McCort, Project Manager

FDA Attendees:

Solomon Sobel, M.D., Division Director, DMEDP, HFD-510

David Orloff, M.D., Medical Team Leader, DMEDP, HFD-510

Duu-Gong Wu, Ph.D., Chemistry Team Leader, ONDC, HFD-820

David Lewis, Ph.D., Chemistry Reviewer, ONDC, HFD-820

Mike Fossler, Ph.D., Biopharm. Reviewer, OCPB, HFD-870

Steven Johnson, Pharm D, Biopharm. Reviewer, OCPB, HFD-870

Chris Rogers, Regulatory Counsel, HFD-007

Steve McCort, Project Manager, DMEDP, HFD-510

GenPharm Inc. Attendees:

Richard Pike, Ph.D., Vice President, R&D and Regulatory Affairs

Tirtho Uppal, Director Regulatory Affairs

Brian Berry, Ph.D., Manager, Scientific Affairs

Sven Alexander Schreder, Ph.D., Head of Laboratory Team Formulation, E. Merck

Bernd Overdiek, Ph.D., Chemistry Group Leader, E. Merck

Background: In a letter dated July 29, 1999, the firm requested a PRE-IND meeting to discuss the information that will be needed before filing an IND and NDA for Levothyroxine Sodium Tablets. The meeting date was confirmed by telephone on August 12, 1999, with a FAX confirmation on August 28, 1999.

Meeting Objectives:

1. To discuss the proposed biostudies
2. To discuss the Stability Studies
3. To discuss the Dissolution studies
4. To discuss the paper portion of the submission

Discussion Points:

1. Bioavailability studies:

The firm has proposed two proposed studies;

A. Study 1: Single Dose Tablets vs Oral Solution

24 subjects (male and female)

2 x 300 mcg tablets vs 600 mcg solution dose

Question 1: Are the commercially available levothyroxine for injection preparations acceptable for preparation of the oral dose?

FDA Response: Yes

Question 2: If so, which brand of injection?

FDA Response:

Any of the brand preparations of levothyroxine for injection available on the US market are acceptable for use in the oral preparation.

B. Study 2: Dosage-Form Equivalence Study:

Compared 8 x 25 mcg vs. 4x 50 mcg

Compared 4 x 50 mcg vs. 2 x 100 mcg

Compare 2 x 100 mcg vs. 1 x 200 mcg

Question 1: Is this approach of separate biostudies acceptable to the FDA, as it will allow reduction in the biostudy timeline while maintaining the dosage comparison?

FDA Response: Yes.

Question 2. Can the firm consider "excipient normalization" in their design of the biopharm studies? The experience with the E. Merck biostudies was that the excipients when multiple tablets are used can vary by 6 fold from subject to subject (example lactose). The firm wishes input on the use of "placebo" tablets to normalize the excipients being received from patient to patient.

FDA Response: The proposed use of placebo to achieve normalization was found acceptable.

Question 3: Are T3 pharmacokinetic parameters needed for the assessment of equivalence between dosage forms?

FDA Response: T3 not needed for assessment of bioequivalence of T4.

Question 4: Merck had previously conducted bioavailability studies using a total dose of 200 mcg., rather than the suggested dose of 600 mcg. Can the firm go with the 200 mcg dose as the maximum dose?

FDA Response: No formal response could be made the meeting. The firm should send to FDA summary data for review.

2. Proposed Stability Studies:

The active raw material for levothyroxine is supplied by _____ will be qualified later as a second supplier.

The Sponsor of the studies will be GenPharm (Canadian firm) with US Agent being ParPharm.

For assay purity tests the firm is using two methods for analysis: Old USP method, and a newer _____ recently developed. The advantage in using the new method is that the impurity peaks show overlapping of the degradation matrix peaks while the newer _____ with the new formulation.

FDA comments:

1. A DMF for the raw supplier, _____ will be needed as soon as possible. This letter from the supplier giving permission to view the DMF will be needed before an IND/NDA review can be started.
2. Manufacturing overages are acceptable provided that the active drug substance, Levothyroxine is 100% at release.
3. Tablets are of the same color. Need to consider color coding of the tablets.
4. Suggestion is to used matrix approach for test of stability batches with three at the lowest strength, three at the highest strength and two at an intermediate strength.

4. Clinical 505(b(2) issues:

Steve McCort will provide information as to what literature will be needed for the NDA submission.

5. Questions from meeting package:

a. Why is an IND filing required since specific guidelines have been published by the FDA specifying requirements for an IND?

FDA Response: An IND is a requirement for NDAs.

b. Are the protocols acceptable? If not what changes are needed?

FDA Response: See the Discussion section above.

c. Genpharm will formulate _____ Only manufacturing overages are allowed. The firm needs confirmation that this standard is being applied uniformly to all applicants.

FDA Response: The same standard for release of product and overage is being applied to all applicants.

d. For stability studies the firm wishes to know (a) the number of batches needed, (b) the packaging format, (c) the acceptability of the stability protocol, (d) matrixing (e) why the FDA needs 6 month data for stability.

FDA Response: The questions have been addressed in the Discussion section above.

e. What number of batches will be required other than those used for stability and biopharmaceutics studies?

FDA Response: The firm should submit _____ batch record for each strength on stability.

f. What additional in-vitro data will the Agency wish to see?

FDA Response: In-vitro dissolution profiles on all _____ of product on stability will be needed.

g. Can the firm waiver for doing biostudies/stability studies on all strengths?

FDA Response: The firm can use a matrix approach for both biostudies and the stability studies (low, intermediate and high) per the draft guidance documents, "*Guidance to Industry, In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets, June 1999*," and "*Stability Testing of Drug Substance and Drug Products, June 1998*."

h. Individual labels and package insert - Is this to be based on the literature and Genpharm studies or on the format and content specifically proposed by the FDA?

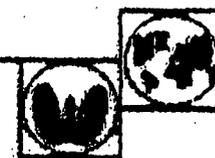
FDA Response: The Agency will communicate to the firm guidelines regarding the format and content of the literature for the NDA submission and what will be needed for the package insert and labels.

Decisions reached:

1. The proposed biostudies as presented appear acceptable except for the use of 200 vs 600 mcg maximum dose for the Dosage-form Equivalence Study. The FDA will give input to the Firm in the future regarding the maximum dose required for this study. After the meeting the FDA staff indicated that the 200 mcg as the maximum dose was not likely to give the desired result and recommended going with the 600 mcg as the maximum dose.
2. The Genpharm Stability proposal as proposed at the meeting appears acceptable. (See Discussion, point 5) Genpharm proposed conducting studies at 25°C/60% RH (3,6,9,12,18,24,36 months) and 30°C/60% Rh(1,2,3,6,12 months) but not test at 40°C/75% RH. Not including the 40°C/75% RH condition as a requirement may need further assessment by the Agency.
3. The proposal to use the USP medium testing to 45 minutes with dissolution profiles will be performed until — of the product is dissolved appears acceptable. The new _____ for analysis and the method will need to be validated. Comparison against the current USP method should be submitted at time of submission.

