

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-402

Correspondence



NDA 21-402

Abbott Laboratories
Attention: Jim Steck
Director, Regulatory Affairs
100 Abbott Park Road
D-491/AP6B-1*
Abbott Park, IL 60064-6108

Dear Mr. Steck:

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: Synthroid (levothyroxine sodium tablets, USP), 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg.

Review Priority Classification: Standard (S)

Date of Application: July 31, 2001

Date of Receipt: August 1, 2001

Our Reference Number: NDA 21-402

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 30, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 1, 2002, and the secondary user fee goal date will be August 1, 2002.

This supplemental application provides for the treatment of hypothyroidism and the treatment and prevention of pituitary TSH suppression.

Be advised that, as of April 1, 1999, all applications for new 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 66631). In this submission you requested a waiver of pediatric studies for newborns through patients 18 years of age. Based upon the justification for your waiver request, the requirement for pediatric studies in patients up to 16 years of age is waived.

NDA 21-402

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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 me at (301) 827-6415.

Sincerely,

{See appended electronic signature page}

Steve McCort
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

**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
8/9/01 10:40:43 AM

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

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 PetitionAGENCY: 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. Rultz,
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 SodiumAGENCY: 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

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 Pharmacopelal 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 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 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, 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. Outschoorn, 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 consistent 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. 321(p)) 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

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

1376 99-117-17-01-03

November 17, 1999

SUPPLEMENT TO CITIZEN PETITION
REGULATORY STATUS OF SYNTHROID® ORALLY ADMINISTERED
LEVOTHYROXINE SODIUM USP
Docket No. 97N-0314/CP2

Knoll Pharmaceutical Company ("Knoll" or "the company") submits this supplement to the above-referenced citizen petition under sections 201(p) and 505 of the Food, Drug, and Cosmetic Act ("FDCA" or "the Act") and 21 C.F.R. § 10.30(g).¹ The Petition asked the Commissioner of Food and Drugs (the "Commissioner") to issue an order declaring that Synthroid® orally administered levothyroxine sodium USP ("Synthroid") is generally recognized as safe and effective ("GRAS/E") within the meaning of section 201(p) of the Act for the treatment of hypothyroidism and the management of thyroid cancer, and therefore not subject to regulation as a "new drug" under the Act. The Petition also requested a specific determination that Synthroid does not require an approved new drug application ("NDA") as called for by the Food and Drug Administration ("FDA") in its Federal Register Notice

1. Citizen Petition on Regulatory Status of Synthroid Orally Administered Levothyroxine Sodium USP, Docket No. 97N-0314/CP2, filed Dec. 15, 1997 and supplemented May 29, 1998 (hereinafter "GRAS/E Petition" or "Petition"). The Petition as previously supplemented is incorporated by reference in this supplement. Unless otherwise noted, references to exhibits in the Petition refer to materials filed on Dec. 15, 1997, and are cited herein as "Petition Exhibit ___". For convenience, the narrative text of the Petition is attached as Exhibit 1.

A related petition addressing certain scheduling and procedural aspects of the Petition and FDA's regulation of orally administered sodium levothyroxine drug products was filed Sept. 25, 1998, and is also incorporated by reference in this supplement. Citizen Petition on Scheduling and Procedure, Docket No. 97N-0314/CP3, filed Sept. 25, 1998 and supplemented Aug. 4, 1999 and Nov. 9, 1999 (hereinafter "Scheduling and Procedure Petition").

entitled "Prescription Drug Products; Levothyroxine Sodium" ("Levothyroxine Notice" or "the Notice"), 62 Fed. Reg. 43,535 (Aug. 14, 1997).²

This supplement presents additional arguments and information in support of the requested actions, including additional evidence derived from FDA files obtained under the Freedom of Information Act ("FOIA").

STATEMENT OF GROUNDS

I. Introduction

Synthroid is not a new drug. As the GRAS/E Petition has already shown, Synthroid is generally recognized as safe and effective by leading thyroid experts on the basis of adequate and well-controlled studies published in the scientific literature and more than forty years of safe and effective use in millions of patients. Moreover, experts specifically rely on studies and experience using Synthroid as evidence of safety and effectiveness for the active ingredient levothyroxine sodium (sometimes referred to herein as "LT4" or "levothyroxine").³

2. Shortly after the Notice appeared, counsel for Knoll filed an extensive request for documents under FOIA (the "FOIA Request"), which was designed to elicit all releasable records bearing on the legal and factual conclusions set forth in the Notice. Letter from Nancy L. Buc and Edward J. Parr, Jr., Buc & Beardsley, to Freedom of Information Staff, HF1-35, FDA (FOI No. 97-31022) (Sept. 12, 1997). Beginning in October, 1997 and continuing through July, 1999, FDA has produced many documents relevant to Knoll's petition, but has failed to produce many others. Knoll currently is pursuing an administrative appeal of FDA's denial of documents covered by the FOIA Request (Administrative Appeal No. 99-A-094, filed Sept. 22, 1999), and will pursue its judicial remedies if need be. The company intends to further supplement the GRAS/E Petition with relevant documents it obtains as a result.

3. See Petition at 9-13.

FDA's own experts have long been part of the general scientific consensus with respect to levothyroxine sodium.⁴ This position was reconfirmed in the 1997 Levothyroxine Notice.⁵ Indeed, FDA officials involved in drafting the Notice referred to published studies on LT4 in the aggregate as "published data which would support the efficacy of synthroid (sic)."⁶

FDA further stated in the Notice and recently restated in a draft guidance that it intends to accept such published studies as evidence of safety and effectiveness in levothyroxine NDAs submitted under section 505(b)(2) of the Act.⁷ Because the evidentiary standard for safety and effectiveness in GRAS/E determinations is the same as that for NDAs,⁸

4. For example, a letter signed by Dr. Solomon Sobel, then as now the head of FDA's Division of Metabolism and Endocrine Drug Products, stated FDA's "position . . . that levothyroxine is the treatment of choice for the hypothyroid patient. . . . [T]his position was not taken arbitrarily but was the result of extensive conferences with our Endocrinology and Metabolism Drugs Advisory Committee, as well as with experts on thyroid physiology and disease which, together with members of the United States Pharmacopoeia ["USP"] convened . . . [at a joint Workshop held in May,] 1982. . . . At this Workshop the experts repeatedly emphasized the fact that levothyroxine is the replacement drug of choice[.]" Letter from Solomon Sobel, M.D., Director of the Division of Metabolism and Endocrine Drug Products, FDA, to Parke Davis Regulatory and Medical Affairs (Attn: Martin Shapiro) (Oct. 12, 1983). The workshop referred to by Dr. Sobel is discussed in the GRAS/E Petition at 23-25 and Petition Exhibit 18. Unless otherwise noted, documents such as Dr. Sobel's letter, which Knoll obtained pursuant to the Freedom of Information Act, as well as FDA Forms 482 and 483, Establishment Inspection Reports, Memorandums of Understanding, pleadings and briefs in FDA litigation, and other FDA documents which are "routinely publicly available," 21 C.F.R. § 10.20(c), are cited in but not attached to this supplement and the attached declarations, pursuant to 21 C.F.R. § 10.20(c).

5. Notice at 43,538 (levothyroxine sodium is effective in treating hypothyroidism and is safe when carefully and consistently manufactured and stored); *id.* (no alternative drug is relied upon by the medical community as an adequate substitute for treatment of hypothyroidism).

6. Specifically, FDA meeting notes state that "[i]t was suggested that the FR notice should contain a list of the published data which would support the efficacy of synthroid." Steve McCort, Consumer Safety Officer, HFD-510, FDA, Memorandum of a Meeting: Levothyroxine (Internal) (June 18, 1996).

7. Notice at 43,538; FDA Draft Guidance for Industry on Levothyroxine Sodium, Docket No. 99D-2636, 64 Fed. Reg. 44,935 (Aug. 18, 1999). Knoll has commented separately on the draft guidance. See Letter from Robert W. Ashworth, Ph.D., and Steven L. Goldberg, Knoll Pharmaceutical Company, to Dockets Management Branch, HFA-305, FDA (Docket No. 99D-2636) (Oct. 18, 1999).

8. See Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); 21 C.F.R. § 314.200(e)(1).

FDA's stated willingness to accept published studies of Synthroid to support NDAs is tantamount to a declaration that Synthroid is GRAS/E.

Nothing that FDA has invoked as so-called "stability and potency problems" in product manufacturing undercuts the conclusion that Synthroid is GRAS/E. As a factual matter, Synthroid is consistently potent and stable. As a matter of law, neither the language of the statutory GRAS/E provision nor the related statutory definitions of "safety" and "effectiveness" authorize FDA to consider manufacturing issues such as potency and stability in determining whether a product is GRAS/E. Rather, the Act provides for regulation of potency and stability issues as elements of current good manufacturing practices ("CGMPs"), which are mandated for all drugs, new and not new, under the adulteration provisions of section 501.⁹

Consistent with the clear language and intent of the FDCA, FDA has described the evidentiary standard for GRAS/E status again and again over the years as requiring (1) general recognition by qualified experts based on adequate and well controlled published studies; and (2) a material time and extent of marketing - without also stating (or even suggesting) that manufacturers must also "demonstrate consistent potency and stability" as the Levothyroxine Notice now contends.¹⁰ Separately, FDA has regularly and successfully used the CGMP provisions to regulate drug potency and stability, whether or not the products at issue also have NDAs.

