CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-342

CORRESPONDENCE

MEMORANDUM

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

DATE: February 27, 2002

TO: NDA 21-342

FROM: Steve McCort
Regulatory Project Manager

SUBJECT: **Financial Disclosure Statement**
NDA 21-342, Levo-T (Levothyroxine sodium tablets)

The sponsor submitted a Financial Disclosure Statement for two bioavailability studies as follows:

Study #1: #099073 "Comparative, randomized, 2-way crossover bioavailability study of Mova 300 ug levothyroxine sodium tablets and Knoll (Synthroid®) 200 ug vials of levothyroxine sodium injection (taken orally) in healthy adult males and females, following administration of a 600 ug dose under fasting conditions.

Study #2: 9900675- Comparative, randomized, 3-way parallel design dosage-form equivalence study of Mova 50 ug, 100 ug, and 300 ug levothyroxine sodium tablets, following administration of 600 ug doses, healthy adult males and females under fasting conditions.

These studies were conducted by [redacted]

The sponsor indicated in their financial disclosure statement that they did not enter into any finical arrangement with [redacted] who conducted the bioavailability studies.

In Jean Temeck's medical review, dated January 30, 2002, page 11, she agreed with the sponsor's financial disclosure statement.

CONCLUSION:

Based upon Dr.Temeck's January 30, 2002, review, the sponsor has fulfilled the financial disclosure requirement for clinical studies.

Steve McCort
Regulatory Project Manager, HFD-510

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

/s/

Stephen McCort
2/28/02 11:12:52 AM
CSO

Jean Temeck
2/28/02 11:29:57 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Advertising materials will be requested in the action letter.

APPEARS THIS WAY
ON ORIGINAL

An advisory committee meeting was not requested or needed.

APPEARS THIS WAY
ON ORIGINAL

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-S

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@lcgnet.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-0338]

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 then 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. Rulis,

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-F

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. Rog[illegible], 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 (T_4). 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

increases to 2.7 percent in men and 7.1 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 Pharmacopeial 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

orally administered levothyroxine 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 Pharmacopeia (USP) XXIL 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 90 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, 1953

(2) Kung, A. W. ..., 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. L. 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. Guerigutan, E. D. Bransome, and A. S. Outschoorn, United States Pharmacopeial 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 ›lacement therapy when endogenous roid hormone production is ficient. The maintenance dosage must › determined on a patient-by-patient ›asis. 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 ›dium products may not be fully ent through the labeled expiration e, or be of consistent potency from 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 ›dministered drug product containing ›thyroxine sodium is a new drug er section 201(p) of the act (21 C. 321(p)) and is subject to the irements 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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 8, 2002

To: Arcelis Ramirez	**From:** Steve McCort
Company: Mova Pharmaceutical Corporation	Division of Division of Metab[illegible] and Endocrine Drug Products
Fax number: 787-745-1750	**Fax number:** 301-443-9282
Phone number: 787-746-8500	**Phone number:** (301) 827-6415

Subject: Labeling recommendations to Levo-T using the revised labeling template for L-Thyroxine Sodium Tablets

Total no. of pages including cover: 17

Comments: Please revise the draft labeling using the enclosed revised labeling template.

Document to be mailed: ☐ YES ☑ NO

APPEARS THIS WAY
ON ORIGINAL

REVISIONS TO FDA's LEVOTHYROXINE SODIUM LABELING TEMPLATE:

1. PRECAUTIONS section: Effects on bone mineral density:
   Replace the first sentence with the following:
   In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase and suppressed serum parathyroid hormone levels.

2. Pregnancy section:
   Revise the beginning of the first sentence in the third paragraph to read: "Thyroid hormones cross the placental barrier to some extent as evidenced by levels in cord blood...

3. ADVERSE REACTIONS section:
   Add: (see PRECAUTIONS and OVERDOSAGE) at the end of the first sentence.
   Replace —— ' with "Cardiovascular";
   Replace ——— ' with "Respiratory";
   Replace — with "Gastrointestinal" and add: "elevation in liver function tests".
   After Dermatologic, add "Endocrine: decreased bone mineral density".

