JONES

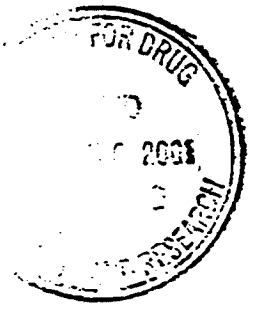
DUPLICATE

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
www.jmedpharma.com

January 29, 2001

BB
ORIG AMENDMENT

VIA FEDERAL EXPRESS



John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Amendment to NDA 21-301
Levoxyl (Levothyroxine Sodium Tablets, USP)

Dear Dr. Jenkins:

JONES PHARMA INCORPORATED is hereby submitting an amendment to our pending New Drug Application (NDA) for Levoxyl (Levothyroxine Sodium Tablets, USP) submitted July 28, 2000. The following information submitted in this amendment was requested by Dr. Steve Johnson, FDA Biopharmaceutic Reviewer, as a result of a teleconference held between FDA and Jones on 1/23/2001.

Average dissolution results at 45 minutes from one lot of each strength were submitted in Section 6.3 of the original NDA. Dr. Johnson requested that Jones provide the 45-minute dissolution data from the individual vessels for the following Levoxyl lots in support of the final averages previously reported. These data are provided as Attachment 1.

Lot Number	Strength	Lot Number	Strength	Lot Number	Strength
TT57	25 mcg	TT25	100 mcg	TT45	150 mcg
TT24	50 mcg	TT36	112 mcg	TT48	175 mcg
TT31	75 mcg	TT39	125 mcg	TT51	200 mcg
TT33	88 mcg	TT43	137 mcg	TT26	300 mcg

Amendment to NDA 21-301
Levoxyl (Levothyroxine Sodium Tablets, USP)

This application consists of a single volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. Additionally desk copies are being sent to Mr. Steve McCort (Project Manager, FDA) and Dr. Steve Johnson (FDA Biopharmaceutic Reviewer).

By this letter, it is certified that a true copy of the application (including a copy of FDA application form 356h and a certification that the contents are a true copy of the application filed with the Center for Drug Evaluation and Research) was sent to the Kansas City District office of the FDA. This "field copy" was contained in a burgundy folder.

We look forward to the approval of this NDA. Should any additional information be required, please do not hesitate to contact me at (314) 576-6100 ext. 3070.

Sincerely,

JONES PHARMA INCORPORATED
(A wholly owned subsidiary of King Pharmaceuticals, Inc.)

Nancy Cafmeyer

Nancy Cafmeyer
Director, Regulatory Affairs

Enclosure

/S/
1-29-01
BC

APPEARS THIS WAY
ON ORIGINAL

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
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December 14, 2000

DUPLICATE

Amendment to NDA 21-301
Levoxyl (Levothyroxine Sodium Tablets, USP)

John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Amendment to NDA 21-301
Levoxyl (Levothyroxine Sodium Tablets, USP)

Dear Dr. Jenkins:

JONES PHARMA INCORPORATED is hereby submitting an amendment to our pending New Drug Application (NDA) for Levoxyl (Levothyroxine Sodium Tablets, USP) submitted July 28, 2000. The following information is included in this amendment.

Additional Information Requested by Dr. David Lewis, Chemistry Reviewer, FDA

a) Executed batch records for one lot of each strength submitted in the stability section of the NDA

b) DMF reference letters from the manufacturers of the resin used to manufacture the ———

c) Updated stability data

New Information:

a) Additional Validation Data for the Analytical Method for Impurity Testing ———

Corrections to Original NDA Submission:

a) CMC Section: Corrections to the Finished Product Certificate of Release for lot TT24 (50 mcg Tablets) originally submitted on page 000580 of the NDA

b) Human Pharmacokinetics and Bioavailability Section: For Study 338-04, adverse event information for Subject 13, originally submitted on pages 002055 and 002061 of the NDA, is being updated

Amendment to NDA 21-301
Levoxyl (Levothyroxine Sodium Tablets, USP)

This amendment is being provided to CDER in duplicate: one Archival copy (blue jacket), a CMC Review copy (red jacket) and a Pharmacokinetics Review copy (orange jacket). Please incorporate this information into the application.

Additionally, a Field Copy (burgundy jacket) containing the CMC section has been forwarded to the FDA District office in Maitland, Florida.

We look forward to the approval of this NDA. Should any additional information be required, please do not hesitate to contact me at (314) 576-6100 ext. 3070.

Sincerely,

JONES PHARMA INCORPORATED

Nancy Cafmeyer

Nancy Cafmeyer
Vice President of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

JONES

ORIGINAL NC

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
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September 7, 2000

John Jenkins, M.D. Acting Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

/S/ 9-22-00 noted

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 12 2000
HFD-510

RE: NDA 21-301 Levoxyl

Reference is made to our New Drug Application for Levoxyl (Levothyroxine Sodium Tablets, USP), NDA 21-301. On August 31, 2000, Jones Pharma Incorporated merged with and is now a wholly owned subsidiary of King Pharmaceuticals, Inc. This merger does not affect the ownership of the NDA. Jones Pharma will still retain ownership of NDA 21-301.

If there are any questions concerning this matter or further clarification is required, please do not hesitate to contact me by telephone at (314) 576-6100 or by fax at (314) 205-9497.

/S/ 9-14-00

Sincerely,

Nancy Cafmeyer

Nancy Cafmeyer
Vice President of Regulatory Affairs

/S/ 9/26/00 Noted

/S/ 9/26/00

/S/ 9/26/00

JONES

JONES PHARMA INCORPORATED
1945 Craig Road, P.O. Box 46903
St. Louis, Missouri 63146
314 576-6100 Fax 314 469-5749
www.jmedpharma.com

July 28, 2000

Food and Drug Administration
Central Document Room
12229 Wilkens Ave.
Rockville, MD 20857

NDA Submission

RE: NDA for Levoxyl (Levothyroxine Sodium Tablets, USP) Tablets

Dear Dr. Jenkins:

JONES PHARMA INCORPORATED is hereby submitting a New Drug Application (NDA) for Levoxyl (Levothyroxine Sodium Tablets, USP) Tablets.

On August 14, 1997, a notice was published in the Federal Register announcing the classification of orally administered drug products containing levothyroxine sodium as new drugs (Volume 62, Number 157, Page 43535). The notice stated that manufacturers who wish to continue to market orally administered levothyroxine sodium products must have an approved NDA by August 14, 2000. On April 26, 2000, the deadline was extended to August 14, 2001 (Volume 65, Number 81, Page 24488).