Both of these points are strikingly illustrated by the agency's recent enforcement action against Sage Pharmaceuticals, Inc. ("Sage"). In that action, FDA asserted that Sage's products, which were marketed without NDAs, were unapproved new drugs because they failed to meet the well established standard of general recognition plus material time and extent

9. See Petition at 15-16.

10. See, e.g., Memorandum in Support of Plaintiff's Motion for Summary Judgment, United States v. Sage Pharmaceuticals, Inc., No. CV 98-0718, W.D. La., filed July 15, 1998 at 2 (hereinafter "Sage Plaintiff's Memorandum"); id. at 2-3 ("In order to be GRAS/E, qualified experts must agree, based on published adequate and well-controlled clinical studies, that the drugs are safe and effective for their intended uses" (emphasis in original); drugs also must be marketed for a material time. FDA did not mention stability, potency, or any other manufacturing issues as criteria for GRAS/E status.) See also Brief for the United States of America as Amicus Curiae, Florida Breckenridge, Inc. v. Solvay Pharmaceuticals, Inc., No. 98-4606, 11th Cir., filed July 23, 1998 (GRAS/E standard requires general recognition of safety and efficacy among qualified experts as a consequence of testing and investigations; drug also must be used to a material extent and for a material time. There is no mention of stability, potency, or manufacturing issues.); FDA, Laetrile Administrative Rule Making Hearing, Docket No. 77N-00481, 42 Fed. Reg. 10,066, 10,068 (Feb. 18, 1977) (Notice of Administrative Rule Making to determine regulatory status of Laetrile; stating GRAS/E standard without mentioning manufacturing).

of marketing.¹¹ FDA also asserted that the products were adulterated under section 501(a)(2)(B) because of (among other things) inadequate stability assurance and process validation.¹² There was no suggestion that potency or stability issues, or any other CGMP issues, had any relevance to the new drug issue.

Knoll now is supplementing its Petition with additional evidence including information and records obtained from FDA's files under the FOIA. Those records reconfirm what Knoll has already shown: that FDA does not need "new drug" authority to regulate the potency and stability of levothyroxine sodium products, and that the "stability and potency problems" asserted in the Notice are nonexistent for Synthroid, whatever may or may not be the case for other products. These points are detailed below.

II. FDA does not need NDAs to regulate the potency and stability of levothyroxine sodium products.

Stripped to its essence, the Notice argues that Synthroid and other oral LT4 products are not GRAS/E because "significant stability and potency problems" in their manufacturing can adversely affect both safety and effectiveness. Thus, FDA argues, NDAs are needed to ensure that levothyroxine sodium "manufacturing process[es] can be carefully and consistently controlled" for consistent potency and stability. In fact, however, FDA can and does regulate the potency and stability of all drug products - including new drugs, GRAS/E old drugs, and drugs whose status under section 201(p) of the Act has yet to be determined - as elements of CGMPs under section 501(a) of the Act.¹³

Notwithstanding its statements in the Levothyroxine Notice, FDA has recently reaffirmed that potential safety risks from drug product quality defects are "controlled through good manufacturing practices, monitoring and surveillance"¹⁴ - not by NDAs. In particular,

11. Sage Plaintiff's Memorandum, supra note 10, at 1-3; see also id. at 3 (Sage products are new drugs for "two independent reasons: (1) they are not GRAS/E; and (2) they have not been marketed for a material time").

12. Id. at 10-11 (explaining that CGMP violations including inadequate process validation and stability testing provide a separate basis for injunction under adulteration provisions).

13. See 21 C.F.R. § 314.170 (adulteration provisions apply to all drugs, not just new drugs); U.S. v. Bel-Mar Labs., Inc., 284 F.Supp. 875, 879 (E.D.N.Y. 1968) (CGMP provision was added to the Act in 1962 to give FDA "additional authority to require that sound methods, facilities, and controls be used in all phases of drug manufacturing and distribution." (citing 1962 U.S. Code Cong. & Adm. News at 2890) (emphasis added)).

14. See Center for Drug Evaluation and Research, FDA, CDER 1998 Report to the Nation: Improving Public Health Through Human Drugs at 21 (1998).

. . . comprehensive regulatory coverage of the production and distribution of drug products . . . helps ensure that drugs are safe, effective and in compliance with applicable current regulations for good manufacturing practices.¹⁵

FDA also recently reconfirmed the importance of CGMPs as the appropriate mechanism for assuring batch-to-batch consistency in the performance of drugs marketed without NDAs.¹⁶ FDA inspections, warning letters, and enforcement actions likewise routinely deal with potency and stability problems as CGMP issues for all drugs, new and not new.¹⁷

Orally administered levothyroxine sodium products are no different from any other drugs when it comes to regulating potency and stability. When such issues arise with LT4 drugs, FDA can and routinely does regulate them as matters of CGMP compliance and enforcement, using the same regulatory mechanisms it applies to other drugs (whether NDA-ed

15. Id. at 25; see generally FDA Investigations Operations Manual, Subchapter 540 - Drugs (1996).

16. Specifically, FDA declined to include requirements for batch-to-batch consistency testing as part of its Final Monograph for Sunscreen Drug Products for Over-The-Counter Human Use, which specifies the conditions under which such products are GRAS/E and do not require NDAs. The agency explained that the proposed requirement would be redundant, because CGMP regulations already "assure that each batch of drug product meets established specifications for the identity and strength of each active ingredient." FDA, Final Monograph; Sunscreen Drug Products for Over-The-Counter Human Use, Docket No. 78N-0038, 64 Fed. Reg. 27,666, 27,668 (May 21, 1999).

17. See, e.g., Sage Plaintiff's Memorandum, supra note 10; Warning Letter from Douglas I. Ellsworth, District Director, New Jersey District Office, FDA, to Wayne Yetter, President & CEO, Novartis Pharmaceuticals, Inc. (July 1, 1999) (describing multiple deficiencies in stability and potency assurance observed during inspection as CGMP violations causing products with NDAs to be adulterated under section 501(a)(2)(B)). Potency and stability issues are among the most common CGMP violations in FDA warning letters for both new and not-new drugs. See, e.g., Schering's Three GMP Warning Letters in 1998 Counter Industry Decline, The Pink Sheet (Mar. 8, 1999) (more than one third of drug warning letters issued in FY 1998 cited CGMP deficient stability testing); Out of Spec Investigations Cited in 30% of FY 1997 Warning Letters, The Pink Sheet (Feb. 23, 1998) (stability programs cited in 40% of FY 1997 drug warning letters); The Pink Sheet (Feb. 24, 1997) (40% of FY 1996 drug warning letters referenced stability-related CGMP deficiencies); see also FDA's Kolaitis on GMP Expectations for Stability Programs, The Gold Sheet (July 1, 1998) (quoting remarks of FDA's New England Regional Director emphasizing and explaining stability and potency issues in CGMP compliance). Cited articles are attached as Exhibit 2.

or not) - including CGMP inspections, recall oversight, market surveillance, complaint investigations, and, where necessary, warning letters and enforcement actions against products thought to be adulterated. Among the LT4 potency and stability issues FDA has dealt with under CGMPs are the following:

- Failures to assure potency through labeled expiration date (i.e., stability);¹⁸
- Potency failures and/or lot-to-lot variations in potency;¹⁹
- Documentation and validation of formulation and process changes potentially affecting potency and stability;²⁰

18. See, e.g., Establishment Inspection Report, Mova Pharmaceutical, Corp., Caguas, PR (EI: Feb. 3 to Apr. 15, 1994) (hereinafter "1994 Mova EIR"); FDA Form 483, issued to President, Mova Pharmaceuticals, Corp. (Apr. 15, 1994) (concerning inspection of Caguas, PR facility from Feb. 3 to Apr. 15, 1994) (hereinafter "1994 Mova 483"); Establishment Inspection Report, Pharmaceutical Basics, Inc., Denver, CO (EI: Apr. 30 to May 27, 1993) (hereinafter "1993 PBI EIR"); Establishment Inspection Report, Chelsea Laboratories Caribe, Inc., Bayamon, PR (EI: June 7 to June 22, 1995) (hereinafter "1995 Chelsea EIR").

19. See, e.g., FDA Form 483, issued to William S. Propst, Sr., President & CEO, Vintage Pharmaceuticals, Inc. (Dec. 10, 1997) (concerning inspection of Charlotte, NC facility from Nov. 10 to Dec. 10, 1997) (hereinafter "1997 Vintage 483"); 1994 Mova EIR, supra note 18; 1994 Mova 483, supra note 18.

20. See Declaration of Gary D. Dolch, Ph.D., at ¶ 10 (FDA review of Synthroid formulation) (hereinafter "Dolch Declaration") (attached as Exhibit 3). Dr. Dolch is Knoll's Vice President of Quality Assurance Management; beginning in March 1992, he held the same title and was responsible for the same functions at Knoll's predecessor, Boots Pharmaceuticals, Inc. See also, e.g., Establishment Inspection Report, Vintage Pharmaceuticals, Inc., Charlotte, NC (EI: July 27 to Aug. 5, 1998); 1997 Vintage 483, supra note 19; Establishment Inspection Report, Rhone-Poulenc Rorer P.R., Inc., Manati, PR (EI: June 13 to July 20, 1994) (hereinafter "1994 RPR EIR"); FDA Form 483, issued to Evaristo Velazquez, Vice President & General Manager, Rhone-Poulenc Rorer P.R., Inc. (July 20, 1994) (concerning inspection of Manati, PR facility from June 13 to July 20, 1994) (hereinafter "1994 RPR 483"); 1993 PBI EIR, supra note 18; Warning Letter from John H. Scharmann, Director, Denver District Office, FDA, to Piet M. Bleyendaal, President, Pharmaceutical Basics, Inc. (Mar. 1, 1993) (hereinafter "1993 PBI Warning Letter").

