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March 12, 2003

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

CITIZEN PETITION

The undersigned submits this petition under § 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. §§ 10.25 and 10.30 to request the Commissioner of Food and Drugs to comply with the policies outlined in the Approved Drug Products With Therapeutic Equivalence Evaluations ("the Orange Book") and the July 2001 Guidance for levothyroxine sodium products. This petition is submitted on behalf of Jones Pharma Inc. ("Jones Pharma"), a wholly owned subsidiary of King Pharmaceuticals, Inc., 501 Fifth Street, Bristol, Tennessee 37620.

A. ACTION REQUESTED

Jones Pharma requests that the Commissioner of Food and Drugs:

(1) remove the designation in the Orange Book of any product other than UNITHROID® as a reference listed drug for levothyroxine sodium oral tablets;

(2) refuse to accept future Abbreviated New Drug Applications ("ANDA") or supplemental ANDAs that designate any product other than UNITHROID® as the reference listed drug unless the applicant has submitted and the FDA has granted the required petition; and

(3) refuse to approve any pending ANDAs or supplemental ANDAs that designate any product other than UNITHROID® as the reference listed drug unless and until the applicant submits and the FDA grants the required petition.

B. STATEMENT OF GROUNDS

1. Background

Levothyroxine is identical to a natural thyroid hormone produced by the body. Oral doses of levothyroxine are most commonly used to return thyroid hormone levels to normal in children and adults with hypothyroidism. Dosage of levothyroxine must be individualized for each patient based on results of regular blood tests.[1]

Since levothyroxine sodium drug products were first introduced before 1962, they were allowed to remain on the market without FDA approval. But on August 14, 1997, the FDA announced in the *Federal Register* that "orally administered drug products containing levothyroxine sodium [were] new drugs" and that "[m]anufacturers who wish[ed] to continue to market orally administered levothyroxine sodium products must submit new drug applications...."[2] Recognizing the medical necessity of these drugs, however, the FDA gave manufacturers four years to obtain approved applications. Thus, any manufacturer marketing a levothyroxine sodium product had to

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1 *See* FDA Talk Paper, "FDA Approves First NDA for Levothyroxine Sodium," August 22, 2000.

2 Prescription Drug Products; Levothyroxine Sodium, 62 Fed. Reg. 43,535 (August 14, 1997) (Exhibit 1).

obtain approval for that product by August 14, 2001.[3] Any levothyroxine sodium product marketed without approval after that date would be subject to regulatory action.

In anticipation of the August 14, 2001 compliance date, the FDA issued *Guidance for Industry, Levothyroxine Sodium Products, Enforcement of August 14, 2001 Compliance Date and Submission of New Applications* ("the July 2001 Guidance").[4] That Guidance noted that as of July 2001, only two orally administered levothyroxine sodium products had been approved by the FDA. First, Jerome Stevens Pharmaceuticals ("Jerome Stevens") received approval of its 505(b)(2) application for UNITHROID® on August 21, 2000. And on May 25, 2001, Jones Pharma received approval of its 505(b)(2) application for LEVOXYL®, having filed for regulatory approval within the original three year requirement.

The July 2001 Guidance also outlined the regulatory action that would be taken against the other manufacturers -- those who had failed to acquire an approved application by the August 14, 2001 compliance date. Noting that it would take time for millions of patients taking unapproved products to switch to UNITHROID® or LEVOXYL®, the FDA established a gradual "phase-out" period for unapproved products. Manufacturers of unapproved products with no pending application had to

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3 Originally, the FDA gave manufacturers three years to comply. A second notice in the *Federal Register*, however, added another year to the deadline. Prescription Drug Products; Levothyroxine Sodium; Extension of Compliance Date, 65 Fed. Reg. 24,488 (April 26, 2000) (Exhibit 2).

4 *Guidance for Industry, Levothyroxine Sodium Products, Enforcement of August 14, 2001 Compliance Date and Submission of New Applications*, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (July 2001) (Exhibit 3).

cease distribution on August 14, 2001. But manufacturers of unapproved products *with* a pending application only had to reduce distribution of their products gradually over a 2-year period, with all distribution ceasing on August 14, 2003. And if such a manufacturer received approval before that date, it could resume distribution without regard to the phase-out schedule.[5]

The July 2001 Guidance also addressed the procedure for filing ANDAs for levothyroxine sodium products after August 14, 2001. First, FDA policy dictated that only UNITHROID® would be designated as the reference listed drug for generic levothyroxine sodium products. Second, as stated in the Orange Book and reiterated in the July 2001 Guidance, a generic manufacturer could petition the FDA to file an ANDA based on an approved product other than UNITHROID®. Thus, as discussed below, an applicant seeking to designate any approved levothyroxine sodium product other than UNITHROID® as the reference listed drug should be required to seek such prior FDA permission by way of a Citizen Petition.

2. FDA Should Grant the Relief Requested by This Petition

The FDA should grant the relief requested by this petition for a number of reasons. First, the relief requested is appropriate under the specific policies established by the FDA for ANDAs submitted for levothyroxine sodium products. Second, the relief requested is appropriate under the procedures traditionally followed by the FDA for the

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[5] Upon information and belief, certain companies who are subject to the "phase-out" period have not complied with and are in violation of the July 2001 Guidance.

submission of ANDAs when multiple NDAs have been approved for a single drug product.

a. The Relief Requested Is Appropriate Under the Specific Policies Established by the FDA for ANDAs for Levothyroxine Sodium Products

The relief requested by this petition is appropriate under the specific procedures established by the FDA for ANDAs for levothyroxine sodium products submitted after August 14, 2001. In the July 2001 Guidance, the FDA explained the process that it was implementing for ANDAs for these products:

> A manufacturer who wishes to submit an application for [a levothyroxine sodium product] after August 14, 2001, should submit an abbreviated new drug application (ANDA). FDA has designated Unithroid as the reference listed drug to which ANDAs should refer. However, the Agency would accept a petition to designate a second reference listed drug.[6]

Thus, the July 2001 Guidance established a uniform but flexible policy for the submission of ANDAs for levothyroxine sodium products. UNITHROID® would be the only reference listed drug, and manufacturers who wished to file an ANDA based on some other approved levothyroxine sodium product could file a Citizen Petition requesting that it be allowed to reference that drug. Without explanation or forewarning, however, the FDA arbitrarily changed this policy.

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[6] *Guidance for Industry, Levothyroxine Sodium Products, Enforcement of August 14, 2001 Compliance Date and Submission of New Applications*, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (July 2001).

Contrary to the procedure outlined in the July 2001 Guidance, UNITHROID® is no longer the only reference listed drug for levothyroxine sodium products. Without explanation, the FDA has designated multiple products as reference listed drugs.[7] Furthermore, this action was taken without the submission of a Citizen Petition requesting such designation or the issuance of another Guidance by the FDA indicating a change in policy, thus apparently violating FDA's own publicly stated procedures with regard to the designation of Reference Listed Drugs. Thus, the policies to be applied to ANDAs for levothyroxine sodium products are once again unclear. The arbitrary actions taken by the FDA have left Jones Pharma, and presumably the rest of the levothyroxine sodium manufacturers, questioning the force of the July 2001 Guidance. Since changing its position on this matter and failing to require compliance with the July 2001 Guidance is arbitrary and capricious, the FDA should now take actions consistent with that Guidance and grant the relief requested by Jones Pharma.

b. The Relief Requested Is Appropriate Under the Procedures Traditionally Followed by the FDA for the Submission of ANDAs When Multiple NDAs Have Been Approved for a Single Drug Product

The relief requested by this petition is also appropriate under the procedures traditionally followed by the FDA for the submission of ANDAs when multiple NDAs have been approved for a single drug product. The Preface in the Orange Book states:

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[7] For example, LEVOXYL® is currently designated as a reference listed drug in its Orange Book listing. *See* Orange Book Listing for LEVOXYL® (Exhibit 4).