Merck & Thyroid

Merck KGaA · Darmstadt · Germany

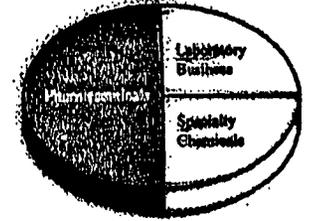


Our generic operations

MERCK GENERICS

| ASIA | EUROPE | NORTH AMERICA | OTHER | |
|---------------------------|-------------------------------|--------------------------------------|---------------------------------|---------------------------------------|
| Alphapharm (Australia) | Generics [UK] (England) | Gerard (Ireland) | Genpharm (Canada) | Merck Generics RSA South Africa |
| Pacific (New Zealand) | Scand Pharm (Sweden) | Generics Deutschland (Germany) | Par Pharmaceuticals (USA) | Merck companies Worldwide |
| Merck Hoei (Japan) | Resolution (England) | Merck Generics (England) | | |
| P T Merck (Indonesia) | Generics BV (Holland) | Merck Generiques (France) | | |
| | Merck dura (Germany) | Merck FEQ (Portugal) | | |
| | Arcana (Austria) | | | |
| | Merck Genericos (Spain) | | | |

Levothyroxine tablets



Merck KGaA has a long history in levothyroxine products:

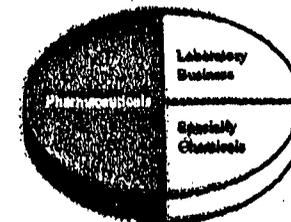
1969: Introduction of Novothyral (combination of Levothyroxine and Liothyronine)

1972: Introduction of _____

1980: Introduction of Jodthyrox (combination of Levothyroxine and Iodine)

1996: Start of the development of a new formulation

Composition of all strengths



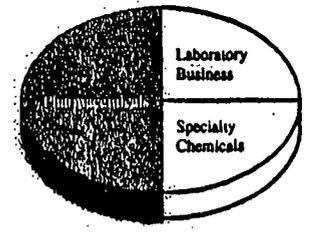
In the table all amounts of the ingredients are [mg]

| | |
|----------------------|----|
| levothyroxine sodium | ↑↑ |
| lactose monohydrate | ↓↓ |
| all other excipients | ⇔ |
| purified water | ⇔ |
| tablet weight | ⇔ |

| levothyroxine sodium* | 0.025 | 0.050 | 0.075 | 0.088 | 0.100 | 0.112 | 0.125 | 0.137 | 0.150 | 0.175 | 0.200 | 0.300 | | | | | | | | | | | | |
|-----------------------|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|---|---|--|--|--|--|--|--|--|--|--|--|
| lactose monohydrate | <table border="1" style="width: 100%; height: 100%;"> <tr> <td style="width: 50%;"></td> <td style="width: 50%; text-align: center;">0</td> </tr> <tr> <td></td> <td></td> </tr> </table> | | | | | | | | | | | | | 0 | | | | | | | | | | |
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| maize starch | | | | | | | | | | | | | | | | | | | | | | | | |
| gelatin | | | | | | | | | | | | | | | | | | | | | | | | |
| croscarmellose sodium | | | | | | | | | | | | | | | | | | | | | | | | |
| magnesium stearate | | | | | | | | | | | | | | | | | | | | | | | | |

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Raw material supplier

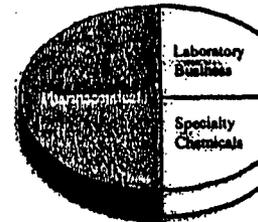


_____ will be the raw material supplier

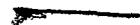
Purest quality of all tested suppliers

_____ shall be qualified later as a second supplier.
Needs to _____

Manufacturing excess



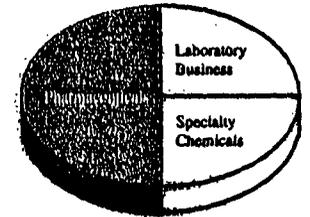
| # batches | strength | manufacturing excess added | assay | proposed excess |
|-----------|--------------------|----------------------------|-------|-----------------|
| | 25 µg - 50 µg | _____ | | _____ |
| | 75 µg - 125 µg | _____ | | _____ |
| | 150 µg - 200 µg | _____ | | _____ |

Proposed ()

Merck KGaA - Genpharm Rockville, September 8, 1999

MERCK

Production site



| Pilot plant — | Production plant — |
|---|--------------------|
| scale > 10 % | 100 % |
| biobatches stability batches | market batches |
| same type of equipment, different scale, same campus | |

* dedicated thyroid area

new facility running

Market supply from

— batches under stability;

Full process validation;

Annual product review)



GENPHARM

Genpharm has submitted a New Drug Submission to TPP using data in the literature to prepare comprehensive summary and Product Monograph.

We propose to take the same approach for preparing the Safety/Efficacy part of the NDA, since the information required is similar; only differs in the format.



GENPHARM

The amount of information provided in this section will be based on the literature available.

The studies being conducted by Genpharm will be incorporated into the Human Pharmacokinetics and Bioavailability section (Section 6).



GENPHARM

The literature information will be
divided into two main sections

Non-Clinical
Clinical

Which will be further divided into
subsections as described in the
table of contents in the
information package (Appendix IV).



ZENPHARM

Questions we have:

- How much information is needed in this section of the application?
- Is the proposed format acceptable?

Other questions as indicated in the information package are with regard to labelling (last page):



GENPHARM

- Are there specific requirements for patient insert and container labels? (Since this product has been on the market for significant length of time and that same references are going to be used by all applicants.)
- Merck KgaA is the innovator in Europe and have the patient insert and labelling. Genpharm proposes to —
—
—



GENPHARM

Levothyroxine sodium

NDA BIOSTUDIES

Two Bioavailability Studies:

Study 1: Single-Dose Tablets vs. Oral Solution

24 + 4 male and female subjects

2 x 300 mcg tablets vs. 600 mcg solution dose

Question 1: Are the commercially available levothyroxine for injection preparations acceptable for preparation of the oral solution?

Question 2: If so, which brand of injection?

Studies performed to date:

Using a typical clinical dose of 200 mcg, E. Merck has successfully showed comparative bioavailability between 1 x 200 mcg tablet vs. 200 mcg oral solution.



GENPHARM

Levothyroxine sodium

Study 2: Dosage-Form Equivalence Study

24 + 6 male and female subjects

12 x 50 mcg vs. 6 x 100 mcg vs. 2 x 300 mcg

Studies performed to date:

Using a typical clinical dose of 200 mcg, E. Merck has successfully shown comparative bioavailability between the 25 mcg, 50 mcg, 100 mcg and 200 mcg tablets.

Three separate studies were performed:

Study 1: Compared 8 x 25 mcg vs. 4 x 50 mcg

Study 2: Compared 4 x 50 mcg vs. 2 x 100 mcg

Study 3: Compared 2 x 100 mcg vs. 1 x 200 mcg

Question: Is this approach of separate biostudies acceptable to the FDA as it would allow a significant reduction in the biostudy timeline while maintaining the dosage comparison?



GENPHARM

Levothyroxine sodium

The above four studies performed by E. Merck differed in study design than that proposed by the FDA.