- Reports and investigations of product defects and adverse events potentially related to product potency or stability;²¹ and
- Stability and labeling implications of storage temperature.²²

In most cases, compliance with CGMPs has enabled manufacturers to ensure consistent potency and stability of their levothyroxine products, and to identify and correct potential problems through voluntary compliance, including, where appropriate, product recalls. This has certainly been the case for Synthroid, as detailed in Section III below. Where manufacturing deficiencies adversely affecting potency and stability have been both serious and uncorrected, FDA has taken steps to correct them by issuing warning letters and where necessary, instituting enforcement actions under section 501.

To highlight just a few examples, FDA addressed manufacturing issues for Levothroid (then manufactured by Rhone-Poulenc Rorer for distribution by Forest Laboratories) in inspections in 1993 and 1994,²³ in response to product recalls and trade complaints relating to subpotency. Issues covered included process validation, product formulations and formulation changes, and detailed aspects of potency/stability assurance. These issues were clearly identified as CGMP violations in a November, 1994 warning letter.²⁴ A March, 1998 inspection of Levothroid resulted in the issuance of another warning letter to Forest identifying

21. See, e.g., Establishment Inspection Report, Daniels Pharmaceuticals, Inc., St. Petersburg, FL (EI: Sept. 17, 18, 22, and 24, 1992); 1995 Chelsea EIR, supra note 18.

22. For example, stability issues relating to storage temperature labeling for both PBI and Chelsea Pharmaceuticals were referred to CDER's Stability Committee, which handled them as CGMP issues using guidelines applicable to all prescription drugs. See 1993 PBI Warning Letter, supra note 20; 1993 PBI EIR, supra note 18; Electronic Mail Message from Barry Rothman, HFD-325, FDA, to Bradford Williams, FDA (Apr. 11, 1994); Electronic Mail Message from Barry Rothman, HFD-325, FDA, to LuAnn Summy, FDA (Jan. 18, 1995); Establishment Inspection Report, Chelsea Laboratories Caribe, Inc., Bayamon, PR (EI: Nov. 23, 1994 to Dec. 13, 1994); 1995 Chelsea EIR, supra note 18 (addressing stability and potency issues in detail).

23. See 1994 RPR EIR, supra note 20; 1994 RPR 483, supra note 20; Establishment Inspection Report, Rhone-Poulenc Rorer P.R., Inc., Manati, PR (EI: Feb. 18 to Mar. 5, 1993); FDA Form 483, issued to Evaristo Velazquez, Vice President & General Manager, Rhone-Poulenc Rorer P.R., Inc. (Mar. 5, 1993) (concerning inspection of Manati, PR facility from Feb. 18 to Mar. 5, 1993).

24. Warning Letter from Samuel Jones, District Director, San Juan District, to Robert E. Cawthorn, President & CEO, Rhone-Poulenc Rorer, Inc. (Nov. 4, 1994) (Rhone-Poulenc Rorer manufactured Levothroid for Forest at that time).

CGMP deficiencies having the potential to affect potency and stability, and therefore causing the product to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA.²⁵

Inspections in 1997 and 1998 at Vintage Pharmaceuticals Inc.'s Charlotte, N.C. plant revealed extensive problems with potency and stability assurance for Vintage's levothyroxine sodium products, among many others.²⁶ FDA treated those problems as CGMP violations to be corrected under the adulteration provisions of the Act. When Vintage failed to correct the violations voluntarily,²⁷ FDA brought a judicial enforcement action to enjoin the company from shipping and manufacturing adulterated drugs in violation of FDCA sections 301(a) and (k).²⁸ A subsequent consent decree outlined specific CGMP compliance conditions that had to be met in order for the company to resume operations.²⁹

FDA had no need to assert in that action that potency and stability defects caused Vintage's levothyroxine sodium products to be new drugs. To the contrary, the agency emphasized for all the Vintage products that "CGMPs are what guarantee that, when a consumer takes a drug, that drug will perform as intended[:]"³⁰

The purpose of CGMPs . . . is to ensure that drugs meet the safety requirements of [the Act] . . . and that they have the identity, strength, quality, and purity that they purport

25. Warning Letter from Henry L. Fielden, Acting District Director, Cincinnati District, FDA, to Howard Solomon, Chief Executive Officer, Forest Laboratories, Inc. (Apr. 9, 1998).

26. See FDA Form 483, issued to William S. Propst, Sr., President & CEO, Vintage Pharmaceuticals, Inc. (Apr. 15, 1998) (concerning inspection of Charlotte, NC facility from Mar. 23 to Apr. 15, 1998).

27. See Warning Letter from Raymond K. Hedblad, Director, Nashville District, FDA, to William S. Propst, Sr., President & CEO, Vintage Pharmaceuticals, Inc. (Aug. 27, 1997); Warning Letter from Ballard H. Graham, Director, Atlanta District, FDA, to William S. Propst, Sr., President & CEO, Vintage Pharmaceuticals, Inc. (Dec. 20, 1995). Like the Forest warning letter discussed above and all past warning letters concerning manufacturing issues for levothyroxine sodium products, the letters relied entirely on FDA's authority to enforce CGMPs under section 501 of the Act, and were silent as to possible "new drug" status resulting from those alleged CGMP violations.

28. Complaint for Injunction, United States v. Vintage Pharmaceuticals, Inc., No. CV-98-S-1843-NE, N.D. Ala., filed July 20, 1998.

29. Consent Decree, United States v. Vintage Pharmaceuticals, Inc., No. CV-98-N-1843-NE, N.D. Ala., entered Nov. 30, 1998.

30. Memorandum in Support of Motion for Preliminary Injunction, United States v. Vintage Pharmaceuticals, Inc., No. CV-98-S-1843-NE, N.D. Ala., filed Aug. 31, 1998 at 19 (emphasis added).

to have. Drugs that are manufactured under conditions that violate CGMPs are deemed to be adulterated. As such, they pose a risk to the consuming public.³¹

The CGMP regulations govern all aspects of drug manufacturing[.] . . . The rationale for the CGMP regulations is that a controlled, reliable manufacturing process will result in safe and effective drug products that meet their identity, quality, purity, and potency specifications each time they are produced.³²

Accordingly, FDA relied on CGMPs as the basis for regulating potency and stability of all the Vintage products, including levothyroxine sodium tablets, whether or not they also had NDAs.

Synthroid is no exception to FDA's longstanding program for regulating potency and stability under CGMPs. It was the subject of numerous CGMP inspections and compliance reviews over the years, as recently as September, 1998,³³ and at least as long ago as the 1960s and 1970s.³⁴ Other LT4 products have a similar history and scope of inspectional oversight.

In addition to directly enforcing CGMP compliance (including compliance with compendial standards), FDA also has the ability to address specific potency and stability concerns for LT4 products by participating in the USP standard-setting process.³⁵ As the Petition has already described, this is exactly what FDA did in the early 1980s, when it worked with the USP and manufacturers to improve stability assurance by replacing the

31. Id. at 2 (citation omitted).

32. Id. at 9 (citing 21 U.S.C. § 351(a)(2)(B); Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996); United States v. Article of Drug . . . Labeled . . . "White Quadrisect", 484 F. 2d 748, 749 (7th Cir. 1973)).

33. See Section III below.

34. See, e.g., Establishment Inspection Report, Travenol Laboratories, Inc., Deerfield, IL (EI: June 2, 18, and 25, 1975) (reflecting detailed inspection of Synthroid quality assurance including product formula, manufacturing processes, and analytical testing; samples were also collected for analysis by FDA). FDA oversight of the potency and stability of Synthroid is discussed in detail in Section III, below.

35. Section 501(a)(2) provides that any drug is adulterated if it is not manufactured in conformity with current good manufacturing practice, or if it deviates from an applicable compendial standard. Id. at (b). The provision further states that, if the tests and assays provided in a compendial standard are insufficient to determine whether product strength, quality, and/or purity satisfy the standard, then FDA "shall" bring the matter to the compendial body's attention, and that the agency "shall" promulgate appropriate regulations to correct the deficiency if the compendial body does not do so within a reasonable time. Thus, the statute explicitly contemplates that issues of product potency and manufacturing quality are to be addressed by FDA under its adulteration authority and through the mechanism of USP standards where applicable.

previous compendial assay with the stability-indicating HPLC method.³⁶ FDA involvement in compendial standard-setting for LT4 tablets has continued since that time, most recently in connection with proposed amendments to dissolution testing requirements.³⁷ There is no reason why FDA could not use the same approach again in the future, if it believes that USP specifications with respect to LT4 potency and/or stability should be amended.

III. Synthroid has no "significant potency and stability problems"

Even if FDA actually had the authority to deny GRAS/E status to products that "lack stability and consistent potency," Synthroid has no such problems. Far from supporting the assertions in the Notice with respect to Synthroid, the record - including documents in FDA's own files - affirmatively demonstrates that Synthroid is consistently potent and stable, a fact that FDA has confirmed over and over in many different ways over many years, both before and after the Levothyroxine Notice was published. The record further confirms that the factual information relied on in the Notice is outdated, incomplete, and wholly unpersuasive as to Synthroid.

To begin with, FDA records of comprehensive CGMP inspections and compliance reviews conducted both before and after publication of the Notice affirmatively demonstrate that the Synthroid manufacturing process yields a consistently potent and stable product. Most recently, FDA's CGMP inspection in September, 1998 "disclosed no objectionable conditions" in any area covered, including batch records, analytical data, failure investigations, stability data, process validation, standard operating procedures, and consumer complaint investigation.³⁸ In particular:

- No problems or discrepancies were found in reviews of batch records representing at least five different strengths manufactured during the three-year period starting in 1995 - well before the Levothyroxine Notice was published - and ending in 1998.³⁹

36. See Petition at 23-25.

37. See, e.g., D.K. Bempong et al., Development of a Dissolution Method for Levothyroxine Sodium Tablets, *Pharmacoepial Forum* 25:7593-7625 (Jan.-Feb. 1999) (noting FDA review of proposed method revisions); Letter from Robert A. Rippere, Microbiologist, Compendial Operations Branch, HFD-335, FDA, to Vivian A. Gray, Scientist, The United States Pharmacopeial Convention, Inc. (Dec. 21, 1994) (relaying comments of FDA's Compendial Operations Branch on proposed revision).