> By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs. However, in some instances when multiple NDAs are approved for a single drug product, a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug may be shielded from generic competition. A firm wishing to market a generic version of an NDA listed drug that is not designated as the reference listed may petition the Agency through the Citizen Petition procedure....[8]

Thus, the July 2001 Guidance was clearly based on a well-established policy outlined in the Orange Book. And the scenario contemplated in the Orange Book is exactly the situation that arose with levothyroxine sodium products. Multiple NDAs have been approved, some of which still carry a BX rating signifying that the data are insufficient to determine therapeutic equivalence.[9] Thus, as explained in the Orange Book, only one of these products should be designated as the reference listed drug, leaving the petition process available to generic manufacturers who wish to base their ANDAs on another approved product. The FDA has been attempting to bring order and

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8 Food and Drug Administration's Approved Drug Products With Therapeutic Equivalence Evaluations, Preface (22nd ed.) (Exhibit 5).

9 LEVOXYL®, for example, still carries a BX rating. *See* Orange Book Listing for LEVOXYL®.

to apply consistent standards to the levothyroxine sodium market for many years.[10] It should now follow its own policies that were developed to further that goal.

3. Conclusion

When the FDA designated products other than UNITHROID® as reference listed drugs, it abandoned not only the specific policies outlined in the July 2001 Guidance for levothyroxine sodium products, but also the traditional policies developed to address these circumstances. As stated in the Orange Book, these policies were developed to "avoid possible significant variations among generic drugs and their brand name counterpart" that could result "if generic drugs were compared to different reference listed drugs." Jones Pharma respectfully requests that the FDA take action to conform to these policies. First, the FDA should remove the designation of products other than UNITHROID® as reference listed drugs in the Orange Book. Second, the FDA should refuse to approve any pending ANDAs or supplemental ANDAs that designate products other than UNITHROID® as reference listed drugs unless and until the applicant submits and the FDA grants the required petition. And finally, the FDA should refuse to accept future ANDAs or supplemental ANDAs that

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[10] It should be noted that the bioequivalence criteria for levothyroxine sodium oral drug products outlined in *Guidance for Industry, Levothyroxine Sodium Tablets – In Vivo Pharmocokinetic and Bioavailability Studies and In Vitro Dissolution Testing*, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (December 2000) (Exhibit 6) have also been brought into question. A recent study sponsored by Abbott Laboratories has concluded that under the FDA's current guidelines, "products that differ by even more than 33% would also have a likelihood of being declared bioequivalent." Abbott Laboratories, Briefing Document for the Advisory Committee for Pharmaceutical Science Meeting of March 12-13, 2003 (Exhibit 7). The resolution of

designate products other than UNITHROID® as reference listed drugs unless an applicant has submitted and the FDA has granted the required petition.

C. ENVIRONMENTAL IMPACT

This petition is entitled to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

D. ECONOMIC IMPACT

Information regarding economic impact will be submitted on request.

E. CERTIFICATION

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

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these issues may also weigh on the determination of whether and to what extent FDA should allow multiple drug products to be designated as reference listed drugs.

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. I et al., "Stability Indicating High-Pressure Liquid Chromatographic Method for Quality Control of Sodium Liothyronine and Sodium Levothyroxine in Tablet Formulations," in "Hormone Drugs," edited by J L. 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

Proposed Project

Assessment of Exposure to Arsenic through Household Water—New—National Center for Environmental Health (NCEH). Arsenic is a naturally occurring element present in food and water as both inorganic and organic complexes. Epidemiologic evidence shows a strong link between ingestion of water containing inorganic arsenic and an increase in a wide variety of cancers (*e.g.*, bladder cancer). Consumption of contaminated food is the major source of arsenic exposure for the majority of United States citizens. There are some areas of the United States where elevated levels of arsenic in water occur with appreciable frequency. In such areas, ingestion of water can be the dominant source of arsenic exposure. Currently, the preferred method of treatment of private, domestic well water containing elevated levels of arsenic is point-of-use (POU) devices. The acceptability of bottled water and POU treatment systems as effective means of managing arsenic exposure is based on the assumption that other water exposures such as bathing, brushing of teeth, cooking, and occasional water consumption from other taps contribute relatively minor amounts to a person's total daily intake of arsenic.

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

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

Dated: April 20, 2000.

Charles W. Gollmar,

Acting Associate Director for Policy, Planning and Evaluation, Centers for Disease Control and Prevention (CDC)

[FR Doc. 00–10351 Filed 4–25–00; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

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

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

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

ACTION: Correction.

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

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

On page 10797, in the State of Colorado, in Denver County, in the local community column for the city of Denver, after the service areas numbered (1)–(4), the following service areas should be added in the city of Denver: "(5) the area bounded by 52nd Avenue on the North, Alameda Boulevard on the South, Broadway Avenue on the East and Sheridan Boulevard on the West." "(6) Beginning at north Broadway and 38th avenue, go east to Yosemite; Yosemite south to 11th Avenue, 11 Avenue west to Quebec; Quebec south to Hampden, Hampden west to Broadway; Broadway north to 35th Avenue." "(7) Beginning at north 54th Avenue and Peoria, go 54th east to Chambers; Chambers south to I–70, I–70 West to Peoria, Peoria north to 54th Avenue." These three areas (5) (6) and (7) are currently being served in the city of Denver in addition to service areas (1) through (4). These seven service areas in the city of Denver are not open to competition to new Early Head Start programs.

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

FOR FURTHER INFORMATION CONTACT: The ACYF Operations Center at 1–800–351–2293 or send an email to *ehs@lcgnet.com*. You can also contact Judith Jerald, Early Head Start, Head Start Bureau at (202) 205–8074.

Dated: April 20, 2000.

Patricia Montoya,

Commissioner, Administration on Children, Youth and Families.

[FR Doc. 00–10378 Filed 4–25–00; 8:45 am]

BILLING CODE 4184–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N–0314]

Prescription Drug Products; Levothyroxine Sodium; Extension of Compliance Date

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; extension of compliance date.

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

time to conduct studies and to prepare applications.

EFFECTIVE DATE: April 26, 2000.

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of August 14, 1997 (62 FR 43535), FDA announced that orally administered drug products containing levothyroxine sodium are new drugs and required manufacturers to have approved applications as a condition of marketing. The notice advised that manufacturers who were marketing levothyroxine sodium drug products on or before August 14, 1997, may continue to market their products until August 14, 2000.[1] The notice stated that a manufacturer who marketed a levothyroxine sodium drug product without an approved application after that date would be subject to regulatory action.

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

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

Dated: April 18, 2000.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 00–10322 Filed 4–25–00; 8:45 am]

BILLING CODE 4160–01–F

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Endocrinologic and Metabolic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

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

Name of Committee: Endocrinologic and Metabolic Drugs Advisory Committee.

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

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

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

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

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

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

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

Dated: April 17, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00–10321 Filed 4–25–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

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

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

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

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

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

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

Guidance for Industry

Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 2001
Procedural

Guidance for Industry

Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch (HFD-210)
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573

(Internet) http://www.fda.gov/cder/guidance/index/htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 2001
Procedural

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Guidance for Industry[1]

Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance discusses how FDA plans to exercise its enforcement discretion after August 14, 2001, with regard to levothyroxine sodium products that are marketed without approved applications. This guidance also answers certain frequently asked questions concerning the submission of applications for levothyroxine sodium products. It replaces the previously issued guidance *Levothyroxine Sodium, Questions and Answers* (February 2001).

II. BACKGROUND

On August 14, 1997, FDA announced in the *Federal Register* (62 FR 43535) that orally administered levothyroxine sodium drug products are new drugs. The notice stated that by August 14, 2000, manufacturers who wish to continue to market these products must obtain approved applications as required by section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR part 314. The notice stated that after August 14, 2000, any orally administered drug product containing levothyroxine sodium that is introduced or delivered for introduction into interstate commerce without an approved

[1] This guidance has been prepared by the Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

application will be subject to regulatory action, unless found by FDA to be not subject to the new drug requirements of the Act under a citizen petition submitted for that product.[2] On April 26, 2000, FDA issued a second *Federal Register* notice (65 FR 24488) extending the deadline for obtaining approved applications until August 14, 2001.

The Agency permitted orally administered levothyroxine sodium products to remain on the market during this period of time without approved new drug applications to give manufacturers time to conduct the required studies, prepare applications, and have them approved because FDA found that levothyroxine sodium products are medically necessary. FDA stated in the 1997 notice that levothyroxine sodium products are used to treat hypothyroidism, and no alternative drug is relied on by the medical community as an adequate substitute. FDA also stated that the permission to remain on the market without an approved application applies only to products marketed on or before the date of the August 14, 1997, notice.