A common approach in E. Merck biostudies, is to add "placebo" tablets containing only excipients in order to normalize the quantity of excipients dosed to the subjects.

This approach is used when there is a large difference in the quantity of excipients when multiple tablets of differing strengths are administered to subjects. With the proposed FDA biostudies, the total tablet excipient differences can differ by as much as $\frac{1}{3}$, as shown below:

12 x 50 mcg tablets ($\frac{1}{3}$ of lactose),
6 x 100 mcg tablets ($\frac{1}{3}$ of lactose),
2 x 300 mcg tablets ($\frac{1}{3}$ of lactose),

Therefore, with the Merck design, the subjects receive the same quantity of excipients and the same quantity of active drug regardless of the difference in number of tablets dosed.

This design has been accepted by both the Swiss and French regulatory authorities regarding the Merck levothyroxine product.

Will the FDA consider this type of "excipient normalizing" design for the NDA submission?



GENPHARM

Levothyroxine sodium

General question:

Are T3 pharmacokinetic parameters needed for the assessment of equivalence between dosage forms?

APPEARS THIS WAY
ON ORIGINAL



GENPHARM

Levothyroxine sodium

COMMITMENT

Will do what is required by FDA to prepare the Application.

WHY THE MEETING?

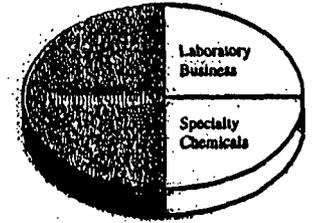
- 1. VERIFY what is required, given the data we already have.**
- 2. ANXIETIES**

That we are being treated the same as other applicants with regard to

- 1) manufacturing excess**
 - 2) number of batches for stability**
 - 3) stability required for filing**
- 3. CLARIFY the first approval effect on other NDAs**
 - 4. TIME LINE submission date of mid April 2000.**

Re: Levothyroxine Meeting with FDA Sept. 8, 1999

New formulation



Levothyroxine sodium:

Sensitive to light, oxygen and humidity, extreme excipient / drug ratio

Evaluation of — formulations \Rightarrow best was chosen

Bioequivalence to old formulation and oral solution was shown

Dose linearity was shown (range 25 μg to 200 μg)
300 μg not tested

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Proposals and Confirmation from the FDA meeting**Date of Meeting: September 8, 1999****Attendee:**

| | | |
|------------------|-------------------------------|------------|
| David Lewis | Chemist Reviewer HFD-820 | FDA |
| Michael Fossler | OCPB | FDA |
| Steven Johnson | OCPB | FDA |
| Solomon Sobel | Director/DMEDP | FDA |
| Hae Young Ahn | OCPB | FDA |
| Duu-Gong Wu | Chemistry Team leader | FDA |
| Christine Rogers | Regulatory Counsel | FDA |
| David Orloff | Med Team leader | FDA |
| Steve McCort | Project Manager | FDA |
| Richard Pike | VP R&D and Regulatory Affairs | Genpharm |
| Tirtho Uppal | Director Regulatory Affairs | Genpharm |
| Brian Berry | Manager Scientific Affairs | Genpharm |
| Sven Schreder | Lab Head Formulation | Merck KgaA |
| Bernd Overdiek | Chemist Group Leader | Merck KgaA |

A. Proposal from the presentation

- Active Raw material supplier is _____ preparing the DMF.
FDA recommend - File DMF ASAP. If letter of access submitted with IND, DMF review will start.
- Manufacturing Losses: Following overages were proposed by Merck due to manufacturing losses and these overages were acceptable to the FDA.

- All the strengths are white tablets with marking to differentiate the different strengths.
FDA - did not see that as an issue with regard to C&M review.
- Stability data
Merck-Genpharm to send FDA Data showing potency results using the _____
_____, which shows that the old method was giving results of 2-3% higher due to interference from placebo.

5. Dissolution

Merck proposed to use USP medium but perform testing to 45 minutes since results show _____ . Dissolution profiles will be performed until _____ percent of the labelled claim is dissolved using 5 time points - FDA agreed to this proposal.

The dissolution analytical procedure (_____ different to USP) is not sensitive enough for the low concentrations of the 25µg strength especially when performing profiles.

Merck suggested combining 4 tablets in each vessel for the 25µg strength - this proposal was not acceptable to the FDA but instead suggested reducing the media volume to 200 ml from 900mL. Merck will proceed to use 200mL media volume when performing profiles on the lowest strength.

6. Stability Studies

Stability data was presented under the three storage conditions (40°C/75%RH; 30°C/60%RH; 25°C/60%RH) on batches manufactured to the proposed formulation (_____). Based on that data a proposal was made to conduct studies at 25°C/60% RH (3,6,9,12,18,24,36 months) and 30°C/60%RH (1,2,3,6,12 month) by Merck and not to test at 40°C/75 % RH. - the proposal was acceptable to the FDA.

Merck proposed following batches for stability studies:

x 25µg
x 50µg,
x 100µg
x 300µg

the lowest and intermediate strengths were acceptable to the FDA but want to see three lots of the highest strength.

Therefore Merck-Genpharm will perform stability studies on the following batches:

x 25µg
x 50µg,
x 100µg
x 300µg

Stability studies will be conducted using matrixing for the highest and the lowest strength as proposed in the information package. No matrixing of the pack size was proposed.

Data at time of submission is 6 months RT and three months intermediate condition. By the time the file is picked up for review will have additional 6 months data (total 12 months). Maximum expiration based on that data is 18 months.

7

Clinical studies

- A. Any of the brand preparations of levothyroxine for injection available on the US Market (e.g. Forest, Schein, Knoll) is acceptable for use in preparation of the oral solution.
- B. The Genpharm proposed to conduct two 2-way crossover studies rather than the suggested single 3-way crossover study, that is, (a) 12 x 50 mcg vs. 6 x 100 mcg tabs and (b) 6 x 100 mcg vs. 2 x 300 mcg tabs, rather than 2 x 50 mcg tabs vs. 6 x 100 mcg vs. 2 x 300 mcg. This proposal was found acceptable to the FDA.
- C. A common approach in E. Merck biostudies, is to add to the dosing regimen a placebo tablets containing only excipients in order to normalize the quantity of excipients dosed to the subjects. This approach is used when there is a large difference in the quantity of excipients when multiple tablets of differing strengths are administered to subjects. For example, with the proposed 600 mcg dose for the FDA biostudies, the total tablet excipient differences in the Merck product can differ by as much as —, as shown below:
- | | |
|---------------------|--------------------|
| 12 x 50 mcg tablets | (—) of lactose), |
| 6 x 100 mcg tablets | (—) of lactose), |
| 2 x 300 mcg tablets | (—) of lactose). |
- By using this approach, the subjects receive the same quantity of excipients and the same quantity of active drug regardless of the difference in number of tablets dosed.
- The Genpharm proposal to add to the dosing regimen placebo tablets in order to excipient normalize. The proposed use of placebo excipients was found acceptable by the FDA. Genpharm may choose to use the excipient normalizing approach method above if desired.
- D. The criteria for equivalence will be based only on the measurement of T4 (levothyroxine) and not on T3 and T4 as outlined in the guidance. The measurement of T3 will be included in the biostudy report for informational purposes only.
- E. Merck had previously conducted bioavailability studies using a total dose of 200 mcg (e.g. 4 x 50 mcg, 2 x 100 mcg, etc) rather than the guidance suggested dose of 600 mcg. FDA had some concerns with regard to the concentrations detected and whether a difference between baseline (pre-dose) and post-dose can be statistically differentiated. FDA has suggested the data be forwarded to them for review.