38. Establishment Inspection Report, BASF Pharmaceuticals, Inc., Jayuya, PR at 1 (EI: Sept. 8 to 16, 1998).

39. Id. at 2.

- Stability data for at least 22 randomly selected lots manufactured in 1995-1998 likewise satisfied all USP and firm specifications.⁴⁰

Those inspectional findings confirm and extend Knoll's own stability record review, reported in the GRAS/E Petition, which showed that there were no failures to meet USP potency specifications for Synthroid manufactured in the 1991-1997 time period. Specifically, retained samples from 320 lots manufactured and monitored in the company's CGMP stability program from 1991 through 1997 were found to meet USP specifications, and lot release records for more than 2000 lots manufactured from January, 1993 to August, 1997 showed that all lots exceeded USP specifications at the time of release.⁴¹

Additional confirmation that Synthroid was shown to be reliably potent and stable well before the Notice was published is found in detailed records of the comprehensive voluntary program conducted by Boots in 1993-1994 to revalidate the Synthroid manufacturing process and to test and confirm the potency of retained samples of distributed batches.⁴² As detailed in the Dolch Declaration, the program was conducted using protocols developed and approved in close consultation with CDER staff, and was expressly designed to establish that Synthroid is reliably potent and stable, and to address specific potency and stability concerns noted by FDA in connection with product recalls, lot rejections, and CGMP inspections in 1989-1992 - i.e., the very same points recited in the 1997 Notice as "new" evidence of stability problems with Synthroid.⁴³ As stated in a letter from Stephanie Gray, Director of FDA's San Juan District Office, the agency viewed the firm's proposal as a "positive, voluntary corrective action" that responded fully to FDA comments and concerns, and would provide "much greater confidence in [Boots'] ability . . . to manufacture Synthroid® tablets which are both safe and effective for their intended use."⁴⁴

Implementation of the voluntary program and related aspects of Synthroid potency, stability, and CGMP compliance were closely monitored by FDA during 1993-1994 and into 1995. For example, FDA reinspected Boots' Synthroid operations at the company's

40. Id.

41. See Petition at 32. See also Dolch Declaration, supra note 20, at ¶ 12.

42. See Petition at 32 and note 103.

43. See Notice at 43,537 (noting recalls Aug., 1989 and Feb. and June, 1991; destruction of out-of-specification lots 1990-1992). As detailed in the GRAS/E Petition and the text below, neither past product recalls nor lot rejections are evidence that Synthroid is not GRAS/E. Other so-called "stability problems" noted in the same section of the Notice apply to products other than Synthroid. See Petition at 30-32 and Exhibit 25.

44. Letter from Stephanie R. Gray, District Director, San Juan District, FDA, to Gary D. Dolch, Ph.D., Vice President, Quality Assurance, Boots Pharmaceuticals, Inc. (Mar. 23, 1993).

Shreveport and Jayuya facilities during January, 1994.⁴⁵ In connection with those inspections, FDA took 33 samples which were found upon analysis to be within USP specifications.⁴⁶ Inspectors also reviewed stability data for 55 lots of Synthroid, all of which were found to be within firm specifications.⁴⁷ Interim and final results of Boots' investigations were presented to the agency in periodic meetings and reports.⁴⁸

The results of Boots' voluntary program, including a special stability study conducted at stressed conditions of 30°C through the expiration period, established three key points with respect to Synthroid:

1. Under the FDA-approved validation protocol, the company extensively evaluated all stages of the manufacturing process for consistent potency from batch to batch and between tablets within each batch, among other criteria. The resulting data confirmed that Synthroid tablets are consistently potent;⁴⁹
2. Retained samples of marketed batches were shown to be fully potent and stable through their expiration period;⁵⁰ and
3. Batches stored on stability at stressed conditions of 30°C were shown to be stable through the expiration period.⁵¹

Unaccountably, FDA appears to have ignored those results when it concluded in the Notice that "no currently marketed . . . [LT4] product has been shown to demonstrate

45. Dolch Declaration, supra note 20, at ¶ 7.

46. Id.

47. Id. A followup inspection conducted in April 1994 to investigate discrepancies in testing results between Boots' and FDA's laboratories resulted in a conclusion that Boots' method worked "just fine," and that "the only problems with the analysis are with FDA, not the firm." Id. at ¶ 8.

48. Dolch Declaration, supra note 20, at ¶ 9. In particular, Boots met with FDA on June 28, 1994 to discuss a wide range of stability and potency issues, including revalidation activities, stability data, and storage temperature issues, among others.

49. Id.

50. Id. FDA's review of Boots' data "agree[d] that the results appear to provide reasonable assurance that remaining marketed products from the 1991 production retain adequate potency and stability." Letter from Richard E. Dent, Acting Director, Compliance Branch, San Juan District Office, FDA, to Dr. Gary Dolch, Vice President, Quality Assurance, Boots Pharmaceuticals, Inc. (June 8, 1993).

51. Dolch Declaration, supra note 20, at ¶ 9.

consistent potency and stability." FDA's close involvement with the voluntary program also belies the agency's suggestion in the Notice that unless it can require NDAs, it will never know exactly what manufacturers are doing. The fact is that FDA knew and knows what is happening with Synthroid and other levothyroxine products - just as it does with other drug products it regulates - as a matter of CGMP oversight.

FDA's reliance on product recalls as evidence that "variations in product potency present actual safety and effectiveness concerns" remains equally unconvincing where Synthroid is concerned. The only Synthroid recall to occur since 1991 was classified by FDA as Class III (no adverse health effects anticipated).⁵² The reason for the recall was a potential loss of stability before expiration due to a defective packaging component, subsequently identified as the cotton packing,⁵³ which was itself recalled by its manufacturer.⁵⁴ Nothing about that recall stands as evidence that Synthroid lacks consistent potency and stability, that it is not GRAS/E, or that consumers face any risk of adverse health consequences due to potency or stability deficiencies. To the contrary, it provides still further confirmation that Knoll's and

52. Recall #D-136/139-9, BASF Pharmaceutical Company, FDA Enforcement Report 99-12 (Mar. 24, 1999). Like the earlier recalls discussed in the Notice and the GRAS/E Petition, subsequent recalls for products other than Synthroid have all been classified as Class II, i.e., potentially causing only temporary or medically reversible adverse health consequences, or having a remote probability of severe adverse health consequences. See Recall #D-277-9, Forest Pharmaceuticals, Inc., FDA Enforcement Report 99-27 (July 7, 1999); Recall #D-265/268-9, Forest Pharmaceuticals, Inc., FDA Enforcement Report 99-25 (June 23, 1999); Recall #D-192-8, Forest Pharmaceuticals, Inc., FDA Enforcement Report 98-29 (July 22, 1998); Recall #D-137-8, D-138-8, D-139-8, and D-142-8, Forest Pharmaceuticals, Inc., FDA Enforcement Report 98-20 (May 20, 1998); Recall #D-066-8, Forest Pharmaceuticals, Inc., FDA Enforcement Report 98-08 (Feb. 25, 1998); Recall #D-256/259-9, Vintage Pharmaceuticals, Inc., FDA Enforcement Report 99-24 (June 16, 1999); Recall #D-024/028-9, Vintage Pharmaceuticals, Inc., FDA Enforcement Report 98-50 (Dec. 16, 1998); Recall #D-186-7, Mova Pharmaceutical Corp., FDA Enforcement Report 97-25 (June 18, 1997); Recall #D-174/184-9, Mova Pharmaceutical Corp., FDA Enforcement Report 99-17 (Apr. 28, 1999). Note also that additional documents obtained under FOIA confirm Knoll's earlier analysis respecting the identity of the various recalled products addressed in the notice. (Exhibit 4).

53. The recall was initiated as a precautionary measure in November, 1998, when routine stability testing of 15 lots manufactured between May and October, 1998 indicated a potential loss of potency before expiration, even though the product was within USP specifications at the time of the withdrawal. Knoll's initial investigation specifically ruled out product ingredients and manufacturing processes as potential causes of the observed stability drop. See Letter from Gary D. Dolch, Ph.D., Vice President, Quality Assurance, Knoll Pharmaceutical Company, to Edward Wilkens, NJ District Office, FDA (Nov. 27, 1998).--

54. Letter from Gary D. Dolch, Ph.D., Vice President, Quality Assurance, Knoll Pharmaceutical Company, to Lewis Rosen, Recall Officer, FDA (Mar. 4, 1999) (reporting conclusions of investigation); Recall Notice from Personna Medical to Customers (Mar. 2, 1999).

FDA's manufacturing quality assurance programs for Synthroid work effectively to assure consistent LT4 potency and stability through compliance with CGMPs.

FDA's contention that adverse drug effects reports ("ADRs") reveal an "actual medical risk" to Synthroid users was thoroughly refuted in the GRAS/E Petition,⁵⁵ and is further undermined by other information in FDA records. In April 1997, only a few months before the Levothyroxine Notice was published, FDA conducted a directed inspection of Knoll's records and handling of adverse reports and quality-related complaints. As part of that inspection, FDA reviewed all Synthroid complaints for April 1997; FDA inspectors also audited related batch records for one lot at issue and found no associated deviations, investigations, or out-of-specification results.⁵⁶ Several years earlier, in August 1994, Boots Pharmaceuticals provided FDA with a detailed analysis of all adverse effects reports and product quality complaints for the period 1990-94. That analysis, which covered much the same period as FDA's analysis in the Notice (1987-94), likewise refuted any notion that increased incidence of ADRs was associated with Synthroid.⁵⁷ In sum, Synthroid ADR data do not and never did support the conclusions asserted in the Notice.