As of June 2001, two orally administered levothyroxine sodium products have been approved by FDA. Unithroid, manufactured by Jerome Stevens Pharmaceuticals, was approved on August 21, 2000. Levoxyl, manufactured by Jones Pharma, was approved on May 25, 2001. These approved products have been evaluated by FDA and found to be safe and effective for their intended uses. FDA has not evaluated the safety and effectiveness of unapproved marketed products, but it has determined that no currently marketed unapproved orally administered levothyroxine sodium product is generally recognized as safe and effective (August 14, 1997 *Federal Register* notice, p. 43538).

Notwithstanding the fact that there are now two approved applications for orally administered levothyroxine sodium, FDA has determined that it will take time for the millions of patients taking unapproved products to switch to approved products, and for manufacturers of approved products to scale up their production and to introduce this increased production into the distribution chain.

To the maximum extent possible, FDA seeks to allow the initial evaluation by a physician regarding the switch to an approved product to occur within the context of a patient's normal visits.[3] Many patients are only seen every 6-12 months, and FDA would like to minimize the number of visits required outside of these routine appointments. In addition, it may take several months for other patients to make an initial appointment to be evaluated.

Therefore, in order for manufacturers of approved products to scale up their production and for patients and health care providers to make a reasonable transition from unapproved to approved products, FDA has decided to continue to exercise its enforcement discretion by establishing a gradual phase-out of unapproved products as described below.

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[2] FDA has not found any orally administered levothyroxine sodium drug products to be generally recognized as safe and effective in response to a citizen petition.

[3] In addition, several physician office visits over as much as 6 months to one year may be necessary to adjust optimally the dose of a new product.

III. DISTRIBUTION PHASE-DOWN

Manufacturers of orally administered levothyroxine sodium products with applications pending at the FDA on August 14, 2001, should reduce the distribution of these products as follows:

- By November 1, 2001, average monthly distribution in the preceding 2 ½ months should have been reduced to 95% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By February 1, 2002, average monthly distribution in the preceding 3 months should have been reduced to 90% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By May 1, 2002, average monthly distribution in the preceding 3 months should have been reduced to 80% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By August 1, 2002, average monthly distribution in the preceding 3 months should have been reduced to 60% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By November 1, 2002, average monthly distribution in the preceding 3 months should have been reduced to 45% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By February 1, 2003, average monthly distribution in the preceding 3 months should have been reduced to 30% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By May 1, 2003, average monthly distribution in the preceding 3 months should have been reduced to 15% of the average monthly distribution over the 6 months preceding August 1, 2001.
- By August 14, 2003, all distribution should cease.

Starting November 1, 2001, an applicant should submit quarterly amendments to its pending application certifying that the applicant has reduced average monthly distribution in accordance with the above phase-down schedule. Each certification should include a clear statement of the total amount of each strength of the product actually distributed in that quarter. The first certification should include clear and complete information on how the average monthly distribution over the 6 months preceding August 1, 2001, was determined. If FDA approves the application before August 14, 2003, the product may be distributed after the date of approval without regard to the phase-down schedule.

Manufacturers of levothyroxine sodium products who do not have an application approved or pending before the Agency on August 14, 2001, should cease distribution of their products immediately on August 14, 2001, or on any date thereafter that they do not have an application approved or pending with the Agency (e.g., if the application is withdrawn). If they do not cease distribution, they will be subject to regulatory action.

IV. BASIS FOR ENFORCEMENT ACTION

Orally administered levothyroxine sodium drug products are new drugs. Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) states: "No person may introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug." A manufacturer who introduces or delivers for introduction into interstate commerce an unapproved drug product is subject to injunction, prosecution, or seizure as authorized by sections 302, 303, and 304 of the Act (21 U.S.C. 332, 333, 334). Violation of an injunction could result in a contempt proceeding or such other penalties as a court may order (e.g., fines). However, FDA does not intend to take action for marketing without an approved application against a manufacturer of a levothyroxine sodium drug product who complies with the plan for phased reduction of distribution described in section III.

V. NEW APPLICATIONS

Until August 14, 2001, FDA will continue to accept 505(b)(2) applications for levothyroxine sodium products. After that time, FDA will exercise its authority under section 314.101(d)(9) to refuse to file a 505(b)(2) application submitted for a levothyroxine sodium product that is eligible for approval under section 505(j).[4] A manufacturer who wishes to submit an application for such a product after August 14, 2001, should submit an abbreviated new drug application (ANDA). FDA has designated Unithroid as the reference listed drug to which ANDAs should refer. However, the Agency would accept a petition to designate a second reference listed drug.

A. Patent Certification

All 505(b)(2) and 505 (j) applications are subject to the patent certification requirements at 21 CFR 314.50(i) and 314.94(a)(12). Now that NDAs have been approved and there is a listed drug, applications that have been submitted or filed, but not yet approved, may need to be amended to include a patent certification for any patent listed for the listed drug. If there are no patents listed for the listed drug (there were none at the time of the

[4] An applicant should submit a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted under section 505(j), because approval will require the review of clinical data. However, after August 14, 2001, section 505(b)(2) applications should not be submitted for duplicates of approved products that are eligible for approval under 505(j) (see 21 CFR 314.101(d)(9)).

issuance of this guidance), the applicant may only need to submit a statement, as described at 314.50(i)(1)(ii) and 314.94(a)(12)(ii), that there are no relevant patents.

B. User Fees

A 505(b)(2) application seeking approval for levothyroxine sodium as single agent therapy for thyroid-related disorders will not be assessed a user fee. A 505(b)(2) application for levothyroxine sodium seeking approval of an indication for a use different from that previously approved will be assessed a fee. An ANDA will not be assessed a user fee. For further information on user fees, see http://www.fda.gov/oc/pdufa.

C. Pediatric Studies

As of April 1, 1999, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment, unless such studies are waived or deferred (63 FR 66632; December 2, 1998, *the pediatric rule*). Applications for levothyroxine sodium are subject to the pediatric rule. Applicants should discuss with the Division of Metabolic and Endocrine Drug Products, or the Office of Generic Drugs if the application is submitted under 505(j), whether a pediatric assessment is needed for the levothyroxine sodium product proposed in the application, or whether a waiver would be appropriate.

D. Therapeutic Equivalence Ratings for Levothyroxine Sodium Products

At the time of the issuance of this guidance, there were two approved 505(b)(2) applications for levothyroxine sodium tablets. These two, and any 505(b)(2) applications approved in the future, will be listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) as BX-rated drug products for which the data are insufficient to determine therapeutic equivalence. To obtain a therapeutic equivalence rating other than BX for levothyroxine sodium tablets, an applicant should submit data comparing its product to a listed drug. If upon review of the data, the two products are determined by FDA to be bioequivalent, they would be AB-rated to each other in the Orange Book.

E. Manufacturing Issues

1. Stability Data

FDA recommends that 6 months' long-term stability data and 3 months' accelerated stability data be included when the application is submitted. Primary stability data should be generated according to guidance developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[5] Additional stability data may be submitted as an amendment during the review process, and an expiration date will be determined based on FDA review of the data submitted.

[5] *Q1A Stability Testing of New Drug Substances and Products* (September 1994).

2. Overages

The finished product should be formulated to be released at 100% of the labeled claim. Similarly, the primary stability studies submitted in support of the application should be performed with lots released for stability testing at 100% of the labeled claim. The proposed shelf life should not depend on the existence of a stability overage.

3. Dissolution Method

505(b)(2) applicants should consult with the Division of Metabolic and Endocrine Drug concerning dissolution testing. 505(j) applicants should consult with the Office of Generic Drugs.

Proprietary Name Search Results from "Rx" table for query on "levoxyl."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.025MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.05MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.075MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.088MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.112MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.125MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.137MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.15MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.175MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.1MG	LEVOXYL	JONES PHARMA
021301	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.2MG	LEVOXYL	JONES PHARMA
021301	BX	Yes	LEVOTHYROXINE SODIUM	Tablet; Oral	0.3MG	LEVOXYL	JONES PHARMA

Thank you for searching the Electronic Orange Book

Return to Electronic Orange Book Home Page

APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2001.