In June and August 1999, two guidelines were published by FDA concerning the submission of NDAs for levothyroxine sodium products. These guidelines entitled, "Guidance for Industry: In-Vivo Pharmacokinetics and Bioavailability Stuides and In Vitro-Dissolution Testing for Levothyroxine Sodium Tablets" and "Guidance for Industry: Levothyroxine Sodium", as well as meetings and telephone communications between FDA and Jones, form the basis of this NDA submission.

The reason for the reclassification of oral levothyroxine sodium products as new drugs can best be described by stating from the 1997 notice. "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".

Levoxyl Tablets have been commerically available since the mid-1980s. Jones Pharma has done extensive research on developing a formulation of levothyroxine sodium tablets with the intent of increasing the shelf life of the product without the addition of a stability

overage. The formulation of Levoxyl, which is presented in this NDA, was chosen because it demonstrates improved stability characteristics over the current formula.

During product development, Jones performed a comparison forced degradation study (60°C) on the active ingredient (levothyroxine sodium), the current formulation of Levoxyl tablets and on the formulation which is presented in this NDA. The purpose of this study was to compare the relative loss in potency under the extreme heat condition. The results of this study, presented in table form below, illustrate the improved stability characteristics of the new formulation of Levoxyl tablets.

[redacted]

The safety and effectiveness of Levoxyl tablets have been demonstrated during the over 20 year period that the product has been commercially available. The intent of this NDA is to provide evidence that reaffirms Levoxyl tablets are safe and effective and perform as the 1997 Federal Register notice intends for levothyroxine sodium products.

The number of volumes in this application are as follows:

Contents	Jacket Color	# of Volumes
Archival Copy	blue	21
Review Copy		
Chemistry	red	3
Pharmacology	yellow	1
Pharmacokinetics	orange	6
Appendices 1 and 2 (Case Report Forms)	orange	9
Clinical	light-brown	1

Additionally, a field copy in burgundy jackets containing the CMC section has been forwarded to the FDA District office in Maitland, Florida.

We look forward to the approval of this NDA. Should any additional information be required, please do not hesitate to contact Nancy Cafmeyer at (314) 576-6100 ext. 3070.

Sincerely,

Nancy Cafmeyer
Vice President of Regulatory Affairs

Elaine Strauss
Vice President of QA/QC JMI-Daniels

JONES MEDICAL INDUSTRIES, INC.

1945 Craig Rd. P.O. Box 46903
St. Louis, Missouri 63146

314 576-6100
Fax 314 469-5749

January 22, 1998

Dr. Solomon Sobol
Director, Division of Metabolic and Endrocrine Products
HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Docket No.: 97N-0314

Dear Dr. Sobol:

Reference is made to the August 14, 1997 notice in the federal register *Prescription Drug Products; Levothyroxine Sodium* (Figure 1) and our letter of November 18, 1997. As a manufacturer of an affected product we are requesting a meeting with the FDA to discuss issues resulting from this notice. Attached are the concerns for which we are requesting clarification in order for us to proceed in a logical, timely way in preparation of the NDA.

The following persons will be attending from our organization: Andrew Franz, Senior Vice President of Operations-Pharmaceuticals, Nancy Cafmeyer, Vice President of Regulatory Affairs, Dr. C.T. Rhodes, President, PharmaCon Inc., and Jess H. Stribling, with the law firm of King and Spalding.

After reviewing the attached list of questions and concerns, you can decide who the appropriate persons from FDA should be in attendance.

We would like to try and set the meeting for one of the following dates: February 9, 10, 11, 25 or 26. We will be contacting Steve McCort to verify which of the above dates would be acceptable.

Sincerely,

Nancy Cafmeyer

Nancy Cafmeyer
Vice President of Regulatory Affairs

attachments

cc: Steve McCort

HFU-554 C/F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 7 1997

Joseph G. Valentino, J.D.
Senior Vice President and General Counsel
The United States Pharmacopeial
Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 7-97-003-R

Dear Dr. Valentino:

This letter is in regard to both the USP 23 monograph and an In-process Revision proposal for Levothyroxine Sodium Tablets that appeared in the September-October 1996 issue of Pharmacopeial Forum, Vol. 22, No. 5, on pages 2823-2825.

We recently completed a partial market survey of this product. The survey uncovered analytical problems associated with the analytical steps under the Dissolution test in both Test 1 and Test 2, and gave results that, perhaps, have not been anticipated by the proposed Test 2. We wish to share this information with the USP.

Manufacturers on the enclosed Table 2 are identified by the following code:

1. Jerome Stevens Pharmaceuticals
2. Daniels Pharmaceuticals, Inc.
3. _____
4. _____

One notes that ——— products probably will not meet the proposed Test 2; clearly they can label the products that they will meet Test 1.

The laboratory was instructed to perform the Dissolution test according to the proposed Test 2. This did not work. It was determined that the chromatographic method lacks adequate sensitivity to accurately quantitate dissolved drug from the lower strengths of tablets, there was interference from unidentified peaks that may have been caused by the 200 µL injections, and levothyroxine is unstable at low concentrations in water.

The laboratory performed a limited stability study of Levothyroxine RS in various diluents. The standard was dissolved in Ammoniated solution as directed in PF 20:2.

It was then diluted to 0.05 µg/mL in

a) water,
b) water + 1 drop of NH_4OH per 50 mL,
c) pH 7.4 buffer (Test 1 Medium),
d) pH 7.4 buffer + 1 drop H_3PO_4 per 5 mL,
e) 0.01M methanolic sodium hydroxide,

and tested. The following results were obtained:

Table 1

Diluent	Conditions	% Loss in Levothyroxine Peak Area
(a) water	Room temperature, 3 hours	21%
	Room temperature, 6 hours	36%
	Refrigerator, overnight	essentially all, multiple peaks
(b) water + NH_4OH	Room temperature, 3 hours	0%
	Refrigerator, 3 days	5%
(c) pH 7.4	Room temperature, 3 hours	0%
	Refrigerator, overnight	0%
	Refrigerator, 3 days	16%
(d) pH 7.4 + H_3PO_4	Room temperature, 3 hours	0%
	Refrigerator, 3 days	43%

Diluent (e) produced unsuitable chromatographic peaks.

Based on these data, we consider water to be an unsuitable Medium for Dissolution testing of Levothyroxine Sodium Tablets.

Further, because of the analytical difficulties described above, the chromatography described in PF 20:2 also was investigated. Experiments determined that a Mobile phase of somewhat different proportions (water:acetonitrile(64:36) + 0.1% H_3PO_4) prolonged the retention of levothyroxine on the column so that it was better resolved from the baseline. This Mobile phase was used with an —— column that contained packing L1, instead of L10, with a flow rate of 1.5 mL per minute and detection at 225 nm. However, this system still was incapable of achieving suitable reproducibility of peak areas at the lowest concentration, 0.05 µg/mL.