FDA's contention that serious potency and stability problems may present actual safety risks to Synthroid users is also squarely refuted by FDA's own assessments of Synthroid while carrying out its responsibilities under the Compliance Status Information System ("COMSTAT") and its predecessor program, the Government Wide Quality Assurance

55. As detailed in the Petition at 20-21, the vast majority of adverse events reported to date for Synthroid through the post-marketing surveillance system are predictable and manageable based on the known pharmacology of LT4, and result from a host of factors other than potency or stability issues, such as under- or over-titration, poor compliance, changes in disease status, and substitution of therapeutically inequivalent products.

56. Establishment Inspection Report and Annotated 483, Knoll Pharmaceutical Company, Whippany, NJ (EI: Apr. 25, 28, and 30, 1997). At the conclusion of the inspection, the inspectors noted several observations about Knoll's complaint-handling procedures. *Id.* at 4-5. A followup letter from FDA in July, 1997 said that proposed corrective measures appeared to be acceptable. Letter from Sarah A. Della Fave, Acting Compliance Officer, New Jersey District, FDA, to Jeanmarie Kline, Director, Quality Assurance, Knoll Pharmaceutical Company (July 7, 1997).

57. Dolch Declaration, *supra* note 20, at ¶ 11.

Other FDA inspections over the years have looked for - and failed to find - connections between adverse effects reports and Synthroid manufacturing. *See, e.g.*, Memorandum from Paul F. Vogel, Chief of the Drug Section for Medical Products, HFO-26, Quality Assurance Staff, FDA, to Rueobka/Chief Technical Operations Division, Directorate of Medical Materiel (Attn: Capt. Dennis G. Anderson) (Sept. 5, 1984) (complaint investigation revealed no manufacturing problem and no similar complaints); *cf.* Letter from David L. Horvitz, M.D., Ph.D., Medical Director, Flint Laboratories, to Mark Abramowicz, M.D., The Medical Letter, Inc. (Mar. 2, 1984) (followup report on 1982 Synthroid reformulation finding no associated increase in ADRs).

Program ("GWQAP").⁵⁸ Under these programs, U.S. Government purchasers of prescription drugs, including the Department of Defense, the Veterans Administration, and the Public Health Service, rely on FDA to assure that the drugs supplied to these agencies meet government-wide quality standards.⁵⁹ These quality standards are essentially a question of compliance with FDA's Current Good Manufacturing Practices. The Memorandum of Understanding ("MOU") between FDA and the Department of Defense, for example, provides that FDA's "Good Manufacturing Practice Regulations will be the quality standard applied to industry for the manufacturing, processing, packaging or holding of [drugs] acquired on government contracts," and adds that "quality standards prescribed by the United States Pharmacopeia (USP) . . . and FDA will satisfy the DoD quality requirements" in most circumstances.⁶⁰ FDA's agreements with the Veterans Administration and the Public Health Service also make FDA's CGMPs the measure of quality.⁶¹ As is the case with CGMPs generally, stability and potency are important aspects of CGMPs when FDA is carrying out its quality assurance functions for government purchasers of levothyroxine.⁶² Thus, if FDA signs off on/interposes no objection to a government contract for a drug manufacturer, it is saying that the drug manufacturer is in compliance with CGMPs.

In carrying out its responsibilities under the COMSTAT program, FDA maintains "profiles" which state whether a particular site is "acceptable" (i.e., satisfactory from a

58. See generally FDA COMSTAT Guidance - Field and Centers (hereinafter "COMSTAT Guidance"); FDA Government-Wide Quality Assurance Program Manual (1982).

59. Memorandum of Understanding Between the Food and Drug Administration and the Department of Defense, FDA-225-97-4000, 62 Fed. Reg. 43,170 (Aug. 12, 1997) (hereinafter "DoD MOU"); Interagency Agreement Between the Veterans Administration and the Food and Drug Administration, FDA Compliance Policy Guides, Guide 7155h.01 (1980) (hereinafter "VA Agreement"); Memorandum of Understanding Between the Health Services Administration and the U.S. Department of Health, Education and Welfare (Food and Drug Administration), FDA Compliance Policy Guides, Guide 7155e.01 (1980) (It is our understanding that the Public Health Service's ("PHS") Health Resources and Services Administration succeeded the Health Services Administration in carrying out HSA's responsibilities under this MOU. Accordingly, we refer to this MOU as the "PHS/HSA MOU.")

60. DoD MOU, supra note 59, at ¶ IV.C and ¶ IV.E.

61. VA Agreement, supra note 59, at ¶ III.B; PHS/HSA MOU, supra note 59, at ¶ III.B; see also Declaration of Barbara A. Missaggia at ¶ 6 (hereinafter "Missaggia Declaration") (attached as Exhibit 5).

62. See, e.g., Letter from Paul B. Donnelly, Medical Products Quality Assurance Staff, HFC-121, FDA, to Ernest L. Kelly, Director of Quality Control (U.S. Operations), Rorer Pharmaceutical Corp. (Mar. 29, 1989); Letter from Paul B. Donnelly, Medical Products Quality Assurance Staff, HFC-121, FDA, to William S. Hitchings, V.P. for Scientific Affairs, Rorer Pharmaceutical Corp. (July 17, 1989).

CGMP standpoint) or unacceptable.⁶³ Profiles for Knoll's Jayuya location, where Synthroid is manufactured, show that its status was acceptable in 1988-1991, 1994, and 1998.⁶⁴ (Missing years are a reflection of FDA's failure to provide profiles for those years or state that they do not exist in response to Knoll's FOIA request. Except as noted herein, Knoll has no reason to believe that its profile was "unacceptable" at any time.⁶⁵)

Another way of looking at this issue is to review sales of Synthroid to the government, sales which would not have been made had FDA objected on GMP or other quality grounds. Pursuant to contract, Knoll supplied literally millions of Synthroid tablets to the U. S. Government during the three-year period immediately preceding publication of the Notice and has done so for two years (and counting) since then. Its contracts to continue to do so are still in effect.⁶⁶

For example, Knoll currently supplies substantial quantities of Synthroid to the Veterans Administration under a contract that was originally signed in 1991 and was renewed in March, 1998, well after the Notice was published.⁶⁷ Knoll also currently has a contract to supply Synthroid to the Public Health Service, and has done so for several years.⁶⁸ Yet

63. See COMSTAT Guidance, *supra* note 58, at Chapter 15. COMSTAT/GWQAP profiles apply to manufacturing sites and general product classes (for Synthroid, "compressed tablets" or "TCM") rather than to individual drugs; specific problems with particular drugs appear as "comments" on the profile sheet.

64. See Exhibit 6 (profiles).

65. Boots' rating was "unacceptable" in 1992, but that rating had returned to "acceptable" by 1994, after Boots conducted the voluntary revalidation and stability review programs described above at 12-13. See *supra* note 64.

Contract acceptance for Synthroid also appears to have been briefly suspended, then restored, in the early 1980's after it became apparent that the iodometric assay then specified by the USP monograph was not stability-indicating. As detailed in the GRAS/E Petition, then-manufacturer Travenol played a leading role in developing the now-standard HPLC assay to address that problem, and Synthroid was reformulated (with FDA's full knowledge and approval) to permit the use of the new assay. See Petition at 23-28. Accordingly, FDA's quality review staff concluded that denial of contract acceptance was not justified in light of the company's reformulation program. See Memorandum from Joel S. Davis, Division of Drug Product Quality, HFD-334, FDA, to Medical Product Quality Assurance Staff, HFO-26, FDA (Feb. 1, 1982).

66. Missaggia Declaration, *supra* note 61, at ¶ 3.

67. *Id.* at ¶¶ 4, 5, 6, and 7.

68. *Id.* at ¶¶ 8 and 9.

another current contract for Synthroid, this one with the Department of Defense, was renewed within a year after the Notice was published; at that time, it had been in effect for five years.⁶⁹

It seems unlikely that FDA would permit such contracts to continue if it had any real evidence of potency and stability problems with Synthroid. FDA's approval of past, current, and on-going federal contracts for Synthroid amounts to the agency's ratification of the quality of Synthroid as assessed under CGMPs, in direct contradiction of its assertions in the Notice.

Finally, FDA's conclusions are further undermined by assay results from periodic FDA market surveys showing that Synthroid is reliably potent and stable. For example, a 1995 internal memorandum noted that 30 samples analyzed by FDA's Seattle laboratory met compendial limits for assay, identification, uniformity of dosage units, and dissolution.⁷⁰ FDA staff also reviewed Synthroid potency data in 1993 as part of an industry-wide summary of GMP-related potency and stability issues for LT4 products, and concluded that "[r]ecent [Synthroid] sample collections do not reveal potency problems."⁷¹ An earlier survey including over 1200 individual tablets from 42 separate batches of Synthroid performed by FDA's St. Louis laboratory in 1988 found no individual tablets outside the USP-allowed first stage acceptable range of 85-115, and the average content of all batches was within the 90-110 potency specification.⁷² Those data further supplement the evidence presented in the GRAS/E petition to show that any potency or stability concerns associated with earlier product formulations and assay methods had long been resolved by the time the Levothyroxine Notice was published. Indeed, FDA criticized Boots in 1990 for promotional statements suggesting that competing products were subpotent based on earlier literature studies, which FDA believed might "scare the profession into falsely believing that 5+ year old data . . . represents

69. *Id.* at ¶¶ 10, 11, and 12.