22ND EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATA MANAGEMENT AND SERVICES

2002

product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and Cmax) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

For statistical reasons, all data is log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90% confidence interval for each pharmacokinetic parameter (Cmax and AUC). The confidence interval for both pharmacokinetic parameters, AUC and Cmax, must be entirely within the 80% to 125% boundaries cited above. Because the mean of the study data lies in the center of the 90% confidence interval, the mean of the data is usually close to 100% (a test/reference ratio of 1). Different statistical criteria are sometimes used when bioequivalence is demonstrated through comparative clinical trials, pharmacodynamic studies, or comparative in-vitro methodology.

The bioequivalence methodology and criteria described above simultaneously control for both, differences in the average response between test and reference, as well as the precision with which the average response in the population is estimated. This precision depends on the within-subject (normal volunteer or patient) variability in the pharmacokinetic parameters (AUC and Cmax) of the two products and on the number of subjects in the study. The width of the 90% confidence interval is a reflection in part of the within-subject variability of the test and reference products in the bioequivalence study. A test product with no differences in the average response when compared to the reference might still fail to pass the bioequivalence criteria if the variability of one or both products is high and the bioequivalence study has insufficient statistical power (i.e., insufficient number of subjects). Likewise, a test product with low variability may pass the bioequivalence criteria, when there are somewhat larger differences in the average response.

This system of assessing bioequivalence of generic products assures that these substitutable products do not deviate substantially in in-vivo performance from the reference product. The Office of Generic Drugs has conducted two surveys to quantify the differences between generic and brand name products. The first survey included 224 bioequivalence studies submitted in approved applications during 1985 and 1986. The observed average differences between reference and generic products for AUC was 3.5% (JAMA, Sept. 4, 1987, Vol. 258, No. 9). The second survey included 127 bioequivalence studies submitted to the agency in 273 ANDAs approved in 1997. The three measures reviewed include $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and Cmax. The observed average differences between the reference and generic products were $\pm$ 3.47% (SD 2.84) for $AUC_{(0-t)}$, $\pm$ 3.25% (SD 2.97) for $AUC_{(0-inf)}$, and $\pm$ 4.29% (SD 3.72) for Cmax (JAMA, Dec. 1, 1999, Vol. 282, No. 21).

The primary concern from the regulatory point of view is the protection of the patient against approval of products that are not bioequivalent. The current practice of carrying out two one-sided tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved.

1.4 Reference Listed Drug

A reference listed drug (21 CFR 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

FDA has identified in the Prescription Drug Product and OTC Drug Product Lists those reference listed drugs to which the *in vivo* bioequivalence and, in some instances, the *in vitro* bioequivalence of the applicant's product is compared. By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs. However, in some instances when multiple NDAs are approved for a single drug product, a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug may be shielded from generic competition. A firm wishing to market a generic version of an NDA listed drug that is not designated as the

reference listed may petition the Agency through the Citizen Petition procedure (see 21 CFR 10.25(a) and CFR 10.30). When the Citizen Petition is approved, the second NDA will be designated as an additional reference listed drug and the petitioner may submit an Abbreviated New Drug Application citing the designated reference listed drug. Section 1.7, *Therapeutic Equivalence Evaluations Codes — Products meeting necessary bioequivalence requirements* explains the ***(AB, AB1, AB2, AB3...*** coding system for multisource drug products listed under the same heading with two reference listed drugs.

In addition, there are two situations in which two listed drugs that have been shown to be bioequivalent to each other may both be designated as reference listed drugs. The first situation occurs when the *in vivo* determination of bioequivalence is self-evident and a waiver of the *in vivo* bioequivalence may be granted. The second situation occurs when the bioequivalence of two NDA drug products may be determined through *in vitro* methodology. The reference listed drug is identified by the symbol "+" in the Prescription and Over-the Counter (OTC) Drug Product Lists. These identified reference listed drugs represent the best judgment of the Division of Bioequivalence at this time. The Prescription and OTC Drug Product Lists identify reference drugs for oral dosage forms, injectables, ophthalmics, otics, and topical products. It is recommended that a firm planning to conduct an *in vivo* bioequivalence study, or planning to manufacture a batch of a drug product for which an *in vivo* waiver of bioequivalence will be requested, contact the Division of Bioequivalence, Office of Generic Drugs, to confirm the appropriate reference listed drug.

Acyclovir 200MG Tablet-Reference Listed. Novopharm's single source acyclovir tablets have been declared to be a reference listed drug for the 200 mg tablet in addition to the acylcovir (Zovirax) 800 mg tablet of the innovator. A generic firm wishing to submit an ANDA for a duplicate of the 200 mg acyclovir tablet will be eligible for a waiver of the *in vivo* determination of bioequivalence (1) if their product is proportionally similar in its active and inactive ingredients to their own 800 mg acyclovir tablet and (2) by doing an acceptable comparative dissolution test (dissolution profile) against Novopharm's 200 mg acyclovir reference listed drug.

Before a waiver of the *in vivo* determination of bioequivalence can be granted for the 200 mg acyclovir tablet, the generic firm must have completed an acceptable fasting and fed study comparing their acyclovir 800 mg tablet against the Zovirax 800 mg tablet.

For further information on the study designs, you should contact the Division of Bioequivalence, Office of Generic Drugs.

1.5 General Policies and Legal Status

The List contains public information and advice. It does not mandate the drug products which may be purchased, prescribed, dispensed, or substituted for one another, nor does it, conversely, mandate the products that should be avoided. To the extent that the List sets forth FDA's evaluations of the therapeutic equivalence of drug products that have been approved, it contains FDA's advice to the public, to practitioners and to the states regarding drug product selection. These evaluations do not constitute determinations that any product is in violation of the Act or that any product is preferable to any other. Therapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, intended to reduce the cost of drugs to consumers. To the extent that the List identifies drug products approved under Section 505 of the Act, it sets forth information that the Agency is required to publish and that the public is entitled to under the Freedom of Information Act. Exclusion of a drug product from the List does not necessarily mean that the drug product is either in violation of Section 505 of the Act, or that such a product is not safe or effective, or that such a product is not therapeutically equivalent to other drug products. Rather, the exclusion is based on the fact that FDA has not evaluated the safety, effectiveness, and quality of the drug product.

Guidance for Industry

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

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

December 2000
Clinical Medical

Guidance for Industry

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

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GUIDANCE FOR INDUSTRY[1]

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) for levothyroxine sodium tablets who wish to conduct in vivo pharmacokinetic and bioavailability studies and in vitro dissolution testing for their products. Information from these studies would generally be submitted in section 6 of an NDA. Sponsors who wish to use approaches other than those recommended in this guidance should discuss their plans with the FDA prior to preparing an NDA.

II. BACKGROUND

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine. 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.

The production of levothyroxine hormone is regulated by the hypothalamus-pituitary axis through a negative feedback system. When hormone levels are inadequate, the hypothalamus secretes thyroid stimulating hormone-releasing hormone (TSH-RH), which stimulates the anterior pituitary to produce thyroid stimulating-hormone (TSH). TSH then stimulates the thyroid gland to produce levothyroxine

[1] This guidance has been prepared by the Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics, which operates under the direction of the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). The guidance has also been reviewed by the Guidances Technical Committee of the Biopharmaceutics Coordinating Committee, as well as the Division of Metabolic and Endocrine Drug Products in CDER.

(T_4) and triiodothyronine (T_3). T_4 is subsequently converted to the highly active T_3 in the peripheral tissues. High levels of T_4 inhibit the production of TSH and (to a lesser degree) TSH-RH. This effect in turn decreases the further production of T_4 (Farwell 1996).

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.

Levothyroxine sodium is a compound with a narrow therapeutic range. If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on another product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestation of hyperthyroidism such as cardiac pain, palpitation, or cardiac arrhythmia. 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 (Paul et al. 1988). To minimize the risk of osteoporosis, it is advisable that levothyroxine sodium be titrated to the lowest effective dose. Because of the risks associated with over- or under-treatment with levothyroxine sodium, it is critical that patients have available to them products that are consistent in potency and bioavailability.