7.

Literature portion of the submission

Steve McCort to provide information how much information needs to be submitted.

B. Answers to the questions submitted in the information Package.

1. IND is a requirement for NDAs. There is a 30-day review time for INDs
2. See above
3. Manufacture overages accepted as indicated above
4. Addressed above
5. Submit executed batch documents for one lot of each strength on stability and submit blank documents for the intermediate strengths only (no need to include executed documents for the intermediate strengths)
6. Waiver for bioequivalence as per the guidelines. Are in-vitro Dissolution profiles on all the _____ product (lots manufactured for stability) acceptable to support a waiver for not conducting studies on the lowest and intermediate strengths?
7. Need to follow the guidelines, each section has to be completed, no section to be left out.

**APPEARS THIS WAY
ON ORIGINAL**

Supplemental Data:

Results from the new formulation being tested with the new analytical method

| Strength | Assay results |
|----------|---------------|
| 50 µg | % |
| 75 µg | % |
| 125 µg | % |
| 150 µg | % |
| 150 µg | % |
| 175 µg | % |
| 175 µg | % |
| 200 µg | % |
| 200 µg | % |

It can be easily seen that for the

**APPEARS THIS WAY
ON ORIGINAL**

Advisory committee meeting not needed.

APPEARS THIS WAY
ON ORIGINAL

Notices

Federal Register

This section of the FEDERAL REGISTER contains documents other than rules or proposed rules that are applicable to the public. Notices of hearings and investigations, committee meetings, agency decisions and rulings, delegations of authority, filing of petitions and applications and agency statements of organization and functions are examples of documents appearing in this section.

DISPLAY DATE: 7-12-01 PUBLICATION DATE: 7-13-01

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N-0314]

Guidance for Industry on Levothyroxine Sodium Products—Enforcement of August 14, 2001, Compliance Date and Submission of New Applications; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled "Levothyroxine Sodium Products—Enforcement of August 14, 2001, Compliance Date and Submission of New Applications." This guidance discusses how FDA plans to exercise its enforcement discretion after August 14, 2001, with regard to levothyroxine sodium products that are marketed without approved applications. This guidance also answers certain frequently asked questions concerning the submission of applications for levothyroxine sodium products. It replaces the previously issued guidance entitled "Levothyroxine Sodium, Questions and Answers" (February 2001).

DATES: Submit written or electronic comments on agency guidances at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit

electronic comments to <http://www.fda.gov/dockets/ecomments>. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: David T. Read, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "Levothyroxine Sodium Products—Enforcement of August 14, 2001 Compliance Date and Submission of New Applications." This guidance discusses how FDA plans to exercise its enforcement discretion after August 14, 2001, with regard to levothyroxine sodium products that are marketed without approved applications. This guidance also answers certain frequently asked questions concerning the submission of applications for levothyroxine sodium products and replaces the previously issued guidance entitled "Levothyroxine Sodium, Questions and Answers" (February 2001) (see 66 FR 13935, March 8, 2001).

In the Federal Register of August 14, 1997 (62 FR 43535), FDA announced that orally administered levothyroxine sodium drug products are new drugs. The notice stated that by August 14, 2000, manufacturers who wish to continue to market these products must obtain approved applications as required by section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) and 21 CFR part 314. The notice stated that after August 14, 2000, any orally administered drug product containing levothyroxine sodium that is introduced or delivered for introduction into interstate commerce without an approved application will be subject to regulatory action, unless found by FDA to be not subject to the new drug requirements of the act under a citizen petition submitted for that product. FDA issued a second Federal Register notice on April 26, 2000 (65 FR 24488), extending the deadline for obtaining approved applications until August 14, 2001.

The agency permitted orally administered levothyroxine sodium products to remain on the market during this period of time without approved new drug applications to give manufacturers time to conduct the required studies, prepare applications, and have them approved. FDA stated in the 1997 Federal Register notice that levothyroxine sodium products are used to treat hypothyroidism, and no alternative drug is relied on by the medical community as an adequate substitute.

As of June 2001, two orally administered levothyroxine sodium products have been approved by FDA. These approved products have been evaluated by FDA and found to be safe and effective for their intended uses. FDA has not evaluated the safety and effectiveness of unapproved marketed products, but it has determined that no currently marketed unapproved orally-administered levothyroxine sodium product is generally recognized as safe and effective (see 62 FR 43535 at 43538, August 14, 1997).

Notwithstanding the fact that there are now two approved applications for orally administered levothyroxine sodium, FDA has determined that it will take time for the millions of patients taking unapproved products to switch to approved products, and for manufacturers of approved products to scale up their production and to introduce this increased production into the distribution chain. To provide time for manufacturers of approved products to scale up their production and for patients and health care providers to make a reasonable transition from unapproved to approved products, FDA has decided to continue to exercise its enforcement discretion by establishing a gradual phase-out of unapproved products. The phase-out plan and a number of frequently asked questions are addressed in this guidance.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115; 65 FR 56468, September 19, 2000). The guidance is being implemented immediately without prior public comment because there are public health reasons for the immediate implementation of the guidance document. The guidance pertains to the agency's exercise of enforcement discretion and it is being issued to facilitate planning by patients, health care providers, manufacturers, and distributors who need information about the agency's plans to transition patients from unapproved to approved levothyroxine sodium products after August 14, 2001. The guidance represents the agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may, at any time, submit written or electronic comments on the guidance to the Dockets Management Branch (address above). Two copies of any

comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments are available for public examination in the Dockets Management

Branch between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/cder/guidance/index.htm> or

<http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: July 9, 2001.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 01-????? Filed ??-??-01; 8:45 am]

BILLING CODE 4160-01-5

APPEARS THIS WAY
ON ORIGINAL

Proposed Project

Assessment of Exposure to Arsenic through Household Water—New—National Center for Environmental Health (NCEH). Arsenic is a naturally occurring element present in food and water as both inorganic and organic complexes. Epidemiologic evidence shows a strong link between ingestion of water containing inorganic arsenic and an increase in a wide variety of cancers (e.g., bladder cancer). Consumption of contaminated food is the major source of arsenic exposure for the majority of United States citizens. There are some areas of the United States where

elevated levels of arsenic in water occur with appreciable frequency. In such areas, ingestion of water can be the dominant source of arsenic exposure. Currently, the preferred method of treatment of private, domestic well water containing elevated levels of arsenic is point-of-use (POU) devices. The acceptability of bottled water and POU treatment systems as effective means of managing arsenic exposure is based on the assumption that other water exposures such as bathing, brushing of teeth, cooking, and occasional water consumption from other taps contribute relatively minor

amounts to a person's total daily intake of arsenic.