We obtained generally suitable chromatography using the system currently described for Test 1, except that our instrumentation system cannot accommodate 800 µL injections. Thus, we lowered the injection volume to 150 µL. However, this resulted in improperly integrated peaks with unacceptable % RSD and linearity values for the lowest strengths of samples and standard. Other than that difficulty, Test 1 as written worked for our analyses.

We have determined that water is not a suitable Medium and that suitable chromatography cannot be obtained using the L10 column proposed for use with Test 2. These problems should have significant repercussions with regard to the recently-previewed USP bioequivalence guidance for Levothyroxine Sodium Tablets. Thus, we recommend that the USP develop a suitable dissolution test, including the determinative step, for marketed Levothyroxine Sodium Tablets. Earlier this year, (REF: 4-97-005-R, dated April 28, 1997), we suggested that 0.1 *N* hydrochloric acid appeared to be a preferable Medium to the official pH 7.4 phosphate buffer for dissolution testing of the dominant brand of tablets. We also stated that 0.1 *N* hydrochloric acid appeared to be suitable for tablets that dissolve in water. It might be worth USP's time to investigate the suitability of this reagent for testing of all marketed formulations. If such suitability is found, an appropriately rugged determinative step can be built around the revised Medium. We encourage the USP to undertake this important project.

We hope this information and these comments will be helpful to the USP. Please feel free to contact Bob Rippere on my staff if there are any questions or if additional information is needed. We would appreciate use of the reference number provided above on any ensuing correspondence.

Sincerely,

/S/

Yana Ruth Mille
Chief
Compendial Operations Staff, HFD-354
Office of Pharmaceutical Science
Center for Drug Evaluation & Research

cc: Vivian A. Gray, USP

Enclosure

TABLE 2

DISSOLUTION

MFR.	LOT #.	LABEL (mg)	MEAN (%)	RANGE (%)
3	MKT0612B	0.025	86.6	
3	JT3672	0.025	80.9	
3	MKT1271A	0.025	75.5	
3	382-110	0.075	76.6	
3	JT10195	0.075	81.7	
3	MKT0632A	0.075	92.9	
3	JT3603	0.125	60.4	
3	MKT0092A	0.15	71.2	
3	MKT0081A	0.15	91.1	
3	MKT0091A	0.15	98.9	
3	MKT0351A	0.2	109.2	
3	MKT0711A	0.2	89.0	
3	MKT0011A	0.2	82.7	
3	JT10177	0.3	84.6	
3	MKT0391A	0.3	78.0	
3	JT10175	0.3	80.7	
3	MKT0611A	0.05	69.9	
4	504PR005	0.1	61.2	
4	504PR008	0.1	64.0	
4	504PR009	0.15	73.7	
4	504PR003	0.3	63.3	
1	030594	0.1	100.2	
1	000895	0.1	99.5	
2	4902	0.3	79.7	

c:\table2bo.wpd

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97F-0336]

General Electric Co.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

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

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

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

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

Dated: July 31, 1997.

Alan M. Rulis,

Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 97-21436 Filed 8-13-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N-0314]

Prescription Drug Products; Levothyroxine Sodium

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

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

EFFECTIVE DATE: August 14, 1997.

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

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

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

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

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

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

FOR FURTHER INFORMATION CONTACT: Christine F. 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 (T_4). Thyroid hormones affect protein, lipid, and carbohydrate metabolism; growth; and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production, and possess a cardiostimulatory effect that may be the result of a direct action on the heart.

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

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

increases to 2.7 percent in men and 7.1 percent in women. Because congenital hypothyroidism may result in irreversible mental retardation, which can be avoided with early diagnosis and treatment, newborn screening for this disorder is mandatory in North America, Europe, and Japan.

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

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

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

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

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

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

III. Adverse Drug Experiences

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

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

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

IV. Formulation Change

Because orally administered levothyroxine sodium products are marketed without approved applications, manufacturers have not sought FDA approval each time they reformulate their products. In 1982, for example, one manufacturer reformulated its levothyroxine sodium product by removing two inactive ingredients and changing the physical form of coloring agents (Ref. 6). The reformulated product increased significantly in potency. One study found that the reformulated product contained 100 percent of stated content compared to 78 percent before the reformulation (Ref. 7). Another study estimated that the levothyroxine content of the old formulation was approximately 70 percent of the stated value (Ref. 8).

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

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

V. Stability Problems

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

orally administered levothyroxine sodium products, including the market leader, has reported recalls that were the result of potency or stability problems.

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

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

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

In March 1993, FDA sent a warning letter to a firm stating that its levothyroxine tablets were adulterated because the expiration date was not supported by adequate stability studies. Five lots of the firm's levothyroxine sodium tablets, labeled for storage within controlled room temperature range, had recently failed stability testing when stored at the higher end of the range. The warning letter also objected to the labeled storage conditions specifying a nonstandard storage range of 15 to 22 °C. FDA objected to this labeling because it did not conform to any storage conditions defined in United States Pharmacopeia (USP) 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. L. et al., "Stability Indicating High-Pressure Liquid Chromatographic Method for Quality Control of Sodium Liothyronine and Sodium Levothyroxine in Tablet Formulations," in "Hormone Drugs," edited by J. L. Gueriguian, E. D. Bransome, and A. S. Outschoorn, United States Pharmacopeial Convention, pp. 504–516, Rockville, 1982.

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

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

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

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

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

VII. Legal Status

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

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

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

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

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

(4) A drug which is subject to paragraph (1) shall be deemed to be misbranded if at any time prior to dispensing its label fails to bear the statement "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.". A drug to which paragraph (1) does not apply shall be deemed to be misbranded if at any time prior to dispensing its label bears the statement specified in the preceding sentence.

(g)(1) The Secretary shall designate a component of the Food and Drug Administration to regulate products that constitute a combination of a drug, device, or biological product. The Secretary shall determine the primary mode of action of the combination product. If the Secretary determines that the primary mode of action is that of—

(A) a drug (other than a biological product), the persons charged with premarket review of drugs shall have primary jurisdiction,

(B) a device, the persons charged with premarket review of devices shall have primary jurisdiction, or

(C) a biological product, the persons charged with premarket review of biological products shall have primary jurisdiction.

(2) Nothing in this subsection shall prevent the Secretary from using any agency resources of the Food and Drug Administration necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article.

(3) The Secretary shall promulgate regulations to implement market clearance procedures in accordance with paragraphs (1) and (2) not later than 1 year after the date of enactment of this subsection.