It is a challenge to determine the bioavailability of levothyroxine sodium products because levothyroxine is naturally present in minute quantities in the blood, with the total levels reaching 5.0-12.0 μg/dl and free (or unbound) levels reaching 0.8-2.7 ng/dl in a healthy adult. To assess the bioavailability of levothyroxine sodium after a single dose, several times the normal dose should be given to raise the levels of the drug significantly above baseline to allow measurement. Furthermore, levothyroxine has a long half-life of 6 to 9 days, and therefore, a long washout period is necessary between treatments.

III. PHARMACOKINETIC AND BIOAVAILABILITY STUDIES IN VIVO

Information on the pharmacokinetics (absorption, distribution, metabolism, and excretion) of levothyroxine sodium can 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 marketing, the submission should contain information identifying how those formulations differ from the to-be-marketed formulation.

For sponsors who have a product on the market, we recommend that in vivo bioavailability studies be conducted using the formulation(s) already on the market, assuming that the 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. Stability evaluations should 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 on the market, the usual approaches to developing pilot-scale batches for bioavailability studies apply.[2]

A. Inclusion Criteria

For each pharmacokinetic and bioavailability study outlined below, at least 24 volunteers should complete the trial. The subjects should be healthy volunteers, 18 to 50 years of age and within 15 percent of ideal body weight for their height and build. Sponsors should attempt to enroll an equal number of men and women, if possible. 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 sodium 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 should be obtained from all volunteers before they are accepted into the study.

B. 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.

Tablet Strength and Dose: A multiple of the highest tablet strength to achieve a total dose of 600 μg should be given to detect T_4 above baseline levels.

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 strength of levothyroxine sodium tablets to be marketed.

Treatment 2: Levothyroxine sodium as an oral solution at an equivalent dose with treatment 1. The intravenous formulation can be used as a convenient source of an oral levothyroxine solution.

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[2] See *Q1A Stability Testing of New Drug Substances and Products* (59 FR 48754, September 1994).

Volunteers should remain fasted for 4 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 -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) T_4 and T_3 should be included in the report. The plasma/serum profiles and pharmacokinetic measures should be presented without the adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study. The following pharmacokinetic measures 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 (C_{max})
- Time to peak concentration (T_{max})

Analysis of variance (ANOVA) should be performed for both log-transformed AUC_{0-t} and C_{max} using the SAS General Linear Models (GLM) procedure. The oral solution should be used as the reference formulation. The geometric means and 90 percent confidence intervals of the geometric mean ratio (test/reference) in AUC_{0-t} and C_{max} should be presented as evidence of bioavailability.

C. Dosage-Form Proportionality Study

Objective: To determine the dosage-form proportionality among the to-be-marketed tablet strengths of levothyroxine sodium.[3]

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. A multiple of each tablet strength should be given to detect T_4 above baseline levels. The total dose given for each treatment in the study will usually be 600 µg and should be the same dose for each treatment.

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[3] Available strengths of levothyroxine sodium tablets from many manufacturers include 25, 50, 75, 88, 100, 112, 125, 137, 150, 200 and 300 µg.

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

Treatment 1: Multiples of the representative low strength tablets (usually 50 μg).

Treatment 2: Multiples of the representative mid-strength tablets. 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 tablets (usually 300 μg).

Volunteers should fast for an additional 4 hours after dosing, with only water allowed after the first hour. Volunteers should be served standardized meals throughout the study according to the schedule.

Blood Sampling: The blood sampling schedule for this study should be identical to that recommended for the bioavailability study.

Data Analysis: Individual and mean plasma/serum concentration-time profiles of total (bound + free) T_4 and T_3 should be included in the report. The plasma/serum profiles and pharmacokinetic measures should be presented without adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study.

The pharmacokinetic measures, including AUC_{0-t}, C_{max} and T_{max}, should be computed for both total T_4 and T_3. For the assessment of proportionality between strengths, both log-transformed AUC_{0-t} and C_{max} should be analyzed with ANOVA using the SAS GLM procedure. The geometric means and 90 percent confidence intervals of the geometric mean ratio of AUC_{0-t} and C_{max} should be presented for each pairwise comparison. Dosage-form proportionality is demonstrated if the 90 percent confidence intervals fall within the 80-125 percent range.

For both single-dose bioavailability and dosage-form proportionality studies, the assessment of bioavailability should be based on the measurement of total (bound + free) T_4 and total T_3 levels. The determination of free T_4 and T_3 is not necessary. However, if sufficiently precise and accurate assays are available for free T_4 and T_3, these moieties can be measured as well. Statistical analyses of free T_4 and T_3 should then be performed, with the results used as supportive data. If free T_4 and T_3 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 TSH should be measured as part of the volunteer-screening process as well as post-study examination. These TSH data should be reported in the NDA.

IV. DISSOLUTION TESTING IN VITRO

Dissolution studies can be performed using an appropriate method developed by a sponsor[4] or the current USP method. 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 used should be 10, 20, 30, 45, 60, 80, 100, and 120 minutes, or until 80 percent of the labeled claim is dissolved, so that a complete profile may be obtained. Dissolution testing should include lots used in the bioavailability studies.

V. FORMULATION

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

VI. BIOWAIVER

For tablet strengths not studied in the dosage-form proportionality study (see section III. C), the sponsor should request biowaivers and provide appropriate formulation information as well as in vitro dissolution data as covered under 21 CFR 320.22(d)(2). Specifically, all of the following conditions should be met:

1. The dosage-form proportionality study among the to-be-marketed tablet strengths of levothyroxine sodium (low, medium, and high strengths) has been found acceptable, and proportionality has been shown among the strengths included in the study (also see section III. C. *Data Analysis).*

2. For tablet strengths to be covered under the waiver request, they should differ only in the amount of levothyroxine sodium and filler needed to maintain the tablet weights.

3. Multi-point dissolution profiles are similar across tablet strengths using an f2 test. If both test and reference products dissolve 85 percent or more of the label amount of the drug in $\leq$ 15 minutes, the f2 test is not necessary.[4] The dissolution method as well as dissolution data have been found acceptable by the Agency.

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

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[4] See FDA's guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).

VII. ASSAY VALIDATION

Assays used for both in vivo and in vitro studies should be fully validated, 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 insufficient.

REFERENCES

Farwell A. P., and L. E. Braverma, 1996, "Thyroid and Antithyroid Drugs," *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*, 9th ed. pp. 1383-1409, McGraw-Hill.

Paul T. L., J. Kerrigan, A. M. Kelly et al., 1988, "Long-term Thyroxine Therapy Is Associated with Decreased Hip Bone Density in Premenopausal Women," *JAMA*, vol. 259, pp. 3137-3141.

Advisory Committee for Pharmaceutical Science

Briefing Document

Levothyroxine Bioequivalence

Advisory Committee Meeting – 12-13 March 2003

THIS DOCUMENT CONTAINS FULLY RELEASABLE INFORMATION

Abbott Laboratories

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1.0 Executive Summary

The purpose of this document, and Abbott's participation in the March 13, 2003 Pharmaceutical Science Advisory Committee meeting, is to identify and discuss scientific issues related to the bioequivalence assessment criteria of levothyroxine sodium (LT_4) products.

Levothyroxine or thyroxine (T_4) is an endogenous hormone secreted from the thyroid gland and is subject to complex biologic regulation. As such, it has characteristics different from drugs for which there are no endogenous levels. Exogenously administered LT_4 hormone is indistinguishable from endogenously secreted T_4, both in its physiologic effects and its quantification as measured in blood. The current FDA guidance for assessment of bioequivalence of administered LT_4 products does not take into account the contribution of endogenous T_4. The presence of endogenous T_4 and its dynamic regulation confound the assessment of bioequivalence of LT_4 products in healthy normal subjects, and consequently, preclude any conclusions about their therapeutic substitution in patients.

We describe a recent study conducted by Abbott Laboratories that highlights these issues with the current FDA Guidance for assessing bioequivalence of LT_4 products. The study demonstrates that, following the current FDA criterion for levothyroxine sodium products, the use of T_4 pharmacokinetic parameters uncorrected for endogenous T_4 would result in declaring two products bioequivalent when they actually differ in drug content by as much as 33%. Considering the margin by which the conditions for declaring bioequivalence were passed in this study, products that differ by even more than 33% would also have a high likelihood of being declared bioequivalent. Three methods of correction for endogenous T_4 levels were evaluated, but none of the methods could discern products that differ by 12.5%; dosage changes of such magnitude are clinically important.