We propose to conduct a study to methodically test the validity of the commonly-made assumption that secondary exposures such as bathing will not result in a significant increase in arsenic intake over background dietary levels. Specifically, we are interested in assessing urine arsenic levels among individuals where ingestion of arsenic-containing water is controlled by either POU treatment or use of bottled water, combined with use of short-term diaries to record diet, water consumption, and bathing frequency. Total annual burden is 510.

| Respondents | Number of respondents | Responses/ respondent | Average burden response (in hours) |
|--|-----------------------|-----------------------|------------------------------------|
| Prescreening postcard completion | 1,000 | 1 | 5/60 |
| Recruiting telephone interview | 320 | 1 | 15/60 |
| Survey interview (in person) | 520 | 1 | 30/60 |
| Biologic specimen collection | 520 | 1 | 10/60 |

Dated: April 20, 2000.
 Charles W. Gollmar,
 Acting Associate Director for Policy, Planning and Evaluation, Centers for Disease Control and Prevention (CDC).
 [FR Doc. 00-10351 Filed 4-25-00; 8:45 am]
 BILLING CODE 4163-18-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

[Program Announcement No. ACYF-PA-HS-2000-03B]

Fiscal Year 2000 Discretionary Announcement of the Availability of Funds and Request for Applications for Nationwide Expansion Competition of Early Head Start; Correction

AGENCY: Administration for Children, Youth and Families, ACF, DHHS.

ACTION: Correction.

SUMMARY: This document contains a correction to the Notice that was published in the Federal Register on Tuesday, February 29, 2000.

On page 10797, in the State of Colorado, Arapahoe County, in the local community column the following service area should be added: Colfax Avenue (county line) on the North, Mississippi Avenue on the South, Chambers Road on the East and Yosemite Street (county line) on the West. This area is currently being served and is not open for competition to new

Early Head Start programs. The remaining part of Arapahoe County is not currently being served and is open to competition to new Early Head Start programs.

On page 10797, in the State of Colorado, in Denver County, in the local community column for the city of Denver, after the service areas numbered (1)-(4), the following service areas should be added in the city of Denver:

“(5) the area bounded by 52nd Avenue on the North, Alameda Boulevard on the South, Broadway Avenue on the East and Sheridan Boulevard on the West.”
 “(6) Beginning at north Broadway and 38th avenue, go east to Yosemite; Yosemite south to 11th Avenue, 11 Avenue west to Quebec; Quebec south to Hampden, Hampden west to Broadway; Broadway north to 35th Avenue.”
 “(7) Beginning at north 54th Avenue and Peoria, go 54th east to Chambers; Chambers south to I-70, I-70 West to Peoria, Peoria north to 54th Avenue.”
 These three areas (5) (6) and (7) are currently being served in the city of Denver in addition to service areas (1) through (4). These seven service areas in the city of Denver are not open to competition to new Early Head Start programs.

On page 10802, of the State of Minnesota, Hennepin County, in the local community column delete “City of North Minneapolis” and replace with “Minneapolis, Brooklyn Park, Golden Valley, and Richfield.”

FOR FURTHER INFORMATION CONTACT: The ACYF Operations Center at 1-800-351-

2293 or send an email to ehs@cgnet.com. You can also contact Judith Jerald, Early Head Start, Head Start Bureau at (202) 205-8074.

Dated: April 20, 2000.
 Patricia Montoya,
 Commissioner, Administration on Children, Youth and Families.
 [FR Doc. 00-10378 Filed 4-25-00; 8:45 am]
 BILLING CODE 4184-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N-0314]

Prescription Drug Products; Levothyroxine Sodium; Extension of Compliance Date

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; extension of compliance date.

SUMMARY: The Food and Drug Administration (FDA) is announcing that manufacturers who were marketing orally administered drug products containing levothyroxine sodium on or before August 14, 1997, may continue to market these products without approved applications until August 14, 2001. FDA is extending by 1 year the compliance date given in the notice published in the Federal Register of August 14, 1997 (62 FR 43535). The agency is taking this action to give manufacturers additional

time to conduct studies and to prepare applications.

EFFECTIVE DATE: April 26, 2000.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION: In the Federal Register of August 14, 1997 (62 FR 43535), FDA announced that orally administered drug products containing levothyroxine sodium are new drugs and required manufacturers to have approved applications as a condition of marketing. The notice advised that manufacturers who were marketing levothyroxine sodium drug products on or before August 14, 1997, may continue to market their products until August 14, 2000.¹ The notice stated that a manufacturer who marketed a levothyroxine sodium drug product without an approved application after that date would be subject to regulatory action.

FDA permitted this period of continued marketing because it regards levothyroxine sodium products as medically necessary and, therefore, wanted to allow sufficient time for manufacturers to conduct the required studies and to prepare and submit applications, as well as to allow the agency sufficient time to review these applications. FDA has now concluded that manufacturers may need additional time to conduct studies and to prepare applications. Therefore, the agency extends by 1 year the compliance date given in the Federal Register notice of August 14, 1997, to permit continued marketing of these products until August 14, 2001.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505 (21 U.S.C. 352, 355)) and under authority delegated to the Associate Commissioner for Regulatory Affairs (21 CFR 5.20).

Dated: April 18, 2000.

Margaret M. Dotzel,
Acting Associate Commissioner for Policy.
[FR Doc. 00-10322 Filed 4-25-00; 8:45 am]
BILLING CODE 4160-01-F

¹ After August 14, 1997, a new levothyroxine drug product may not be introduced into the market unless FDA has approved an application for that product.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Endocrinologic and Metabolic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting is open to the public.

Name of Committee: Endocrinologic and Metabolic Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on May 19, 2000, 10 a.m. to 2 p.m.

Location: Holiday Inn, Ballroom, 8120 Wisconsin Ave., Bethesda, MD.

Contact Person: Kathleen R. Reedy or LaNise S. Giles, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane, (for express delivery, 5630 Fishers Lane, rm. 1093), Rockville MD, 301-827-7001, email: reedyk@cder.fda.gov, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12536. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will hear a presentation of the data and rationale for the regulatory action regarding the withdrawal from the U.S. market of Rezulin™ (troglitazone, Parke-Davis Pharmaceutical Research, a Division of Warner-Lambert) for the treatment of type 2 diabetes mellitus.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by May 15, 2000. Oral presentations from the public will be scheduled between approximately 10 a.m. and 11 a.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before May 15, 2000, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: April 17, 2000.

Linda A. Suydam,
Senior Associate Commissioner.
[FR Doc. 00-10321 Filed 4-25-00; 8:45 am]
BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Agency Information Collection Activities; Submission for OMB Review; Comment Request

Periodically, the Health Resources and Services Administration (HRSA) publishes abstracts of information collection requests under review by the Office of Management and Budget, in compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. Chapter 35). To request a copy of the clearance requests submitted to OMB for review, call the HRSA Reports Clearance Office on (301) 443-1129.