(4) As used in this subsection:

(A) The term "biological product" has the meaning given the term in section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)).

(B) The term "market clearance" includes—

(i) approval of an application under section 505, 507, 515, or 520(g),

(ii) a finding of substantial equivalence under this subchapter, and

(iii) approval of a product or establishment license under subsection (a) or (d) of section 351 of the Public Health Service Act (42 U.S.C. 262).

NEW DRUGS

SEC. 505.[1] [355] (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an ap-

[1] The application of this section as amended by the Drug Amendments of 1962 (P.L. 87-781) is stated as follows by sec. 107(c) of that Act:

[Sec. 107] (c)(1) As used in this subsection the term "enactment date" means the date of enactment of this Act [October 10, 1962]; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

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proval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

(b)(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (F) specimens of the labeling proposed to be used for such drug. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asseted if a person not licensed by the owner engaged in the manufacture use, or sale of the drug. If a application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences.

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application 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 shall also include—

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(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act, insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c)—

(i) that such patent information has not been filed,
(ii) that such patent has expired,
(iii) of the date on which such patent will expire, or
(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3)(A) An applicant who makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give the notice required by subparagraph (B) to—

(i) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and

(ii) the holder of the approved application under subsection (b) for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

(B) The notice referred to in subparagraph (A) shall state that an application has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.

(C) If an application is amended to include a certification described in paragraph (2)(A)(iv), the notice required by subparagraph (B) shall be given when the amended application is submitted.

(c)(1) Within one hundred and eighty days after the filing of an application under subsection (b), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not

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agency's review and approval of the application, whichever is later. The notification to FDA of the legal action shall include:

(i) The abbreviated new drug application or 505(b)(2) application number.

(ii) The name of the abbreviated new drug or 505(b)(2) application applicant.

(iii) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.

(iv) A certification that an action for patent infringement identified by number, has been filed in an appropriate court on a specified date.

The applicant of an abbreviated new drug application shall send the notification to FDA's Office of Generic Drugs (HFD–600). A 505(b)(2) applicant shall send the notification to the appropriate division in the Center for Drug Evaluation and Research reviewing the application. A patent owner or its representative may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in this paragraph.

(3) If the patent owner or approved application holder who is an exclusive patent licensee waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or approved application holder who is an exclusive patent licensee submits to FDA a valid waiver before the 45 days elapse, approval of the abbreviated new drug application or the 505(b)(2) application will be made effective upon completion of the agency's review and approval of the application. FDA will only accept a waiver in the following form:

(Name of patent owner or exclusive patent licensee) has received notice from *(name of applicant)* under *(section 505(b)(3) or 505(j)(2)(B) of the act)* and does not intend to file an action for patent infringement against *(name of applicant)* concerning the drug *(name of drug)* before *(date on which 45 days elapses. (Name of patent owner or exclusive patent licensee)* waives the opportunity provided by *(section 505(c)(3)(C) or 505(j)(B)(iii) of the act)* and does not object to FDA's approval of *(name of applicant)*'s *(505(b)(2) or abbreviated new drug application)* for *(name of drug)* with an immediate effective date on or after the date of this letter.

[59 FR 50367, Oct. 3, 1994]

§ 314.108 New drug product exclusivity.

(a) *Definitions.* The following definitions of terms apply to this section:

Active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Approved under section 505(b) means an application submitted under section 505(b) and approved on or after October 10, 1962, or an application that was "deemed approved" under section 107(c)(2) of Pub. L. 87–781.

Clinical investigation means any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

Conducted or sponsored by the applicant with regard to an investigation means that before or during the investigation, the applicant was named in Form FDA–1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation. To demonstrate "substantial support," an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation why FDA should consider the applicant to have conducted or sponsored the study if the applicant's financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all

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rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

Date of approval means the date on the letter from FDA stating that the new drug application is approved, whether or not final printed labeling or other materials must yet be submitted as long as approval of such labeling or materials is not expressly required. "Date of approval" refers only to a final approval and not to a tentative approval that may become effective at a later date.

Essential to approval means, with regard to an investigation, that there are no other data available that could support approval of the application.

FDA means the Food and Drug Administration.

New chemical entity means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.

New clinical investigation means an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.

(b) *Submission of and effective date of approval of an abbreviated new drug application submitted under section 505(j) of the act or a 505(b)(2) application.* (1) [Reserved]

(2) If a drug product that contains a new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application, except that the 505(b)(2) application or abbreviated application may be submitted after 4 years if it contains a certification of patent invalidity or noninfringement described in §314.50(i)(1)(i)(A)(*4*) or §314.94(a)(12)(i)(A)(*4*).

(3) The approval of a 505(b)(2) application or abbreviated application described in paragraph (b)(2) of this section will become effective as provided in §314.107(b)(1) or (b)(2), unless the owner of a patent that claims the drug, the patent owner's representative, or exclusive licensee brings suit for patent infringement against the applicant during the 1-year period beginning 45 months after the date of approval of the new drug application for the new chemical entity and within 45 days after receipt of the notice described at §314.52 or §314.95, in which case, approval of the 505(b)(2) application or abbreviated application will be made effective as provided in §314.107(b)(3).

(4) If an application:

(i) Was submitted under section 505(b) of the act;

(ii) Was approved after September 24, 1984;

(iii) Was for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act; and

(iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, the agency will not make effective for a period of 3 years after the date of approval of the application the approval of a 505(b)(2) application or an abbreviated new drug application for the conditions of approval of the original application, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original new drug application.

(5) If a supplemental application:

(i) Was approved after September 24, 1984; and

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[59 FR 50368, Oct. 3, 1994]

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(ii) Contained reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant that were essential to approval of the supplemental application, the agency will not make effective for a period of 3 years after the date of approval of the supplemental application the approval of a 505(b)(2) application or an abbreviated new drug application for a change, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting a change approved in the supplemental new drug application.

[59 FR 50368, Oct. 3, 1994]

§314.110 Approvable letter to the applicant.