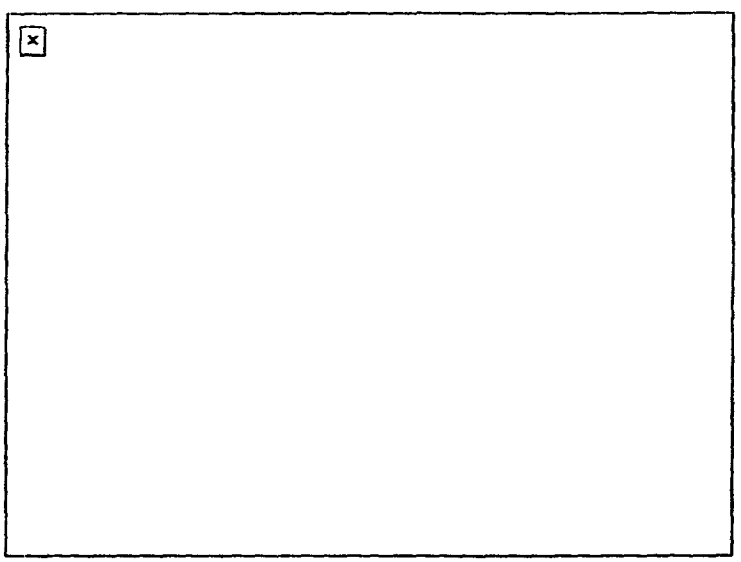
The clinical relevance of a 12.5% difference in dose is substantiated by product labeling, standard medical management of thyroid patients, and data from clinical studies. In class labeling for all LT_4 products, it is recommended that titration be done in 12.5 to 25 μg increments for elderly patients with cardiac disease; who represent a significant number of the 13 million LT_4-treated patients in the U.S. In fact, the FDA has explicitly recognized the clinical relevance of these dosage increments particularly with respect to patient safety. In addition, physicians employ a large number of dosage strengths to effectively titrate patients to normal thyroid status, which generally requires a dose between 100 and 150 μg. In this dose titration process, 12-13 μg is the second most commonly used dose increment or decrement. Finally, mildly abnormal thyroid function, which may result from slight under- or over-dosing, has been demonstrated in clinical studies to have adverse effects on fetal development, lipids, and cardiovascular disease. For patients with thyroid cancer there is an extra concern, in that slight under-treatment increases the risk of cancer recurrence and metastatic disease.

Careful consideration should be given to developing a specific guidance for the assessment of bioequivalence of levothyroxine sodium products. This guidance must adequately consider the unique

nature of the thyroid hormone system and the demonstrated limitations of the current guidance not adequately remedied by simple methods for baseline correction.

2.0 Thyroid Biology

Thyroxine (T_4) is an endogenous molecule that is synthesized and released from the thyroid gland in response to thyrotropin or thyroid-stimulating hormone (TSH) (Figure 1). T_4 is a "pro-hormone" that is converted via deiodination in tissues to triiodothyronine (T_3), the most biologically potent form of thyroid hormone. Thyroid hormones (T_4 and T_3) 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 cardiac stimulatory effect that may be the result of a direct action on the heart. Thyroid hormones, T_4 and T_3, are specifically bound by three different plasma transport proteins, each with its specific affinity and capacity for T_4 and T_3. T_3 controls the transcription of numerous genes that are vital to growth and development. With thyroid hormone receptors in virtually every tissue in the body, thyroid hormone affects, via control of specific genes, proper brain development (myelin basic protein gene) and growth (growth hormone gene), and muscle function (myosin heavy chain gene, sarcoplasmic reticulum ATPase gene) and cholesterol levels (LDL-receptor gene). [1, 2]



The thyroid hormone system is under the tight feedback regulation by the hypothalamic-pituitary axis, which senses the levels of T_3 and T_4, and modulates the release of hypothalamic thyrotropin-releasing hormone (TRH) and pituitary TSH (Figure 1).

Figure 1. Basic Schematic of the Thyroid Hormone System

The pituitary is the key "biosensor" in the feedback loop, with the magnitude of TSH release controlled primarily by blood levels of T_4 and T_3 and some "fine-tuning"contributed by the TRH level. Figure 2

demonstrates the inverse relationship between TSH and free T_4 levels, as observed in over 500 ambulatory subjects. [3]

Linear regression analysis of the data points demonstrates that, for every 2-fold change in free T_4, the TSH level will change 100-fold (refer to triangle on the graph). Thus, TSH is considered to be the most sensitive measure of thyroid function, and is used clinically for the diagnosis and monitoring of thyroid patients. In fact, the diagnosis of hypo- or hyperthyroidism rests on the finding of an abnormal TSH, which is more sensitive than an abnormal T_4. Furthermore, titration of LT_4 dosage is performed by monitoring TSH levels, and a euthyroid state is considered achieved when TSH levels move to within the normal range (see Section 4.1).

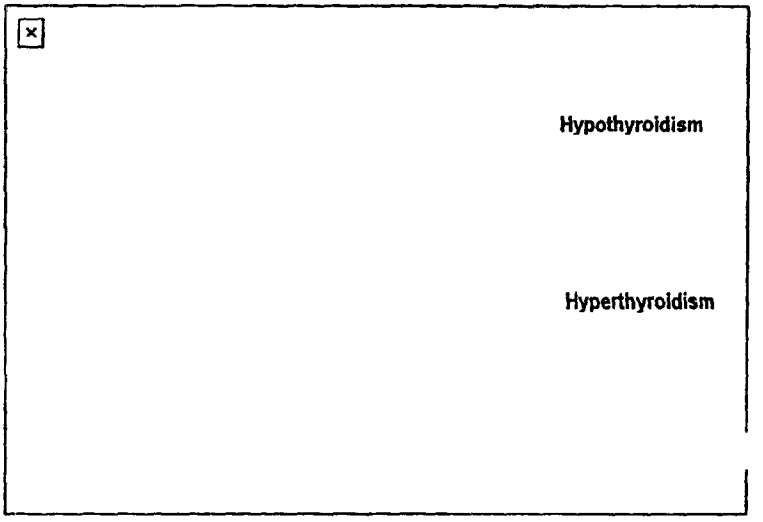


Figure 2. The Relationship Between Serum TSH And Free T_4 Concentrations in Individuals With Stable Thyroid Status and Normal Hypothalamic-Pituitary Function.

In summary, thyroid hormones are produced by the thyroid gland and regulated by a complex control system such that, in healthy subjects with normal thyroid function (euthyroid), T_4 and T_3 are tightly controlled within narrow ranges.

3.0 Assessment of the Current Guidance for LT_4 Bioequivalence

3.1 Background and rationale for M02-417 study

Evaluation of the pharmacokinetic curves generated for the NDA filings of LT_4 products led Abbott to question the sensitivity of bioavailability studies done in healthy volunteers with no adjustment made for the endogenous baseline concentrations of T_4. We hypothesized that given the magnitude of the endogenous T_4 measured at baseline, LT_4 products with large differences in bioavailability could be declared bioequivalent if this method were used. The current FDA bioequivalence methodology is to evaluate pharmacokinetic (PK) parameters using healthy volunteers, comparing 600 µg of the test

compound to 600 µg of the reference compound in a crossover study, without correction for endogenous T_4 baseline level.[4] Abbott conducted a "bioequivalence" study in healthy volunteers using known dosages of a single formulation of LT_4 (Synthroid®) to test the sensitivity of the current FDA Guidance. We evaluated if the current methodology was able to differentiate two known lower dosages (400 and 450 µg) from the reference dose of 600 µg. We went on to evaluate the impact of various methods of correcting for endogenous T_4 baseline on the bioequivalence assessment in this study.

3.2 Results of M02-417 study

Results for bioequivalence assessment are presented below for 400 µg *versus* 600 µg, 450 µg *versus* 600µg, and 450 µg *versus* 400 µg, using PK parameters uncorrected for baseline T_4 levels and corrected for baseline T_4 levels are listed below.