The following request has been submitted to the Office of Management and Budget for review under the Paperwork Reduction Act of 1995:

Proposed Project: Loan Information System Records for the DHHS and DHUD Hospital Mortgage Insurance, Guarantee, and Direct Loan Programs (OMB 0915-0174)—EXTENSION

The Division of Facilities and Loans within the Health Resources and Services Administration monitors outstanding direct and guaranteed loans made under Section 621 of Title VI and Section 1601 of Title XVI of the Public Health Service Act, as well as loans insured under the Section 242 Hospital Mortgage Insurance Program of the National Housing Act. These programs were designed to aid construction and modernization of health care facilities by increasing the access of facilities to capital through the assumption of the mortgage credit risk by the Federal Government.

Operating statistics and financial information are collected annually from hospitals with mortgages that are insured under these programs. The information is used to monitor the financial stability of the hospitals to protect the Federal investment in these facilities. The form used for the data collection is the Hospital Facility Data Abstract. No changes in the form are proposed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97F-0336]

General Electric Co.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that General Electric Co. has filed a petition proposing that the food additive regulations be amended to change the intrinsic viscosity specifications for poly(2,6-dimethyl-1,4-phenylene) oxide resins intended for use in contact with food.

FOR FURTHER INFORMATION CONTACT: Vir D. Anand, Center for Food Safety and Applied Nutrition (HFS-215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3081.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 7B4551) has been filed by General Electric Co., One Lexan Lane, Mt. Vernon, IN 47620-9364. The petition proposes to amend the food additive regulations in § 177.2460 Poly(2,6-dimethyl-1,4-phenylene) oxide resins to change the intrinsic viscosity specifications for the poly(2,6-dimethyl-1,4-phenylene) oxide resins intended for use in contact with food from "not less than 0.40 deciliter per gram" to "not less than 0.30 deciliter per gram" as determined by ASTM method D1243-79.

The agency has determined under 21 CFR 25.24(9) that this action is of the type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Dated: July 31, 1997.

Alan M. Rulla,
Director, Office of Premarket Approval,
Center for Food Safety and Applied Nutrition.
[FR Doc. 97-21436 Filed 8-13-97; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N-0314]

Prescription Drug Products,
Levothyroxine Sodium

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that orally administered drug products containing levothyroxine sodium are new drugs. There is new information showing significant stability and potency problems with orally administered levothyroxine sodium products. Also, these products fail to maintain potency through the expiration date, and tablets of the same dosage strength from the same manufacturer vary from lot to lot in the amount of active ingredient present. This lack of stability and consistent potency has the potential to cause serious health consequences to the public. Manufacturers who wish to continue to market orally administered levothyroxine sodium products must submit new drug applications (NDA's); manufacturers who contend that a particular drug product is not subject to the new drug requirements of the Federal Food, Drug, and Cosmetic Act (the act) should submit a citizen petition. FDA has determined that orally administered levothyroxine sodium products are medically necessary, and accordingly the agency is allowing current manufacturers 3 years to obtain approved NDA's.

EFFECTIVE DATE: August 14, 1997.

DATES: A citizen petition claiming that a particular drug product is not subject to the new drug requirements of the act should be submitted no later than October 14, 1997.

After August 14, 2000, any orally administered drug product containing levothyroxine sodium, marketed on or before the date of this notice, that is introduced or delivered for introduction into interstate commerce without an approved application, unless found by FDA to be not subject to the new drug requirements of the act under a citizen petition submitted for that product, will be subject to regulatory action.

ADDRESSES: All communications in response to this notice should be identified with Docket No. 97N-0314 and directed to the appropriate office named below:

Applications under section 505 of the act (21 U.S.C. 355): Documents and Records Section (HFA-224), 5600 Fishers Lane, Rockville, MD 20857.

Citizen petitions (see § 10.30 (21 CFR 10.30)) contending that a particular drug product is not subject to the new drug requirements of the act: Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

Requests for an opinion on the applicability of this notice to a specific product: Division of Prescription Drug Compliance and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish PL, Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine (T₄). Thyroid hormones affect protein, lipid, and carbohydrate metabolism; growth; and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production, and possess a cardiostimulatory effect that may be the result of a direct action on the heart.

Levothyroxine sodium was first introduced into the market before 1962 without an approved NDA, apparently in the belief that it was not a new drug. Orally administered levothyroxine sodium is used as replacement therapy in conditions characterized by diminished or absent thyroid function such as cretinism, myxedema, nontoxic goiter, or hypothyroidism. The diminished or absent thyroid function may result from functional deficiency, primary atrophy, partial or complete absence of the thyroid gland, or the effects of surgery, radiation, or antithyroid agents. Levothyroxine sodium may also be used for replacement or supplemental therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

Hypothyroidism is a common condition. In the United States, 1 in every 4,000 to 5,000 babies is born hypothyroid. Hypothyroidism has a prevalence of 0.5 percent to 1.3 percent in adults. In people over 60, the prevalence of primary hypothyroidism

percent in women. Because congenital hypothyroidism may result in irreversible mental retardation, which can be avoided with early diagnosis and treatment, newborn screening for this disorder is mandatory in North America, Europe, and Japan.

In addition to the treatment of hypothyroidism, levothyroxine sodium may be used to suppress the secretion of thyrotropin in the management of simple nonendemic goiter, chronic lymphocytic thyroiditis, and thyroid cancer. Levothyroxine sodium is also used with antithyroid agents in the treatment of thyrotoxicosis to prevent goitrogenesis and hypothyroidism.

II. Levothyroxine Sodium Products Must Be Consistent in Potency and Bioavailability

Thyroid replacement therapy usually is a chronic, lifetime endeavor. The dosage must be established for each patient individually. Generally, the initial dose is small. The amount is increased gradually until clinical evaluation and laboratory tests indicate that an optimal response has been achieved. The dose required to maintain this response is then continued. The age and general physical condition of the patient and the severity and duration of hypothyroid symptoms determine the initial dosage and the rate at which the dosage may be increased to the eventual maintenance level. It is particularly important to increase the dose very gradually in patients with myxedema or cardiovascular disease to prevent precipitation of angina, myocardial infarction, or stroke.

If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on one product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestations of hyperthyroidism such as cardiac pain, palpitations, or cardiac arrhythmias. In patients with coronary heart disease, even a small increase in the dose of levothyroxine sodium may be hazardous.

Hyperthyroidism is a known risk factor for osteoporosis. Several studies suggest that subclinical hyperthyroidism in premenopausal women receiving levothyroxine sodium for replacement or suppressive therapy is associated with bone loss. To minimize the risk of osteoporosis, it is advisable that the dose be titrated to the lowest effective dose (Refs. 1 and 2).

Because of the risks associated with overtreatment or undertreatment with

levothyroxine sodium, it is critical that patients have available to them products that are consistent in potency and bioavailability. Recent information concerning stability problems (discussed in section V of this document) shows that this goal is not currently being met.

III. Adverse Drug Experiences

Between 1987 and 1994, FDA received 58 adverse drug experience reports associated with the potency of orally administered levothyroxine sodium products. Forty-seven of the reports suggested that the products were subpotent, while nine suggested superpotency. Two of the reports concerned inconsistency in thyroid hormone blood levels. Four hospitalizations were included in the reports; two were attributed to product subpotency and two were attributed to product superpotency. More than half of the 58 reports were supported by thyroid function blood tests. Specific hypothyroid symptoms included: Severe depression, fatigue, weight gain, constipation, cold intolerance, edema, and difficulty concentrating. Specific hyperthyroid symptoms included: Atrial fibrillation, heart palpitations, and difficulty sleeping.