(a) In selected circumstances, it is useful at the end of the review period for the Food and Drug Administration to indicate to the applicant that the application or abbreviated application is basically approvable providing certain issues are resolved. An approvable letter may be issued in such circumstances. FDA will send the applicant an approvable letter if the application or abbreviated application substantially meets the requirements of this part and the agency believes that it can approve the application or abbreviated application if specific additional information or material is submitted or specific conditions (for example, certain changes in labeling) are agreed to by the applicant. The approvable letter will describe the information or material FDA requires or the conditions the applicant is asked to meet. As a practical matter, the approvable letter will serve in most instances as a mechanism for resolving outstanding issues on drugs that are about to be approved and marketed. For an application or an abbreviated antibiotic application, the applicant shall, within 10 days after the date of the approvable letter:

(1) Amend the application or abbreviated antibiotic application or notify FDA of an intent to file an amendment. The filing of an amendment or notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period for 45 days after the date FDA receives the amendment. The extension is to permit the agency to review the amendment;

(2) Withdraw the application or abbreviated antibiotic application. FDA will consider the applicant's failure to respond within 10 days to an approvable letter to be a request by the applicant to withdraw the application under §314.65 or the abbreviated antibiotic application under §314.99. A decision to withdraw an application or abbreviated antibiotic application is without prejudice to a refiling;

(3) For a new drug application or abbreviated antibiotic application, ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) of the act. The applicant shall submit the request to the Division of Regulatory Affairs (HFD–360), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the approvable letter, or within a different time period to which FDA and the applicant agree, the agency will either approve the application or abbreviated antibiotic application under §314.105 or refuse to approve the application or abbreviated antibiotic application under §314.125 and give the applicant written notice of an opportunity for a hearing under §314.200 and section 505(c)(2) of the act on the question of whether there are grounds for denying approval of the application under section 505(d) of the act;

(4) For an antibiotic, file a petition or notify FDA of an intent to file a petition proposing the issuance, amendment, or repeal of a regulation under §314.300 and section 507(f) of the act; or

(5) Notify FDA that the applicant agrees to an extension of the review period under section 505(c) of the act, so that the applicant can determine whether to respond further under paragraph (a)(1), (a)(2), (a)(3), or (a)(4) of this section. The applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under §314.65

Bioequivalence of Generic and Brand-name Levothyroxine Products in the Treatment of Hypothyroidism

Betty J. Dong, PharmD; Walter W. Hauck, PhD; John G. Gambertoglio, PharmD; Lauren Gee, MPH; John R. White, PharmD; Jeff L. Bubp, PharmD; Francis S. Greenspan, MD

Objective.—To compare relative bioavailability of Synthroid, Levoxine (Levoxine has been renamed Levoxyl), and 2 generic levothyroxine sodium preparations.

Design.—Single-blind (primary investigators blinded), randomized, 4-way crossover trial.

Setting.—Ambulatory care.

Patients.—Twenty-two women with hypothyroidism who were clinically and chemically euthyroid and were receiving levothyroxine sodium, 0.1 or 0.15 mg.

Interventions.—All patients received each of the 4 levothyroxine products for 6-week periods in the same dosage as their prestudy regimen with no washout period. The order of the drug sequences was randomly determined before study initiation.

Main Outcome Measures.—Area under the curve, time to peak serum concentrations, and peak serum concentrations of thyroxine, triiodothyronine, and free thyroxine index for all 4 products.

Results.—All data analyses were completed prior to unblinding of the product codes. No significant differences between the 4 products were found in area under the curve or peak serum concentrations of total thyroxine, total triiodothyronine, or free thyroxine index. Although Synthroid produced a more rapid rise in total serum triiodothyronine concentration and a higher total peak serum triiodothyronine concentration than the other products, these differences were not statistically significant ($P=.08$). The Food and Drug Administration criterion for relative bioequivalence within 90% confidence intervals (0.8-1.25) was demonstrated ($P<.05$) for all pairs of products. Relative bioequivalence of 0.95 to 1.07 was demonstrated, tighter than the current bioequivalence criterion for oral formulations.

Conclusions.—The 4 generic and brand-name levothyroxine preparations studied are different but are bioequivalent by current Food and Drug Administration criteria and are interchangeable in the majority of patients receiving thyroxine replacement therapy. Further investigation is required to determine whether our results are equally applicable to all existing levothyroxine preparations.

JAMA. 1997;277:1205-1213

LEVOTHYROXINE sodium is a lifelong medication taken by a large proportion of the population. It is estimated that about 8 million Americans receive thyroid replacement and suppression therapy. Brand-name products are often recommended as the levothyroxine preparations of choice because of widespread concern about the therapeutic equivalency of less costly generic products. However, it is controversial whether different brands of levothyroxine are therapeutically interchangeable and bioequivalent because variations in thyroxine levels have been observed in patients taking either generic or brand-name preparations.[1-3] Although several brand-name levothyroxine preparations have been deemed bioequivalent, similar information is not available regarding comparable generic preparations.[4-6] Contributing to this presumed nonequivalence is that in vivo bioavailability testing is not required by the Food and Drug Administration (FDA) for marketing of levothyroxine products. The mean bioavailability of a brand-name levothyroxine product is 81.3%,[7] while the bioavailability of generic levothyroxine preparations is unknown.

See also pp 1199, 1224, and 1238.

Such unresolved concerns about the therapeutic bioequivalence of generic and brand-name levothyroxine have prompted many clinicians to recommend that patients continue to receive the brand of levothyroxine that achieved euthyroidism and adequate thyroid replacement. Regardless of these appro-

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The statements and opinions expressed in this article reflect the views of the authors and not necessarily those of the sponsors.

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is required to determine whether our results are equally applicable to all existing levothyroxine preparations on the market or to patients who require thyroxine suppression therapy. Demonstration of bioequivalence between brand-name and generic preparations should enhance cost-effectiveness for patients receiving lifelong thyroxine replacement therapy.

This study was supported in part by a grant from Boots Pharmaceuticals Inc, Lincolnshire, Ill.

The authors thank Leslie Z. Benet, PhD, for his invaluable assistance in making this article possible. We also thank Gamal Hussein, PharmD, and Jose P. Franco, PhD, for technical support, and Mohammed K. Hassanzedeh, PhD, for analytical support.

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is about 1 mL per minute. Chromatograph five replicate injections of the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative standard deviation is not more than 2.0%, and the tailing factor is not more than 1.8.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{15}H_{10}I_4NNaO_4$ in the portion of Levothyroxine Sodium taken by the formula:

$$(798.86/776.88)(2.5C)(r_U/r_S),$$

in which 798.86 and 776.88 are the molecular weights of levothyroxine sodium and levothyroxine, respectively, C is the concentration, in µg per mL, of USP Levothyroxine RS in the *Standard preparation*, and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Levothyroxine Sodium Oral Powder

» Levothyroxine Sodium Oral Powder contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{10}I_4NNaO_4$.

Packaging and storage—Preserve in tight, light-resistant containers.

Labeling—Label it to indicate that it is for veterinary use only.

USP Reference standards ⟨11⟩—*USP Levothyroxine RS.*

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 3 hours: it loses not more than 2.0% of its weight.