3.2.1 T_4 without correcting for endogenous T_4 baseline concentrations

The relative bioavailabilities for the 450 µg and 400 µg doses as compared to the reference dose of 600 µg, using PK parameters (C_{max} and AUC_{48}) of T_4 without correction of the baseline are listed in Table 1. In addition, the relative bioavailability of 450 µg compared to the 400 µg is listed.

Table 1. Bioequivalence and Relative Bioavailability–Uncorrected Levothyroxine (T_4)

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value* Test	Central Value* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
450 µg *vs.*600 µg	C_{max}	13.0	14.0	0.928	0.890 – 0.968
	AUC_{48}	481.7	504.8	0.954	0.927 – 0.982
400 µg *vs.* 600 µg	C_{max}	12.9	14.0	0.921	0.883 – 0.960
	AUC_{48}	469.6	504.8	0.930	0.904 – 0.958
450 µg *vs.* 400 µg	C_{max}	13.0	12.9	1.007	0.967 – 1.050
	AUC_{48}	481.7	469.6	1.026	0.997 – 1.055

* Antilogarithm of the least squares means for logarithms.

\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Bioequivalence is concluded for each of the comparator pairs (450 µg *versus* 600 µg; 400 µg *versus* 600 µg and 450 µg *versus* 400 µg) because the 90% confidence intervals from the analyses of the natural logarithms of C_{max} and AUC_{48} are within the 0.80 to 1.25 range.

3.2.2 T_4 after correction for endogenous T_4 baseline concentrations

Three methods of correction were evaluated. These three methods are defined in Appendix A, Criteria for Evaluation. The relative bioavailabilities for the 450 µg and 400 µg doses as compared to the reference dose of 600 µg, using PK parameters (C_{max} and AUC_{48}) of T_4 with correction of the baseline (Correction Method 3) are listed in Table 2. The relative bioavailability of 450 µg compared to the 400

µg is also listed.

Results using Correction Method 3 are listed here because the point estimates for relative bioavailability as defined by AUC_{48} were generally further from unity than were the point estimates for that parameter using Corrections Method 1 and 2. The results using the other correction methods are listed in the expanded summary of the M02-417 study (see Appendix A for details). The determination for bioequivalence did not differ, no matter which correction method was used.

Table 2. Bioequivalence and Relative Bioavailability for T_4 (Correction Method 3)

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate+	90% Confidence Interval
450 µg *vs.* 600 µg	C_{max}	5.7	6.9	0.820	0.757 – 0.888
	AUC_{48}	125.1	172.9	0.723	0.672 – 0.779
400 µg *vs.* 600 µg	C_{max}	5.3	6.9	0.775	0.715 – 0.839
	AUC_{48}	115.4	172.9	0.667	0.620 – 0.718
450 µg *vs.* 400 µg	C_{max}	5.7	5.3	1.058	0.979 – 1.145
	AUC_{48}	125.1	115.4	1.084	1.008 – 1.165

* Antilogarithm of the least squares means for logarithms.
\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

These analyses indicate that the use of baseline corrected T_4 pharmacokinetic parameters allow 400 and 450 µg to be differentiated from 600 µg. However, analyses using these simple methods of correction, each method limited by its inherent assumptions, failed to distinguish 450 µg from 400 µg.

3.2.3 Other observations

Analysis of the T_4 concentration data obtained during the 24 hours prior to the administration of the PK dose for each period confirmed that T_4 has a diurnal cycle. Likewise, the serum concentrations of TSH showed a clear diurnal variation for Study Day –1 of each period. Administration of all three doses had homeostatic effects, but did not completely suppress the serum TSH concentration during the 24 hours following the PK dose. Analyses of the AUC_{24} for Study Day –1 revealed that the regimens (dose levels) had statistically significant different carryover effects from one period to the next (first-order carryover) and from Period 1 to Period 3 (second-order carryover).

3.3 Conclusions from M02-417 study

First, the results indicate that the use of baseline uncorrected T_4 pharmacokinetic parameters would result in declaring two products bioequivalent when they actually differ by as much as 25% to 33% (450 µg and 400 µg *versus* 600 µg). Considering the margin by which the conditions for declaring bioequivalence were passed in this study, products that differ by even more than 33% would also have a high likelihood of being declared bioequivalent products, stemming from the significant and complex contribution of endogenous T_4.

Second, the results from this study indicate that the use of baseline corrected T4 pharmacokinetic parameters would reduce the likelihood that two products would be declared bioequivalent when they actually differ by 25% to 33%. However, analyses using three simple methods of correction, each method limited by its inherent assumptions, failed to distinguish 450 µg from 400 µg. This is a 12.5% difference which, when applied to the range of doses typically used in clinical practice, is a clinically significant difference, as reflected in product labeling, clinical usage, and data from clinical studies. Furthermore, it is apparent that simple methods of correction for endogenous T_4 concentrations in healthy volunteers are inadequate since these concentrations not only fluctuate on a diurnal cycle but may also be differentially affected by products with different rates and extents of absorption. Additionally, there is evidence of significant carryover from one dosing period to subsequent periods even with washout periods up to 53 days.

This study illustrates important flaws in the design and analysis of single-dose crossover studies in healthy volunteers to assess bioequivalence of LT_4 products, stemming from the significant and complex homeostatic mechanisms associated with administration of supraphysiologic doses of LT_4. We now know that better characterization of and correction for endogenous T_4 is required to provide proper interpretation of results in healthy volunteer studies. Alternative approaches to account for endogenous T_4 need to be identified and investigated. A change to the current FDA criterion beyond adding a simple correction for baseline T_4 is necessary.

4.0 LT_4 Therapy and the Clinical Consequences of Under- or Over-Treatment

Levothyroxine sodium is the treatment of choice as replacement or supplemental hormone therapy, or to suppress pituitary TSH in the treatment of thyroid carcinomas and nodules. According to the DOSAGE AND ADMINISTRATION section in the product labels for all levothyroxine sodium products, [5-7] "The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state. The goal of suppressive therapy is to inhibit growth and/or function of abnormal thyroid tissues." The fundamental guiding principle of therapy is the maintenance of TSH in the desired range by individual titration of LT_4 dose.

4.1 TSH is the measurement of adequacy of treatment

Professional societies and product labels state that TSH is the biochemical endpoint to determine the thyroid hormone status. [5-10] The recommended management (under LABORATORY TESTS) is as follows: "The diagnosis of hypothyroidism is confirmed by measuring TSH levels using a sensitive assay....and measurement of free-T_4. The adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation."

The labels recommend testing in ADULTS, as follows: "The frequency of TSH monitoring during

levothyroxine dose titration depends on the clinical situation but it is generally recommended at 6-8 week intervals until normalization. For patients who have recently initiated levothyroxine therapy and whose serum TSH has normalized or in patients who have had their dosage or brand of levothyroxine changed, the serum TSH concentration should be measured after 8-12 weeks. When optimum replacement dose has been attained, clinical (physical examination) and biochemical monitoring may be performed every 6-12 months, depending on the clinical situation, and whenever there is a change in the patient's status. It is recommended that a physical examination and a serum TSH measurement be performed at least annually..." [5-7]

The product labels and professional societies recognize the importance of using TSH measurements as the endpoint for evaluating the biochemical thyroid status. They state that once the patient is stabilized on an LT_4 dose, periodic assessment needs only be done every six to twelve months. [5-8, 10]

4.2 LT_4 therapy is individualized and carefully titrated

Treatment with LT_4 products is individualized for each patient, based on their underlying thyroid status, age, and presence or absence of other clinical conditions, particularly their cardiac function. With the exception of young healthy thyroid patients, the treated hypothyroid population is initiated with a low LT_4 dose and titration of the dose is done in small increments until they are able to achieve their euthyroid state. Thyroid cancer patients are carefully titrated to keep their TSH levels in the marginally hyperthyroid range. Recalling the inverse log-linear relationship of TSH to T_4 levels, titration to the marginally hyperthyroid state can require small dose increments.