4. OVERDOSAGE section:
   Replace "approximately —mg" with "18 mg" in the fourth sentence of the first paragraph.
   Acute Massive Overdosage- Revise the fourth sentence to read: "Central and peripheral increased sympathetic activity may be treated by administering β-receptor antagonists, e.g. propranolol, provided there are no medical contraindications to their use". In the fifth sentence, add: "and arrhythmia" after "congestive heart failure". After the fifth sentence add: "Large doses of antithyroid drugs (e.g. methimazole or propylthiouracil) followed in one to two hours by large doses of iodine may be given to inhibit synthesis and release of thyroid hormones". Before the last sentence add: "Plasmapheresis, charcoal hemoperfusion and exchange transfusion have been reserved for cases in which continued clinical deterioration occurs despite conventional therapy".

5. DOSAGE AND ADMINISTRATION section:
   Infants and Children
   Table 3:
   After ">12 years" add "but growth and puberty incomplete"
   Replace footnote "A" with "a".

WITHHOLD 14 PAGE (S)

Draft

Labeling

DRAFT LABELING DATED April 30, 2002
(ORIGINAL)

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 63 PAGE (S)

Draft

Labeling

MOVA Pharmaceutical Corporation
Levothyroxine Tablets, USP
New Drug Application NDA # 21-342

Levothyroxine Tablets, USP Commitment for In-process Specifications

MOVA Pharmaceutical Corporation is hereby committing to establish in –process specification for the levothyroxine —— in the ——— stage.

The in-process specifications for the —— of levothyroxine in the ——— will be determined with the data obtained in the manufacture of future lots in a period of time of a year.

Aracelis Ramirez by Hyalo Quiz

02/08/02

Aracelis Ramírez
Vice-President of Quality & Regulatory Affairs

Date

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE:

To: MS RAMIROZ	**From:**
Company: NOVA	Division of Metabolic and Endocrine Drug Products
Fax number: 787-754-1150	**Fax number:** (301) 443-9282
Phone number:	**Phone number:** 301-827-6415
Subject: APPROVAL letter NDA 21-372	
Total no. of pages including cover:	

Comments:

Document to be mailed: ☐ YES ☑ NO

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-342

Mova Pharmaceutical Corporation
Attention: Aracelis Ramirez
Vice President, Regulatory & Quality Affairs
Villa Blanca Industrial Park
State Street Road No. 1 Km 34.8/Jose Garrido Avenue (End)
Caquas, P.R. 00725

Dear Ms. Ramirez:

Please refer to your new drug application (NDA) dated April 30, 2001, received May 1, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Levo-T® (levothyroxine sodium tablets, USP), 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg.

We acknowledge receipt of your submissions dated May 21, September 11, October 26, November 8, and December 7, 2001, and January 24 and February 4, 6, 8, 13, and 28(2), 2002.

This new drug application provides for the use of Levo-T (levothyroxine sodium tablets, USP) for hypothyroidism and suppression of thyroid-stimulating hormone.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to, except for the indicated revision, the submitted draft labeling (package insert [enclosed] submitted February 28, 2002, and the immediate container label for the 25 mcg x 5000 count bottle submitted February 28, 2002.) In your February 28, 2002, letter, you agreed to revise the other 43 labels submitted on April 30, 2001, to add the word "permitted" to the end of the first storage condition sentence exactly as in the 25 mcg x 5000 bottle label submitted February 28, 2002. The revision is a term of the NDA approval. Marketing the product before making the revision, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar

January 23, 2002

Food and Drug Administration
Office of Information Resources Management
Division of Freedom of Information
5600 Fischers Lane
Rockville, Maryland 20857

540
5940 F

Dear Sir or Madam,

I would like to request copies of the pharmacology and medical reviews for the drug product ACTINEX. The corresponding NDA is N19940 for the ingredient called masoprocol. This drug was approved on September 4, 1992. In addition, I would like to request copies of the corresponding pharmacology and medical IND reviews.

In compliance with your instructions, I am willing to pay the fees associated with obtaining these records. Please let me know what the cost will be for these records.

I can be reached at:

Javier Avalos, Ph.D.
421 Lyman Circle
Sacramento, California 95835

(916) 712-7796
(9160 419-3173 fax

Thank you for your consideration of this request.

Best regards,

Javier Avalos, Ph.D.

02-1269

RECEIVED
JAN 25 2002
FDA DIV FOI(HFI-35)

HFD-130(F)