Assay—

Mobile phase, 0.01 M Methanolic sodium hydroxide, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Levothyroxine Sodium.*

Assay preparation—Transfer an accurately weighed portion of Oral Powder, equivalent to about 5 mg of levothyroxine sodium, to a 250-mL volumetric flask. Dilute with *0.01 M Methanolic sodium hydroxide* to volume, mix, and allow to stand for 4 hours, with occasional mixing. Filter a portion of this mixture through a filter that does not absorb levothyroxine. Transfer 10.0 mL of the filtrate to a 50-mL volumetric flask, dilute with *0.01 M Methanolic sodium hydroxide* to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Levothyroxine Sodium.* Calculate the quantity, in mg, of $C_{15}H_{10}I_4NNaO_4$ in the portion of Oral Powder taken by the formula:

$$(798.86/776.87)(1.25C)(r_U/r_S),$$

in which the terms are as defined therein.

Levothyroxine Sodium Tablets

» Levothyroxine Sodium Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{10}I_4NNaO_4$.

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩—*USP Liothyronine RS. USP Levothyroxine RS.*

Identification—

Solvent system—Mix 5 volumes of *tert*-amyl alcohol, 4 volumes of water, and 1 volume of ammonium hydroxide, shake, and allow to stand. Transfer the upper phase to a suitable chromatographic chamber, arranged for thin-layer chromatography, pouring it over the paper lining, cover the chamber, and allow to stand for 1 hour.

Detection reagent—Add 65 mL of 2 *N* hydrochloric acid to 50 mL of a 1 in 10 solution of sodium arsenite in 1 *N* sodium hydroxide, with vigorous stirring. Mix 1 volume of this solution with 5 volumes of a 27 in 1000 solution of ferric chloride in 2 *N* hydrochloric acid and 5 volumes of freshly prepared potassium ferricyanide solution (35 in 1000).

Standard preparation—Prepare a solution of about 15 mg of USP Levothyroxine RS, accurately weighed, in 100 mL of a mixture of 19 volumes of methanol and 1 volume of ammonium hydroxide. Dilute 10.0 mL of this solution with the same solvent to 50.0 mL, and mix.

Test preparation—Shake an amount of powdered Tablets equivalent to about 60 µg of levothyroxine sodium, with 2 mL of a mixture of 19 volumes of methanol and 1 volume of ammonium hydroxide in a centrifuge tube for 10 minutes, and centrifuge.

Procedure—Apply 10-µL volumes of the *Test preparation* and of the *Standard preparation*, respectively, to a thin-layer chromatographic plate coated with a 0.1-mm layer of cellulose. Develop the plate in the *Solvent system* until the solvent front has moved not less than 10 cm beyond the point of application of the *Test preparation*, air-dry, and spray the plate with *Detection reagent:* the chromatogram of the *Test preparation* shows a blue spot corresponding in R_f value to the chromatogram from the levothyroxine *Standard preparation.*

Dissolution ⟨711⟩—[NOTE—All containers that are in contact with solutions containing levothyroxine sodium are to be made of glass.]

Medium: 0.05 *M*, pH 7.4 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 500 mL.

Apparatus 2: 100 rpm.

Time: 80 minutes.

Determine the amount of levothyroxine sodium dissolved using the following method.

0.01 M Methanolic sodium hydroxide—Add 1 mL of 10 *N* sodium hydroxide to 750 mL of methanol in a 1-liter volumetric flask, and mix. Dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol and 0.1% phosphoric acid (60:40).

Standard solutions—Prepare a stock solution of USP Levothyroxine RS in *0.01 M Methanolic sodium hydroxide* having an accurately known concentration of about 0.5 mg per mL. Dilute aliquots of this stock solution with 0.05 *M*, pH 7.4 phosphate buffer to obtain solutions having concentrations similar to those expected in the Test solutions. Add 1 drop of phosphoric acid to 5.0 mL of this solution, and mix.

Test solution—[NOTE—Prior to use, check the filters for absorptive loss of drug.] Transfer 5.0 mL of a filtered portion of the solution under test to a flask, add 1 drop of phosphoric acid, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph replicate injections of the *Standard solutions*, and record the peak responses as directed under *Procedure:* the relative standard deviation is not more than 4.0%, and the tailing factor is not more than 1.5.

Procedure—Separately inject equal volumes (about 800 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved.

Tolerances—Not less than 55% (*Q*) of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 80 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Soluble halides—Place a portion of finely powdered Tablets, equivalent to about 2.5 mg of anhydrous levothyroxine sodium, in a large test tube, add 1 g of chloride-free activated charcoal and 25 mL of water, insert the stopper in the tube, heat to about 40°, and shake for 5 minutes. Add 3 drops of dilute nitric acid (2 in 5), and filter. To the filtrate add 8 drops of silver nitrate TS: any turbidity produced does not exceed that in a control containing 0.25 mL of 0.020 *N* hydrochloric acid (7.1%).

the number of mL of 0.1 *N* sodium thiosulfate used in the *Assay for iodine*, multiplied by 16.60 represents the number of mg of KI in the volume of Strong Iodine Tincture taken.

Isosorbide Dinitrate Sublingual Tablets, *USP 23* page 859 and page 2018 of *PF* 22(2) [Mar.–Apr. 1996]—See briefing under *Acetaminophen and Aspirin Tablets.*

2I10325 (DBA) RTS—16719-09

Change to read:

Dissolution,

Procedure for a Pooled Sample ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 20 minutes.

Mobile phase—Prepare a suitable degassed and filtered mixture of pH 3.0, 0.1 *M* ammonium sulfate and methanol (50:50).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed under *Procedure:* the tailing factor is not more than 1.5, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and a filtered aliquot of the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_6H_8N_2O_8$ dissolved in comparison with a *Standard solution* having a known concentration of USP Isosorbide Dinitrate RS, similarly prepared and chromatographed.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_6H_8N_2O_8$ is dissolved in 20 minutes.

Kanamycin Sulfate Capsules, *USP 23* page 862 and page 2018 of *PF* 22(2) [Mar.–Apr. 1996]—See briefing under *Acetaminophen and Aspirin Tablets.*

2K00200 (DBA) RTS—16719-10

Change to read:

Dissolution,

Procedure for a Pooled Sample ⟨711⟩—

Medium: 0.1 *N* hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure—Determine the amount of kanamycin ($C_{18}H_{36}N_4O_{11}$) dissolved, employing the procedure set forth in the *Assay*, making any necessary modifications.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{18}H_{36}N_4O_{11}$ is dissolved in 45 minutes.

Ketorolac Tromethamine, page 2472 of the *First Supplement.*

2K00970 (CH4) RTS—17856-01

Erratum:

Identification test *C*, line 7: Change "0.25-cm" to: 0.25-mm.