Some of the problems reported were the result of switching brands. However, other adverse events occurred when patients received a refill of a product on which they had previously been stable, indicating a lack of consistency in stability, potency, and bioavailability between different lots of tablets from the same manufacturer.

Because levothyroxine sodium products are prescription drugs marketed without approved NDA's, manufacturers are expressly required, under 21 CFR 310.305, to report adverse drug experiences that are unexpected and serious; they are not required, as are products with approved applications (see 21 CFR 314.80) periodically to report all adverse drug experiences, including expected or less serious events. Some adverse drug experiences related to inconsistencies in potency of orally administered levothyroxine sodium products may not be regarded as serious or unexpected and, as a result, may go unreported. Reports received by FDA, therefore, may not reflect the total number of adverse events associated with inconsistencies in product potency.

IV. Formulation Change

Because orally administered levothyroxine sodium products are marketed without approved applications, manufacturers have not

sought FDA approval each time they reformulate their products. In 1982, for example, one manufacturer reformulated its levothyroxine sodium product by removing two inactive ingredients and changing the physical form of coloring agents (Ref. 6). The reformulated product increased significantly in potency. One study found that the reformulated product contained 100 percent of stated content compared to 78 percent before the reformulation (Ref. 7). Another study estimated that the levothyroxine content of the old formulation was approximately 70 percent of the stated value (Ref. 8).

This increase in product potency resulted in serious clinical problems. On January 17, 1984, a physician reported to FDA: "I have noticed a recent significant problem with the use of [this levothyroxine sodium product]. People who have been on it for years are suddenly becoming toxic on the same dose. Also, people starting on the medication become toxic on 0.1 mg [milligram] which is unheard of." On May 25, 1984, another physician reported that 15 to 20 percent of his patients using the product had become hyperthyroid although they had been completely controlled up until that time. Another doctor reported in May 1984 that three patients, previously well-controlled on the product, had developed thyroid toxicity. One of these patients experienced atrial fibrillation.

There is evidence that manufacturers continue to make formulation changes to orally administered levothyroxine sodium products. As discussed in section V of this document, one manufacturer is reformulating in order to make its product stable at room temperature. In a 1990 study (Ref. 5), one manufacturer's levothyroxine sodium tablets selected from different batches showed variations in chromatographs suggesting that different excipients had been used.

V. Stability Problems

FDA, in conjunction with the United States Pharmacopoeial Convention, took the initiative in organizing a workshop in 1982 to set the standard for the use of a stability-indicating high-performance liquid chromatographic (HPLC) assay for the quality control of thyroid hormone drug products (Ref. 3). The former assay method was based on iodine content and was not stability-indicating. Using the HPLC method, there have been numerous reports indicating problems with the stability of orally administered levothyroxine sodium products in the past several years. Almost every manufacturer of

sodium products. Including the market leader, has reported recalls that were the result of potency or stability problems.

Since 1991, there have been no less than 10 firm-initiated recalls of levothyroxine sodium tablets involving 150 lots and more than 100 million tablets. In all but one case, the recalls were initiated because tablets were found to be subpotent or potency could not be assured through the expiration date. The remaining recall was initiated for a product that was found to be superpotent. During this period, FDA also issued two warning letters to manufacturers citing stability problems with orally administered levothyroxine sodium products.

At one firm, potency problems with levothyroxine sodium tablets resulted in destruction of products and repeated recalls. From 1990 to 1992, the firm destroyed 46 lots of levothyroxine sodium tablets that failed to meet potency or content uniformity specifications during finished product testing. In August 1989, this firm recalled 21 lots due to subpotency. In 1991, the firm recalled 26 lots in February and 15 lots in June because of subpotency.

An FDA inspection report concerning another manufacturer of levothyroxine sodium showed that 14 percent of all lots manufactured from 1991 through 1993 were rejected and destroyed for failure to meet the assay specifications of 103 to 110 percent established by the firm.

In March 1993, FDA sent a warning letter to a firm stating that its levothyroxine tablets were adulterated because the expiration date was not supported by adequate stability studies. Five lots of the firm's levothyroxine sodium tablets, labeled for storage within controlled room temperature range, had recently failed stability testing when stored at the higher end of the range. The warning letter also objected to the labeled storage conditions specifying a nonstandard storage range of 15 to 22 °C. FDA objected to this labeling because it did not conform to any storage conditions defined in United States Pharmacopoeia (USP) XXII. In response, the firm changed the labeling instruction to store the product at 8 to 15 °C. The firm informed FDA that it would reformulate its levothyroxine sodium tablets to be stable at room temperature.

The five failing lots named in FDA's warning letter were recalled in April 1994. Previously, in December 1993, a lot of levothyroxine sodium tablets was recalled by the same firm because potency was not assured through the

expiration date. In November 1994, the renamed successor firm recalled one lot of levothyroxine sodium tablets due to superpotency.

Another firm recalled six lots of levothyroxine sodium tablets in 1993 because they fell below potency, or would have fallen below potency, before the expiration date. The USP specifies a potency range for levothyroxine sodium from 80 percent to 110 percent. Analysis of the recalled tablets showed potencies ranging from 74.7 percent to 90.4 percent. Six months later, this firm recalled another lot of levothyroxine sodium tablets when it fell below labeled potency during routine stability testing. Content analysis found the potency of the failed lot to be 85.5 percent to 86.2 percent. Subsequently, an FDA inspection at the firm led to the issuance of a warning letter regarding the firm's levothyroxine sodium products. One of the deviations from good manufacturing practice regulations cited in that letter was failure to determine by appropriate stability testing the expiration date of some strengths of levothyroxine sodium. Another deviation concerned failure to establish adequate procedures for monitoring and control of temperature and humidity during the manufacturing process.

In April 1994, one manufacturer recalled seven lots of levothyroxine sodium products because potency could not be assured through the expiration date. In February 1995, the same manufacturer initiated a major recall of levothyroxine sodium affecting 60 lots and 50,436,000 tablets. The recall was initiated when the product was found to be below potency at 18-month stability testing.

In December 1995, a manufacturer recalled 22 lots of levothyroxine sodium products because potency could not be assured through the expiration date.

In addition to raising concerns about the consistent potency of orally administered levothyroxine sodium products, this pattern of stability problems suggests that the customary 2-year shelf life may not be appropriate for these products because they are prone to experience accelerated degradation in response to a variety of factors. Levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity (Ref. 4). One study found that some excipients used with levothyroxine sodium act as catalysts to hasten its degradation (Ref. 5). In addition, the kinetics of levothyroxine sodium degradation is complex. Stability studies show that levothyroxine sodium exhibits a biphasic first order degradation profile,

with an initial fast degradation rate followed by a slower rate (Ref. 4). The initial fast rate varies depending on temperature. To compensate for the initial accelerated degradation, some manufacturers use an overage of active ingredient in their formulation, which can lead to occasional instances of superpotency.