70. Electronic Mail Message from Andrea Schaub, HFD-333, FDA, to Kathy Miracco and Ralph Schmid, FDA (Feb. 23, 1995), citing results of Survey 94-33; FDA inspection records indicate that the cited survey covered Synthroid. Dolch Declaration, *supra* note 20, at ¶ 7.

71. Memorandum from LuAnn M. Summy, HFD-325, FDA, to Chief, Generic Drugs Compliance Branch, HFD-325, FDA, and Consumer Safety Officer, Generic Drugs Compliance Branch, HFD-325, FDA; the document is not dated, but internal references indicate it was written after Dec. 1993. (Although this document contemplated additional levothyroxine sodium surveys in future years, no more recent survey data appear in FDA's FOIA response.)

72. Division of Drug Analysis, FDA, Final Report - Study 833 - Thyroxine (Aug. 22, 1988).

the true state of thyroxine production today."⁷³ The same criticism applies equally to FDA's current effort to present Synthroid as a health risk based on so-called "new information."

In sum, numerous sources consistently show that Synthroid is and has been consistently potent and stable. Knoll is required to and does check Synthroid's potency and stability, and Synthroid has met potency and stability standards for years. When FDA checked during its most recent inspection, it specifically agreed that the 22 lots it checked were stable. FDA is also responsible for assuring the Veterans Administration, the Department of Defense, and the Public Health Service that drugs those agencies purchase meet government quality standards, including the stability and potency requirement imposed by FDA's good manufacturing practices regulations. Knoll has been and is supplying Synthroid to all three agencies, contracts it could not fill without FDA's agreement that the product is stable and potent. Finally, FDA's own laboratories have checked on Synthroid, and found it both potent and stable. The Notice's naked assertion that some levothyroxine products may not be potent or stable cannot stand against this raft of proof that Synthroid is potent and stable - and that FDA knows that Synthroid is potent and stable. The contention that Synthroid is not stable and potent is clearly arbitrary and capricious in light of the overwhelming evidence to the contrary, and the agency's failure to collect and consider pertinent data from its own files is likewise arbitrary and capricious.

Conclusion

There can be no doubt that Synthroid is generally recognized by thyroid experts as safe and effective for the treatment of hypothyroidism and thyroid cancer, based on substantial evidence in the scientific literature and more than forty years of use by many millions of patients. FDA's contention that Synthroid is a new drug based on purported manufacturing defects misstates the agency's authority over "new drugs" while ignoring FDA's real and proven ability to control the manufacturing of GRAS/E old drugs as a matter of CGMPs. Furthermore, there is overwhelming evidence, much of it in FDA's own files, that Synthroid is

73. Letter from William V. Purvis, Division of Drug Advertising and Labeling, Office of Drug Standards, FDA, to Kenneth F. King, Ph.D., Director, Regulatory Affairs, Boots Pharmaceuticals, Inc. (Oct. 16, 1990). FDA also criticized another manufacturer for "overtly promotional and wholly unsupported" statements based on promotional use of a published study stating that "scrupulous attention to quality control during the manufacturing process . . . contributed to assurance of homogeneity . . . and close adherence (+/- five percent) to the claimed potency." Letter from David Banks, Division of Drug Advertising and Labeling, FDA, to Bernard B. Wolfson, Ph.D., President, Daniels Pharmaceuticals, Inc. (May 18, 1989); Letter from David Banks, Division of Drug Advertising and Labeling, to Robert H. Becker, Kleinfeld, Kaplan & Becker (June 7, 1989) (discussing Stephen H. Curry et al., *Levothyroxine Sodium Tablets: Chemical Equivalence and Bioequivalence*, *Drug Intelligence and Clinical Pharmacy* 22:589-591 (July/Aug. 1988)). See also Letter from Jess H. Stribling, King & Spalding, to Dr. Solomon Sobel, Director, Division of Metabolism and Endocrine Drug Products, FDA, and Jennie C. Butler, Director, Dockets Management Branch, FDA (Docket No. 97N-0314) (Oct. 6, 1999) (correcting earlier assertion on behalf of Jones Medical Industries, Inc. that a competitor's generic LT4 tablets appeared not to maintain stability through expiration).

Indeed reliably potent and stable. For all these reasons, the Commissioner should issue the order requested in the GRAS/E petition.

Environmental Impact

Petitioner claims a categorical exclusion from the requirement of an environmental impact assessment under 21 C.F.R. § 25.30(a) and, by analogy, § 25.31(a).

Certification

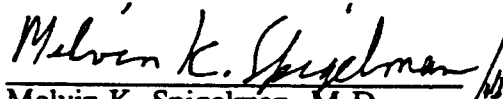
The undersigned certify that, to the best knowledge and belief of the undersigned, this petition supplement includes all information and views upon which the supplement relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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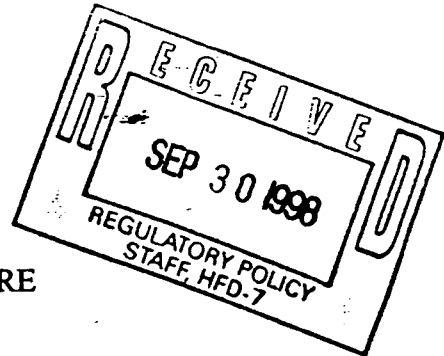
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CITIZEN PETITION
SCHEDULING AND PROCEDURE

Docket No. 97N-0314

Knoll Pharmaceutical Company ("Knoll" or "the Company") submits this Citizen Petition under sections 201 and 505 of the Food, Drug, and Cosmetic Act ("FDCA" or "the Act") to request the Commissioner of Food and Drugs ("the Commissioner") to resolve certain scheduling and procedural issues in connection with the Food and Drug Administration's ("FDA" or "the Agency") August 14, 1997 Federal Register notice entitled "Prescription Drug Products; Levothyroxine Sodium," 62 Fed. Reg. 43,535 ("the Notice"). The Notice announced FDA's tentative view that orally administered levothyroxine sodium drug products are new drugs under the Act, and declared that it will be unlawful to market such products on or after August 14, 2000 without an approved new drug application ("NDA").¹ At the same time, recognizing that no NDA is required for a product that is not subject to the Act's new drug provisions, the agency invited any manufacturer to submit a Citizen Petition demonstrating that its product is not a new drug. Knoll submitted such a petition, which asserts that Synthroid® brand levothyroxine sodium USP ("Synthroid") is generally recognized as safe and effective ("GRAS/E") and therefore is not a new drug (the "GRAS/E Petition").² Knoll now submits this petition to address certain scheduling and procedural issues in connection with FDA's review of Knoll's GRAS/E petition and any applications submitted under the Notice.

1. Notice at 43,538.

2. The GRAS/E petition was submitted in two segments: one filed on December 15, 1997 which addressed the product's indication for primary hypothyroidism (97N-0314/CP2), and a supplement filed on May 29, 1998 which addressed the indication for treatment of thyroid cancer (97N-0314/SUP1). The December 15, 1997 petition was submitted on the date agreed to by FDA, see Petition note 3. Knoll reserved in that petition the right to supplement it as to other indications, id. note 2, and FDA was aware that the supplement would be submitted at the time it was. Additionally, both Knoll and FDA contemplate that Knoll will file at least one additional supplement following receipt and review of FDA's complete response to outstanding document requests under the Freedom of Information Act. See discussion infra at 3-4.

Background

With respect to scheduling, FDA's 1997 Notice stated only that NDAs (if required) must be approved by August 14, 2000 in order for products to remain on the market after that date. While the Notice did not specify a date by which NDAs must be submitted to be assured of receiving timely review and, if warranted, approval, Knoll believes it is reasonable to assume that in general NDA review takes approximately one year.³ As a practical matter, therefore, an NDA would have to be submitted by August, 1999 in order to meet the specified approval deadline. But, the Notice did not provide a means for integrating the timing of a decision on the Citizen Petition it invited with the timing of an NDA should one be required.⁴ Specifically, it did not build in time for a review and decision on any Citizen Petition as solicited by the Notice in advance of the August, 1999 target date for NDA submissions.⁵ So Knoll is now confronted with the distinct possibility that in order to ensure continued marketing after August 14, 2000, it must submit an NDA before FDA (and perhaps the courts) have ruled on its GRAS/E Petition, even though no NDA may ultimately be required. For the reasons detailed below, such an outcome would be neither fair nor lawful.

The timing problem already inherent in the Notice has been seriously compounded by FDA's failure to provide a timely complete response to the Freedom of Information Act ("FOIA") request which Knoll submitted on September 12, 1997.⁶ In correspondence and discussions with FDA staff beginning shortly thereafter, counsel for Knoll emphasized that the requested documents would be used in preparing Knoll's GRAS/E Petition, and were assured that the company would be given sufficient time to supplement its Citizen Petition after FDA provided a complete response. Knoll believes that FDA does intend to allow it such time, but is becoming increasingly concerned that not enough time has been provided in the overall scheme for FDA to complete its FOIA response, allow Knoll time to review the documents

3. This estimate reflects FDA's commitments under recent amendments to the Act. Letter from Donna E. Shalala, Secretary of Health and Human Services, to Hon. James M. Jeffords, Committee on Labor and Human Resources, United States Senate (Nov. 12, 1997).

4. Any statements in this petition about the necessity or procedure for future NDA/ANDA submissions do not constitute agreement by Knoll that it is required to submit any such application for Synthroid. To the contrary, Knoll reasserts its contention that Synthroid is generally recognized as safe and effective and therefore not a new drug.

5. The Notice says the agency will respond to Citizen Petitions within 180 days of receipt of the petition as required by § 10.30 (e)(2) of its regulations, Notice at 43,538, but as FDA well knows, that regulation allows the 180 day response to indicate that the agency has not been able to reach a decision. Thus a "response" need not be - and often is not - dispositive.