Levothyroxine Sodium Tablets, *USP 23* page 884, page 2648 of the *Second Supplement*, and page 2018 of *PF* 22(2) [Mar.–Apr. 1996]. The Dissolution and Bioavailability Subcommittee (DBA) have considered all of the comments received from the publication in *Previews* of changes to this monograph that were first presented in *PF* 21(6) [Nov.–Dec. 1995], and again in *PF* 22(2), and have recommended forwarding *Test 1* and *Test 2* under *Dissolution* to *In-process Revision* and adding a *Labeling* section.

2L02400 (DBA) RTS—15232-01; 16845-01

Add the following:

Labeling—The labeling indicates the *Dissolution Test* with which the product complies.

Change to read:

Dissolution ⟨711⟩—[NOTE—All containers that are in contact with solutions containing levothyroxine sodium are to be made of glass.]

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

Medium: 0.05 *M*, pH 7.4 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 500 mL.

Apparatus 2: 100 rpm.

Time: 80 minutes.

Determine the amount of levothyroxine sodium dissolved using the following method.

0.01 M Methanolic sodium hydroxide—Add 1 mL of 10 *N* sodium hydroxide to 750 mL of methanol in a 1-liter volumetric flask, and mix. Dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol and 0.1% phosphoric acid (60:40).

Standard solutions—Prepare a stock solution of USP Levothyroxine RS in *0.01 M Methanolic sodium hydroxide* having an accurately known concentration of about 0.5 mg per mL. Dilute aliquots of this stock solution with 0.05 *M*, pH 7.4 phosphate buffer to obtain solutions having concentrations similar to those expected in the Test solutions. Add 1 drop of phosphoric acid to 5.0 mL of this solution, and mix.

Test solution—[NOTE—Prior to use, check the filters for absorptive loss of drug.] Transfer 5.0 mL of a filtered portion of the solution under test to a flask, add 1 drop of phosphoric acid, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph replicate injections of the *Standard solutions*, and record the peak responses as directed under *Procedure:* the relative standard deviation is not more than 4.0%, and the tailing factor is not more than 1.5.

Procedure—Separately inject equal volumes (about 800 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved.

Tolerances—Not less than 55% (*Q*) of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 80 minutes.

■*Test 2:* If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: water; 500 mL.

Apparatus 2: 100 rpm.

Time: 45 minutes.

Determine the amount of levothyroxine sodium dissolved using the following method.

Ammoniated solution—Add 0.05 mL of ammonium hydroxide to 200 mL of water.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (55:45) that contains 1 mL of phosphoric acid in each 1000 mL of solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solutions—Prepare two standard stock solutions in *Ammoniated solution* containing known concentrations of about 10 µg per mL of USP Levothyroxine RS in one stock solution and about 10 µg per mL of USP Liothyronine RS in the other stock solution. Dilute a portion of each stock solution quantitatively with water to obtain a concentration of about 0.5 µg per mL of USP Levothyroxine RS (*Standard solution A*) and 0.5 µg per mL of USP Liothyronine RS (*Standard solution B*).

Test solution—Transfer 20 mL of the solution under test into a centrifuge tube, and centrifuge until a clear supernatant liquid is obtained.

System suitability solution—Prepare a solution of USP Levothyroxine RS and USP Liothyronine RS in *Ammoniated solution* having known concentrations of about 10 µg per mL of each Reference Standard. Dilute with water to obtain a concentration of about 0.5 µg per mL of each Reference Standard.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 2 mL per minute. Chromatograph the *System suitability solution* and record the peak responses as directed under *Procedure:* the resolution, *R*, between the liothyronine and levothyroxine peaks is not less than 3.0. Chromatograph each *Standard solution* and record the peak responses as directed under *Procedure:* the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 200 µL) of *Standard solution A* and the *Test solution* into the chromatograph, record the chromatograms,

and measure the responses for the major peaks. Calculate the amount of $C_{15}H_{10}I_4NNaO_4$.

Tolerances—Not less than 70% (*Q*) of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 45 minutes.

Lisinopril Tablets, *USP 23* page 895 and page 2020 of *PF* 22(2) [Mar.–Apr. 1996]—See briefing under *Acetaminophen and Aspirin Tablets.*

2L05075 (DBA) RTS—16720-01

Change to read:

Dissolution,

■*Procedure for a Pooled Sample*■ ⟨711⟩—

Medium: 0.1 *N* hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of lisinopril dissolved using the following method.

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay.*

Procedure—Inject a volume of a filtered portion of the solution under test into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $C_{21}H_{31}N_3O_5$ dissolved in comparison with a Standard solution having a known concentration of USP Lisinopril RS in the same medium and similarly chromatographed.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_{21}H_{31}N_3O_5$ in the Tablets is dissolved in 30 minutes.

Lithium Carbonate Extended-release Tablets, *USP 23* page 898 and page 2594 of *PF* 22(4) [July–Aug. 1996]. The *Medium* under *Drug release Test 2* was omitted in the previous proposal and is consequently added.

2L05350 (DBA) RTS—17542-01

Add the following:

■**Labeling**—The labeling indicates the *Drug release* test with which the product complies.■

Add the following:

■**Drug release** ⟨724⟩—

Test 1: If the product complies with this test, the labeling indicates that the product meets USP *Drug Release Test 1.*

Medium: dilute hydrochloric acid (7:100); 800 mL.

Apparatus 1: 100 rpm.

Times: 15 minutes, 45 minutes, 90 minutes, 120 minutes.

Procedure—Proceed as directed in the *Dissolution* test under *Lithium Carbonate Tablets.*

Tolerances—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 1.*

Time (minutes)	Amount dissolved
15	between 2% and 16%
45	between 25% and 45%
90	between 60% and 85%
120	not less than 85%

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Drug Release Test 2.*

Apparatus and *Procedure*—Proceed as directed under *Test 1.*

Medium: water; 900 mL.

Times: 1 hour, 3 hours, 7 hours.

Tolerances—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
1	not more than 40%
3	between 45% and 75%
7	not less than 70%■

LEVOTHYROXINE PHARMACOKINETICS AND BIOAVAILABILITY STUDIES IN VIVO

A. Pharmacokinetics Studies

Information on the pharmacokinetics (absorption, distribution, metabolism and excretion) of levothyroxine may be obtained from the literature and/or from original studies. If the studies cited have used levothyroxine sodium formulations other than the formulation intended for market, the submission should contain information identifying how those formulations differ from the to-be-marketed formulation.