VI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Paul, T. L. et al., "Long-term L-Thyroxine Therapy Is Associated with Decreased Hip Bone Density in Premenopausal Women." *Journal of the American Medical Association*, 259:3137-3141, 1988.

(2) Kung, A. W. C., and K. K. Pun, "Bone Mineral Density in Premenopausal Women Receiving Long-term Physiological Doses of Levothyroxine." *Journal of the American Medical Association*, 265:2688-2691, 1991.

(3) Garnick, R. I. et al., "Stability Indicating High-Pressure Liquid Chromatographic Method for Quality Control of Sodium Liothyronine and Sodium Levothyroxine in Tablet Formulations." In "Hormone Drugs," edited by J. L. Gueriguan, E. D. Bransome, and A. S. Otschoorn, United States Pharmacopoeial Convention, pp. 504-516, Rockville, 1982.

(4) Won, C. M., "Kinetics of Degradation of Levothyroxine in Aqueous Solution and In Solid State." *Pharmaceutical Research*, 9:131-137, 1992.

(5) Das Gupta, V. et al., "Effect of Excipients on the Stability of Levothyroxine Sodium Tablets." *Journal of Clinical Pharmacy and Therapeutics*, 15:331-336, 1990.

(6) Hennessey, J. V., K. D. Burman, and L. Wartofsky, "The Equivalency of Two L-Thyroxine Preparations." *Annals of Internal Medicine*, 102:770-773, 1985.

(7) Stoffer, S. S., and W. E. Szpunar, "Potency of Levothyroxine Products." *Journal of the American Medical Association*, 251:635-636, 1984.

(8) Fish, L. H. et al., "Replacement Dose, Metabolism, and Bioavailability of Levothyroxine in the Treatment of Hypothyroidism: Role of Triiodothyronine in Pituitary Feedback in Humans." *The New England Journal of Medicine*, 316:764-770, 1987.

VII. Legal Status

Levothyroxine sodium is used as replacement therapy when endogenous thyroid hormone production is deficient. The maintenance dosage must be determined on a patient-by-patient basis. Levothyroxine sodium products are marketed in multiple dosage strengths, that may vary by only 12 micrograms, thus permitting careful titration of dose. Because of levothyroxine sodium's narrow therapeutic index, it is particularly important that the amount of available active drug be consistent for a given tablet strength.

Variations in the amount of available active drug can affect both safety and effectiveness. Patients who receive superpotent tablets may experience angina, tachycardia, or arrhythmias. There is also evidence that overtreatment can cause osteoporosis. Subpotent tablets will not be effective in controlling hypothyroid symptoms or sequelae.

The drug substance levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity. Unless the manufacturing process can be carefully and consistently controlled, orally administered levothyroxine sodium products may not be fully potent through the labeled expiration date, or be of consistent potency from lot to lot.

There is evidence from recalls, adverse drug experience reports, and inspection reports that even when a physician consistently prescribes the same brand of orally administered levothyroxine sodium, patients may receive products of variable potency at a given dose. Such variations in product potency present actual safety and effectiveness concerns.

In conclusion, the active ingredient levothyroxine sodium is effective in treating hypothyroidism and is safe when carefully and consistently manufactured and stored, and prescribed in the correct amount to replace the deficiency of thyroid hormone in a particular patient. However, no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability and, thus, no currently marketed orally administered levothyroxine sodium product is generally recognized as safe and effective. Accordingly, any orally administered drug product containing levothyroxine sodium is a new drug under section 201(p) of the act (21 C.F.R. 314.201) and is subject to the requirements of section 505 of the act.

Manufacturers who wish to continue to market orally administered levothyroxine sodium products must submit applications as required by section 505 of the act and part 314 (21 CFR part 314). FDA is prepared to accept NDA's for these products, including section 505(b)(2) applications. An applicant making a submission under section 505(b)(2) of the act may rely upon investigations described in section 505(b)(1)(A) that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. For example, such an application may include literature supporting the safety and/or the effectiveness of levothyroxine sodium. A bioavailability study must be completed and submitted as part of an NDA, including a 505(b)(2) application, in order to evaluate the safety and efficacy of these products.

If the manufacturer of an orally administered drug product containing levothyroxine sodium contends that the drug product is not subject to the new drug requirements of the act, this claim should be submitted in the form of a citizen petition under § 10.30 and should be filed to Docket No. 97N-0314 no later than October 14, 1997. Sixty days is the time allowed for such submissions in similar proceedings. (See § 314.200(c) and (e).) Under § 10.30(e)(2), the agency will provide a response to each petitioner within 180 days of receipt of the petition. A citizen petition that contends that a particular drug product is not subject to the new drug requirements of the act should contain the quality and quantity of data and information set forth in § 314.200(e). Note especially that a contention that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is to be supported by the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product. (See § 314.200(e)(1).)

Levothyroxine sodium products are medically necessary because they are used to treat hypothyroidism and no alternative drug is relied upon by the medical community as an adequate substitute. Accordingly, FDA will permit orally administered levothyroxine sodium products to be marketed without approved NDA's until August 14, 2000. In order to give manufacturers time to conduct the required studies and to prepare and submit applications, and to allow time for review of and action on these applications. This provision for

continuation of marketing, which applies only to levothyroxine sodium products marketed on or before the publication of this notice, is consistent with the order in *Hoffmann-La Roche, Inc. v. Weinberger*, 425 F. Supp. 890 (D.D.C. 1975), reprinted in the *Federal Register* of September 22, 1975 (40 FR 43531) and March 2, 1976 (41 FR 9001).

After August 14, 2000 any orally administered drug product containing levothyroxine sodium, marketed on or before the date of this notice, that is introduced or delivered for introduction into interstate commerce without an approved application will be subject to regulatory action, unless there has been a finding by FDA, under a citizen petition submitted for that product as described above, that the product is not subject to the new drug requirements of the act.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505 (21 U.S.C. 352, 355)) and under authority delegated to the Deputy Commissioner for Policy (21 CFR 5.20).

Dated: August 7, 1997.

William K. Hubbard,

Associate Commissioner for Policy
Coordination.

(FR Doc. 97-21575 Filed 8-13-97; 8:45 am)

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

National Consumer Forum; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of meeting.

SUMMARY: The Food and Drug Administration (FDA), Office of Consumer Affairs (OCA), is announcing the first in a series of National Consumer Forums. These forums are an opportunity to engage in open dialog with consumers on health issues and agency actions.

DATES: The meeting will be held on Tuesday, September 23, 1997, from 1 p.m. to 3 p.m. Due to space limitations, preregistration is recommended.

ADDRESSES: The meeting will be held in the Truman Room of the White House Conference Center, 726 Jackson Pl. NW., Washington, DC 20006. Use Metro Stop Farragut North, K Street Exit on the Red Line, and Farragut West on Blue/Orange Line.

FOR FURTHER INFORMATION CONTACT: Carol M. Lewis, Office of Consumer

(The firm has not yet submitted any advertising materials.

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**APPEARS THIS WAY
ON ORIGINAL**