6. Letter from Nancy L. Buc and Edward J. Parr, Jr. to Ms. Betty Dorsey, Director, Freedom of Information Staff (September 12, 1997) [hereinafter FOIA Request Cover Letter], attaching Letter from Nancy L. Buc and Edward J. Parr, Jr. to Freedom of Information Staff (Sept. 12, 1997) (FOI No. 97-031022) [hereinafter FOIA Request].

and submit a supplement, and then give the supplemented Citizen Petition full and fair consideration - all before Knoll must submit its NDA, if necessary, and still have time for FDA to review and approve it before August 14, 2000.

Knoll and presumably other manufacturers as well have recently learned of a serious additional issue, one that clearly will affect the content and timing of any application submitted in response to the Notice. That issue is the possibility that FDA may be planning to use some new drug approval procedure other than the one specified in the Notice. The Notice specifically requires applicants who wish to market affected products after August, 2000 to submit New Drug Applications. The Notice makes no reference to Abbreviated New Drug Applications ("ANDAs"). However, subsequent communications have indicated that FDA may intend to review and approve only one application as an NDA, while requiring other applications to be submitted and/or reviewed and approved as ANDAs.⁷ As discussed below, any such departure from FDA's announced procedure would unfairly and unlawfully compound the scheduling problem Knoll already faces, for it would have significant consequences in terms of Knoll's (and indeed other companies') ability to know what kind of application (NDA or ANDA) will be needed and what kinds of supporting studies it therefore will or will not have to conduct. Moreover, any departure from the announced procedure could place Knoll at a further practical disadvantage by effectively forcing the company to choose between waiving either its right to obtain a final ruling on its GRAS/E petition before seeking any new drug approval, or its right to submit an NDA and not an ANDA if Synthroid is found to be a new drug.

The scheduling issues and the procedural issue are intertwined from the legal and practical standpoints. In addition to the scheduling issues, all manufacturers of levothyroxine sodium - including Knoll - have a right to know exactly what procedure will be used. If the procedure is not what the Notice has led them to expect, they will need time to respond.

A. ACTION REQUESTED

Knoll asks the Commissioner to resolve the concerns outlined above. As to scheduling matters, Knoll asks the Commissioner to modify the schedule contemplated by the Notice to provide enough time for Knoll to supplement its GRAS/E Petition after FDA has provided a complete FOIA response; enough time for FDA to give Knoll's GRAS/E Petition full and fair consideration; enough time for judicial review of FDA's GRAS/E determination, if necessary; and enough time for all manufacturers, including Knoll, to conduct or locate and include in

7. Specifically, the Notice docket contains a letter from Jones Medical Industries ("JMI") to FDA, stating JMI's understanding that FDA does not plan to accept NDAs for additional levothyroxine sodium products after the first NDA has been approved. Letter from Jess H. Stribling to Dr. Solomon Sobel, Director, Division of Metabolic & Endocrine Drug Products (May 18, 1998) at 2 ("JMI understands that CDER will refuse to accept § 505(b)(2) applications after approval of the first § 505(b)(2) application. As a result of this policy, manufacturers of levothyroxine are in a race[.]") (emphasis in original). An FDA staff member also has advised Knoll's counsel that the agency would approve only one NDA and would then convert any pending NDAs into ANDAs.

their applications whatever studies are needed. As to procedural matters, Knoll asks FDA to confirm that it will use the Notice procedure and no other.

To these ends, Knoll asks the Commissioner to:

1. Modify the schedule set forth in the Notice so that, instead of stating a date by which NDAs must be approved, the Notice specifies a date by which NDAs must be received by the agency. Further, Knoll requests that FDA set the date by which NDAs must be received so that it is:
 - A. At least 6 months after FDA rules on Knoll's GRAS/E Petition and the courts (if their jurisdiction is invoked) have completed their review of FDA's decision; and
 - B. At least 6 months after FDA rules on the request in this Citizen Petition with respect to the procedure it will use pursuant to the Notice (see Action Requested 3, infra).
2. Confirm that FDA will allow Knoll at least 60 days to submit a supplement to its GRAS/E Petition after Knoll has received a complete response to its September 12, 1997 Freedom of Information request.
3. Declare that the procedure set forth in the Notice is the procedure FDA will follow, viz., that any and all applications for levothyroxine sodium products submitted pursuant to the Notice must be NDAs and will be reviewed and, if warranted, approved as NDAs; and declare that FDA will not follow any other procedure such as approving only one or a few NDAs and treating other submissions as ANDAs.

B. STATEMENT OF GROUNDS

1. Scheduling

Under the FDCA, an NDA is required only for a new drug. Thus, if Synthroid is not a new drug, no NDA (or ANDA) can be required. This critical threshold question remains to be determined, as the Notice itself makes plain. Although FDA purported to announce that all levothyroxine products are new drugs, it also invited Citizen Petitions demonstrating that particular products are not new drugs. That invitation - which Knoll accepted - was the

beginning of a process not yet complete. Until the process is completed, there is no final decision as to the new drug status of Synthroid, and until then, Synthroid is not a new drug.⁸

For these reasons, a final decision (and, if need be, judicial review) on Knoll's GRAS/E Petition must precede the requirement that an NDA be submitted for Synthroid. Putting the NDA process and the Citizen Petition process onto parallel rather than sequential tracks, as the Notice does, would effectively force Knoll to submit an NDA for Synthroid by approximately August 1999, even if Synthroid has not been determined by that time to be a new drug and may never be determined to be a new drug. This FDA cannot do.

Knoll also is concerned that if it is forced as a practical matter to submit an NDA while FDA is still considering its GRAS/E petition, FDA will be sorely tempted to give the GRAS/E petition shorter shrift than it would otherwise receive. Knoll believes it is entitled to full and fair consideration of its GRAS/E petition free of the gravitational pull that may be exerted by an NDA, assuming, as seems evident, that FDA does want an NDA rather than GRAS/E status for Synthroid. Technically, an NDA submitted for Synthroid would not be part of the GRAS/E petition, and FDA would have no right to consider the NDA as part of its GRAS/E deliberations. At the same time, if the same staff are conducting both reviews, it would not be surprising for one review process to influence the other in ways that are only human but outside Knoll's ability ever to know or challenge.

FDA's slowness in providing a complete response to Knoll's FOIA request, although it has had more than a year to do so, has further compounded the timing problems inherent in the Notice by delaying Knoll's ability to muster all available evidence in support of its GRAS/E petition. Knoll submitted its FOIA request on September 12, 1997, less than 30 days after publication of the Notice.⁹ The FOIA request stated that "[t]his request is time sensitive, as the documents are relevant to the FDA's [Notice]." To facilitate a prompt response, the request was as specific as possible, and included extensive information to help FDA staff

8. See, e.g., Rutherford v. United States, 542 F. 2d 1137, 1143 (10th Cir. 1976):

We are unable, however, to see how the FDA can escape the obligation of producing an administrative record to support its determination of the first and more fundamental issue that [a drug product] is a new drug, for it is not a new drug merely because they say it is. Moreover, such a conclusory ruling precludes effective review under 5 U.S.C. Section 706(2).

9. FOIA Request, supra note 6.

identify and locate responsive documents.¹⁰ Knoll also has provided ongoing updates to the agency as to the adequacy of FDA's response, and has continued to press, via letters and telephone calls, for a full answer.¹¹ In these phone calls, FDA staff has acknowledged that Knoll should and will have an opportunity to supplement its Citizen Petition with pertinent information from FDA's complete response (when it arrives).¹²

Knoll has welcomed that acknowledgment, but has grown concerned that the timing currently contemplated by the Notice may render it illusory. The longer it takes for FDA to provide a full response to Knoll's FOIA request, the longer Knoll will be delayed in assembling all the available evidence to support its GRAS/E petition, and the less time will be available for FDA to make a GRAS/E determination and then review an NDA (should one be required) by August, 2000. If Knoll is effectively forced to submit an NDA before it can fully supplement its GRAS/E petition using the materials included in a complete FOIA response, the timing problem would be even more unfair, for Knoll's NDA would be there, full and complete and available for review, while the GRAS/E petition would not. FDA might well decide to go ahead and review the NDA, and if that process were well under way - or, worse,

10. FOIA Request Cover Letter, supra note 6; FOIA Request at 8. This included copies of numerous documents used by Knoll to identify additional relevant documents, and a list of offices within the agency where counsel for Knoll expected responsive documents would likely be located. Id. at 7-8. In addition to sending the request to FDA's central FOIA office, as required by FDA's regulations, copies also were sent to the FOIA officer in the Center primarily responsible for Synthroid as well as to FDA staff known to be working on aspects of the Notice. FOIA Request Cover Letter, supra note 6.

11. See Letter from Edward J. Parr, Jr. to Carolann W. Hooton, Director, Freedom of Information Staff (Oct. 21, 1997); Letter from Edward J. Parr, Jr., to Freedom of Information Staff (Oct. 27, 1997); Letter from Edward J. Parr, Jr., to Freedom of Information Staff (Oct. 31, 1997); Letter from Nancy L. Buc and Edward J. Parr, Jr., to Carolann W. Hooton (Nov. 3, 1997); Letter from Nancy L. Buc and Jane E. Baluss, to Carolann W. Hooton (February 10, 1998); Letter from Nancy L. Buc, to Carolann W. Hooton (April 14, 1998); Letter from Nancy L. Buc and Jane E. Baluss, to Carolann W. Hooton (May 12, 1998); Letter from Nancy L. Buc, to Carolann W. Hooton (June 12, 1998).