B. Bioavailability Studies

This guidance recommends that *in vivo* bioavailability studies be conducted using the formulation(s) already on the market, assuming that a sponsor intends to keep marketing the formulation(s). The tablets used in the study should be made from a full-scale production batch, and should meet all compendial requirements. The formulations used should demonstrate sufficient stability for the length of the study. It is recommended that stability evaluations be made for the bio-batch prior to and after the study. All dissolution, potency and content uniformity data should be submitted to the NDA for review. For sponsors who do not have a levothyroxine sodium formulation in the marketplace, the usual approaches to developing pilot scale batches for bioavailability studies apply. Sponsors are encouraged to review available product quality and other applicable guidances for information on the chemistry, manufacturing and controls (CMC), and other components of an NDA for levothyroxine.

For each pharmacokinetics/bioavailability study outlined below, at least 24 volunteers should complete the trial. The subjects should be healthy volunteers, 18-50 years of age and within 15% of ideal body weight for their height and build. Sponsors should attempt to enroll approximately equal numbers of men and women. Volunteers recruited for the study should have an acceptable medical history, physical examination, and clinical laboratory tests. All thyroid function tests should be within normal limits. Volunteers with any current or past medical condition that might significantly affect their pharmacokinetic or pharmacodynamic response to levothyroxine should be excluded. Female volunteers should be given a pregnancy test prior to beginning the study. Pregnant women should be excluded from the study. Written informed consent must be obtained from all volunteers before they are accepted to the study.

1. Single-Dose Bioavailability Study

Objective

To determine the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference (oral solution) under fasting conditions.

Design

The study is a single-dose, two-treatment, two-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Dose and Number of Studies

One bioavailability study using a multiple of the highest tablet strength (600 µg dose) will be sufficient provided that:

a. The tablet strengths differ only in the amount of levothyroxine sodium and filler needed to maintain the tablet weight,

b. Multi-point dissolution profiles are similar across tablet strengths, and

c. The results of the dosage-form equivalence study indicate that the tablets studied are equivalent.

Sponsors whose products do not meet these criteria should contact the Division of Pharmaceutical Evaluation II for further guidance.

Procedure

Following a 10-hour overnight fast, volunteers should be administered a single dose of levothyroxine sodium orally with 240 mL water. The treatments should be as follows:

Treatment 1- Multiples of the highest levothyroxine sodium tablet to be marketed

Treatment 2- Levothyroxine sodium as an oral solution at an equivalent dose with treatment 1

Volunteers should remain fasted for four hours after dosing, with water only allowed after the first hour. Volunteers should be served standardized meals according to the schedule throughout the study.

Blood Sampling

Blood samples should be drawn at the following times after oral dosing: -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, and 48 hours post-dose.

Data Analysis

Individual and mean plasma/serum concentration-time profiles of total (bound + free) T4 and T3 should be included in the report. The following pharmacokinetic parameters should be computed:

- Area under the plasma/serum concentration-time curve from time 0 to the last measurable time point (AUC_{0-t})
- Peak concentration (Cmax)
- Time to peak concentration (Tmax)

Analysis of variance (ANOVA) should be performed for log-transformed AUC_{0-t} and Cmax data using SAS General Linear Model (GLM) procedure. The oral solution should be used as the reference formulation. The back-transformed means and 90% confidence intervals of the AUC_{0-t} and Cmax ratio (test/reference) should be presented as evidence of bioavailability.

2. Dosage-Form Equivalence Study

Objective

To determine the dosage-form equivalence between the to-be-marketed tablet strengths of levothyroxine sodium.

Design

The recommended study is a single-dose, three-treatment, six-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Tablet Strengths and Dose

Three strengths of tablets should be studied that represent the low, middle, and high strength of the formulations to be marketed. Generally, the middle strength studied is the 100 µg tablet. Multiples of each tablet strength are necessary for detection of T4 above baseline levels. The total dose given for each treatment in the study will usually be 600 µg.

Procedure

Following a 10-hour overnight fast, volunteers should be administered a single dose of levothyroxine sodium orally with 240 mL water. The treatments are as follows:

Treatment 1- Multiples of the representative low strength tablet.

Treatment 2- Multiples of the representative mid-strength tablet. This is normally the 100 µg tablet, and should be considered as the reference for this study.

Treatment 3- Multiples of the representative high strength tablet.

Volunteers should remain fasted for four hours after dosing, with water only allowed after the first hour. Volunteers should be served standardized meals according to the schedule throughout the study.

Blood Sampling

The blood sampling schedule for this study is identical to that recommended for the bioavailability study (Section III.B.1).

Data Analysis

Individual and mean plasma/serum concentration-time profiles of total (bound + free) T4 and T3 should be included in the report.

The pharmacokinetic parameters, including AUC_{0-t}, Cmax and Tmax, should be computed for both total T4 and T3. For the assessment of equivalence between dosage forms, the log-transformed AUC_{0-t} and Cmax data should be analyzed with ANOVA using SAS GLM procedure. The back-transformed means and 90% confidence intervals of the ratio of AUC_{0-t} and Cmax should be presented for each pairwise comparison. Dosage-form equivalence is demonstrated if the 90% confidence intervals

fall within the 80-125% range.

For both single-dose bioavailability and dosage-form equivalence study, the assessment of bioavailability should be based on the measurement of total (bound + free) T4 and total T3 levels. The determination of free T4 and T3 is not necessary. However, if sufficiently precise and accurate assays are available for free T4 and T3, these moieties may be measured as well. Statistical analyses of free T4 and T3 should then be performed, with the results used as supportive data. If free T4 and T3 are measured, the assays used should be based on the immuno-extraction ("two-step") method, rather than the labeled analog ("one-step") method. Levels of thyroid-stimulating hormone (TSH) should be measured as part of the volunteer screening process as well as post-study. These TSH data should be reported in the NDA.

DISSOLUTION

For each tablet strength to be marketed, multi-point dissolution studies should be performed on three production-sized batches using 12 tablets per batch. The time points to be used are 10, 20, 30, 45, 60, 80, 100, and 120 minutes, or until 80% of the labeled claim is dissolved, so that a complete profile may be obtained. Dissolution testing should include lots used in the bioavailability studies.

ASSAY VALIDATION

Assays used for both *in vivo* and *in vitro* studies should be reproducible, precise, accurate, specific, stable and linear. If commercial kits are used, they should be validated "in-house" at the analytical site where the assay for the study is performed. Please note that the validation data from the kit manufacturer alone is not acceptable.

FORMULATION

The composition of the formulation for each tablet strength of levothyroxine sodium to be marketed should be provided in the NDA submission.

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cc:
Archival NDA 21-301
HFD-510/Div. Files
HFD-510/S.McCort
HFD-510/Reviewers and Team Leaders
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