12. To give just one example of documents Knoll is eagerly awaiting, it has not yet received documents related to FDA's Government Wide Quality Assurance Program. Under that program, FDA conducts product quality evaluations on drugs and devices purchased on contract by various other federal agencies. See, Federal Cooperative Agreements Manual, FDA, Office of Regulatory Affairs, Office of Enforcement, Division of Compliance Policy, at 6 (August 1, 1996); 1996 FDA Investigations Operations Manual, section 512.3; FDA Compliance Policy Guides, 100.700 (September 1, 1987). If FDA has regularly issued favorable quality evaluations of Synthroid (and perhaps other oral levothyroxine products as well), that would contradict FDA's assertion in the Notice that stability and potency problems with the products are either serious or new.

virtually complete - by the time the GRAS/E petition were ready for review, it is hard to imagine FDA would still be willing and able to open its mind to the possibility that the NDA review had been unnecessary because Synthroid is not a new drug.

In light of these factors, Knoll believes it is both legally necessary and only fair to revise the schedule contemplated by the Notice so that, rather than specifying an end date by which NDAs must be approved, it specifies sequential milestones. Specifically, the Notice should be revised to state that FDA will not begin its review of Knoll's GRAS/E Petition until the company has had sixty days from the completion of FDA's FOIA production to submit its supplement, and that Knoll's NDA will not be due until six months after the date on which FDA (and the courts, if their jurisdiction is invoked) has ruled on Knoll's Citizen Petition.¹³ Additionally, in order to reduce uncertainty and confusion and put Knoll and other manufacturers on a level playing field, the revised Notice should state that no NDAs (or other applications) will be due until six months after FDA has confirmed that it intends to follow the procedure specified in the Notice, or whatever other procedure it intends to utilize, as discussed below.

2. Procedure

The Notice plainly stated that FDA is seeking New Drug Applications (NDAs): that term is used throughout the Notice, and the term Abbreviated New Drug Application or ANDA is nowhere mentioned. FDA presumably chose its words by reference to the FDCA and FDA's regulations, both of which clearly distinguish between the two.¹⁴ Also, the Notice calls for the submission of bioavailability data, a standard requirement for NDAs, and not for bioequivalence data, which is required for ANDAs.¹⁵ Yet despite the clarity of the Notice

13. Knoll has no objection to applying the same due date for NDA submissions to all manufacturers. This may be particularly desirable because, if FDA agrees with Knoll that GRAS/E status for levothyroxine products is independent of manufacturing issues, see GRAS/E petition at 13-20, it could well conclude that all levothyroxine products are GRAS/E and that NDAs are therefore not required for any of them.

14. Section 505(a) of the Act provides that a new drug may not be introduced or delivered for introduction into interstate commerce unless it is the subject of an approved application under either subsection (b) (i.e., an NDA) or subsection (j) (i.e., an ANDA). The fundamental distinction between the two types of applications is further reflected and elaborated in FDA's new drug approval regulations. See, e.g., 21 C.F.R., § 314.3(b) (separately defining "application" and "abbreviated application"); and compare id. §§ 314.50 (content and format of NDA) and 314.94 (content and format of ANDA).

15. Compare 21 C.F.R. § 320.21(a) (NDA applicant must submit bioavailability data or request for bioavailability waiver) with § 320.21(b) (ANDA applicant must submit bioequivalence data or a request for bioequivalence waiver).

itself, there are ominous hints that FDA may be planning not to follow the procedure stated in the Notice.¹⁶

Having specified the procedure it intends to use, an agency must adhere to it.¹⁷ There can be no doubt what FDA said in the Notice, nor what its words mean in light of the statutory scheme and the agency's own regulations. Thus, it must do what it said it would.

By using some combination of NDAs and ANDAs instead of all NDAs as specified in the Notice, FDA in effect would be doing indirectly what it cannot lawfully do directly. First, section 505(b)(2) and section 505(b)(1) of the Act both provide that "any person" may submit an NDA, and go on to say that FDA "shall approve" it if the applicable conditions are met. Nothing in the statute limits the right of "any person" to submit an NDA should it choose to do so in preference to an ANDA,¹⁸ and FDA cannot limit that right, either directly or indirectly.

Second, having decided that all levothyroxine sodium products are new drugs, FDA would not have been free to pick/compel just one of them to submit an NDA while leaving the others on the market until the NDA was approved and listed in FDA's "Approved Drug Products with Therapeutic Evaluations" ("the Orange Book"), and only then requiring ANDAs of the others.¹⁹ Neither can FDA accomplish that goal by indirection.

Third, the FDCA and FDA's implementing regulations plainly permit the submission and receipt of an ANDA only when there is a reference drug in the Orange Book prior to submission and receipt.²⁰ Until one NDA is approved and listed for levothyroxine sodium, therefore, no applicant can submit and FDA cannot receive any ANDAs for a drug containing

16. See supra note 7.

17. See, e.g., Vitarelli v. Seaton, 359 U.S. 535, 547 (1959); Service v. Dulles, 354 U.S. 363, 372 (1957); Accardi v. Shaughnessy, 347 U.S. 260, 267 (1954); Denny Klepper Oil Company v. United States Department of Energy, 598 F. Supp. 522, 528 (D.D.C. 1984).

18. Section 314.101(d)(9) of FDA's regulations purports to give FDA the discretion to refuse to file an NDA submitted under § 505(b)(2) of the act (the type of application contemplated in the Notice) for a drug "that is a duplicate of a listed drug and is eligible for approval [as an ANDA] under section 505(j) of the act." For the reasons stated in the text, Knoll believes this provision cannot be invoked against an applicant that does not want its NDA converted to an ANDA. In any case, that regulation is inapplicable here, for there is no listed (i.e., NDA-approved) orally administered levothyroxine sodium product.

19. Hoffmann-LaRoche v. Weinberger, 425 F. Supp. 890 (D.D.C. 1975); see also Cutler v. Kennedy, 475 F. Supp. 838 (D.D.C. 1979).

20. FDCA § 505(j)(2)(i); 21 C.F.R. §§ 314.92 and 314.94(a)(3).

that active ingredient. Modifying the Notice procedure to convert an NDA into an ANDA which could not lawfully have been submitted or received as an ANDA is impermissible.

Equally important, there is no workload advantage to FDA in departing from the Notice procedure. The Notice itself announces that levothyroxine sodium is safe and effective, and says the agency "is prepared to accept" applications under 505(b)(2). FDA's willingness to accept 505(b)(2) applications suggests the agency's awareness of a core set of studies applicable to all levothyroxine sodium products. Thus, the agency may well be able to make one decision applicable to all applicants based on these studies - that the products are safe and effective. Likewise, the review of chemistry, manufacturing and controls information to decide whether the applicant has met the good manufacturing practices requirement of the statute and regulations is the same whether the application is an NDA or an ANDA. By contrast, deciding also whether a particular product has been shown to be bioequivalent to another, as must be shown for an ANDA under § 505(j) of the Act, will require more work, not less, on FDA's part.²¹ Indeed, proceeding directly to ANDAs for most products makes even less sense in light of the fact that FDA's announced reason for requiring NDAs for levothyroxine sodium products in the first place was specifically to address concerns about product manufacturing quality.²²

Departing from the Notice procedure by converting one or more NDAs into ANDAs also is likely to create considerable confusion and uncertainty. In the usual situation in which an approved NDA is followed by one or more ANDAs, all parties know in advance whether their application is going to be an NDA or an ANDA, and therefore know what studies to conduct and submit in their applications. But if FDA departs from the procedure announced in the Notice, a manufacturer will not know in advance whether its application will be reviewed as an NDA or an ANDA, and so will not know whether to submit studies demonstrating safety, efficacy, and bioavailability, as required for an NDA, or a study demonstrating

21. Although bioequivalence issues are beyond the scope of the Notice and this Citizen Petition, Knoll notes that they are sufficiently difficult that FDA is unlikely to be able to conduct routine bioequivalence reviews of any ANDAs for levothyroxine products, whether they are submitted pursuant to the Notice or thereafter. Allowing ANDAs rather than NDAs may therefore significantly increase rather than reduce FDA's workload and review time with respect to levothyroxine products.

22. Not only would the review period be shorter for NDAs, but it would seem logical to address bioequivalence issues only after FDA has reviewed bioavailability and manufacturing data for all products and satisfied itself that any manufacturing concerns have been appropriately addressed.

Knoll's disagreement with FDA's position on the prevalence and legal significance of manufacturing quality problems with levothyroxine sodium drug products in general and Synthroid in particular is discussed at length in Knoll's December 15, 1997 GRAS/E Petition. Knoll continues to contend that FDA's conclusions in the Notice are both legally unsupported and factually wrong as to Synthroid.

bioequivalence to another drug, as required for an ANDA. Moreover, no one, not even FDA, will necessarily know in advance which manufacturer's product will be the NDA, which the ANDAs. Thus, a manufacturer which is willing to submit an ANDA rather than an NDA will not know which product is the reference product, and cannot know, therefore, to which product its product must be shown to be bioequivalent.

3. Conclusion

Knoll has worked diligently over the past year to provide FDA with evidence that Synthroid is GRAS/E, as invited in the Notice. The Company stands prepared to further supplement its GRAS/E Petition with additional pertinent materials from FDA's FOIA response, when it is completed. The requested actions will ensure that Knoll's efforts will receive the full and fair consideration they deserve, while also ensuring fair and orderly review of any other submissions required by the Notice. Accordingly, Knoll requests the Commissioner to take the actions requested in this Petition.

C. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from the requirement of an environmental impact assessment under 21 C.F.R. § 23.30(a) and by analogy to §§ 25.30(h) and 25.31(a). To Petitioner's knowledge, no extraordinary circumstances exist which would indicate that the requested action may significantly affect the human environment.