In recognition of the narrow therapeutic window for serum T_4 and TSH, and the log-linear relationship between TSH and T_4 levels, professional societies and the product labels recommend that careful monitoring and titration be done when instituting LT_4 therapy. [5-8, 10] Because of the cardiac and cardiovascular consequences of rapid replacement or over-replacement, definitive recommendations are provided for special patient populations. Under DOSAGE AND ADMINISTRATION – SPECIAL PATIENT POPULATIONS the product label recommends "For most patients older than 50 years of age or for patients under 50 years of age with underlying cardiac disease, an initial starting dose of **25-50 mcg/day** of levothyroxine sodium is recommended, with gradual increments in dose at 6-8 week intervals, as needed. The recommended starting dose for elderly patients with cardiac disease is **12.5-25 mcg/day**, with gradual dose increments at 4-6 week intervals. The levothyroxine sodium dose is generally adjusted in 12.5-25 mcg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized." [5-7]

The medical literature on which FDA based its decision to approve oral levothyroxine tablets uniformly emphasizes the clinical need for fine dosing increments. As FDA stated in its review of Unithroid, "a 25 mcg dosage strength that meets chemistry and biopharm criteria for approval, is essential for proper labeling of the product for safe and effective use given that in certain clinical situations, levothyroxine sodium dosing is initiated at 12.5-25 mcg/day and increased in 12.5-25 mcg dosing increments." [11]

4.3 Fine-dosing increments – importance and medical use

The FDA recognizes that multiple dose strengths are required to accomplish adequate treatment of the thyroid patient population. The FDA, in a final agency decision regarding the regulatory status of Synthroid®, emphasized that PATIENTS NEED A PRECISE DOSE OF LEVOTHYROXINE SODIUM. "The dosage of replacement therapy is increased in gradual increments until the TSH test indicates the correct maintenance dosage has been achieved. In order to allow for fine adjustments of dose, which are necessary due to levothyroxine sodium's narrow therapeutic range, levothyroxine sodium products are marketed in an unusually large number of dosage strengths. Synthroid®, for example, comes in 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg strengths." [12]

Market research demonstrates that 1 in 5 dosage changes is an increase or decrease by 12 or 13 µg.

The impact on thyroid hormone status of small deviations from an optimally titrated dose is demonstrated in a prospective, longitudinal study by Carr et al. Twenty-one patients on LT_4 replacement therapy for hypothyroidism were studied while taking the dose that produced a normal TSH response, and then the patients were restudied at lower and/or higher doses (Figure 3). [14] Dosage changes of as little as 25 µg rendered the patients either hypothyroid or hyperthyroid, dependent upon the direction of the dose change from the dose that maintained them in a euthyroid state.

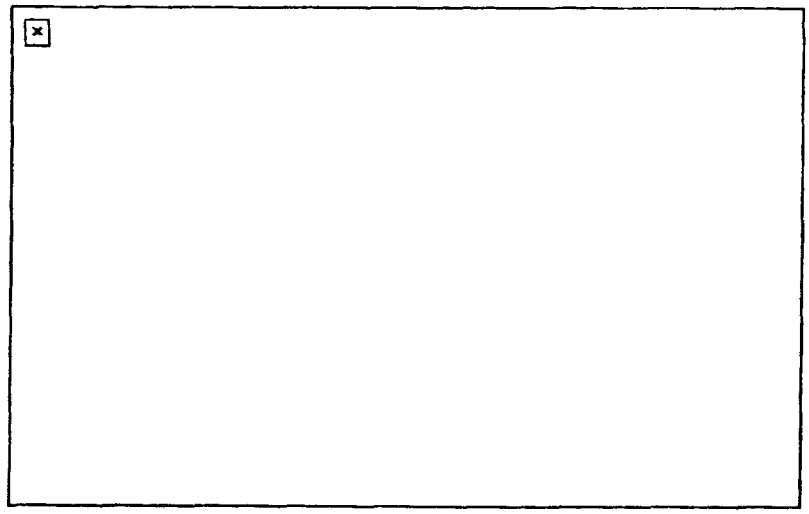


Figure 3. Resultant TSH levels With Incremental 25 µg Changes in LT_4 Dosage

Applying the inverse log-linear relationship of serum TSH to T_4 levels, these data would predict that dose changes that were half those studied in the Carr study would also render some, if not all, of the patients outside of the normal TSH range (0.4 to 4.0 mIU/L).

The ability to carefully titrate and maintain patients in the desired thyroid state is of paramount importance. The FDA acknowledged the same goals when approving the class labeling for all LT_4 products. In the product labels under PRECAUTIONS it states, "Levothyroxine has a narrow

therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under-treatment. These consequences include, among others, effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism."

4.4 Clinical consequences of hypothyroidism and hyperthyroidism

4.4.1 Patient populations treated with LT_4 products

Functional thyroid disease can manifest as either over- or under-active thyroid hormone status. [15, 16] In either case, there is a wide spectrum of the clinical expression of the disease from mild to severe. However, the clinical consequences of each are more severe the further the thyroid function has deviated from normal, i.e., severe thyrotoxicosis (severe hyperthyroidism) and myxedema coma (severe hypothyroidism). Significant clinical consequences also occur with milder forms of the disease ("subclinical" thyroid disease) as may be seen when the patient is not treated to reach and maintain the euthyroid state. In a large health screening study of 25,862 subjects in Colorado, 18% of all patients treated with LT_4 products had TSH levels above the upper limit of the normal range, indicating that those patients were in a subclinical hypothyroid state despite LT_4 treatment. [17]

The American Cancer Society projects the number of new cases of thyroid cancer in 2003 will reach 22,000 with an annual mortality of 1,400. [18] The low mortality rates for this cancer is due in part to the effectivness care delivered for these patients. Thyroid cancer patients undergo surgical removal of their thyroid gland and treatment with radioactive iodine to ablate the remaining thyroid cancer cells. Thereafter, they are purposefully maintained in a marginally hyperthyroid state (TSH < 0.4 mIU/L). [5-7, 9, 19] TSH is a growth factor for normal and cancerous thyroid cells. The goal of LT_4 treatment is to deliver adequate LT_4 to suppress the TSH to just below the normal range. Lowering TSH levels removes the growth stimulus, thereby reducing the probability that any remaining thyroid cancer cells will grow to be of any clinical significance. If these patients are under-treated, they are at risk of having a recurrence of their thyroid cancer or development of metastases. Conversely, if they receive too much LT_4 they are at risk of the complications of over-treatment, described below.

4.4.2 Consequences of hypothyroidism and hyperthyroidism

It is paramount that patients be guaranteed that any LT_4 product substitution produce the same therapeutic response such that the efficacy and safety profile they rely upon is not compromised.

The FDA, in a final agency decision regarding the regulatory status of Synthroid, described the safety risks when patients are inadvertently over- or under-treated. "Superpotent tablets of levothyroxine sodium pose safety risks. Patients who inadvertently receive more levothyroxine than is necessary to control their condition may experience angina, tachycardia, or arrhythmias. There is also evidence that overtreatment can contribute to osteoporosis. Subpotent tablets of levothyroxine sodium are not adequately effective and, therefore, also pose safety risks. Patients inadvertently receiving less than

their proper dose may experience such symptoms as fatigue, lethargy, sleepiness, mental impairment, depression, cold intolerance, hair loss, hoarseness, weight gain, constipation, decreased appetite, dry skin, increased perspiration, arthralgia, menstrual disturbances, and paresthesias. Because of the serious consequences of too much or too little circulating thyroxine, it is very important that patients receive the dose of levothyroxine sodium determined by their physicians to be optimal to replace the amount of hormone that would have been present naturally." [12]

The FDA stated that the potential side effects that occur with mild hypothyroidism and hyperthyroidism involve many different organ systems. [12] Some specific examples highlight the importance of maintaining thyroid hormones in their narrow therapeutic ranges. Maternal thyroid hormone status, particularly during early pregnancy, is important to the well being of the pregnant woman's offspring. Early in pregnancy the fetus is totally dependent on receiving thyroid hormone from the mother. [20] Hypothyroidism during pregnancy has been associated with lower IQ scores in the children. [21]

Mild thyroid failure is associated with elevated total cholesterol and LDL-cholesterol levels. [17, 22-26] This is consistent with the finding that thyroid hormone is a positive regulator for the production of LDL-receptors. [2] In the hypothyroid state removal of LDL-cholesterol particles from the plasma into the liver and other tissues would be limited. Hypothyroidism is an independent risk factor for myocardial infarction. [27]

Hypothyroidism is associated with a slow heart rate (bradycardia) and decreased contractility of heart muscle. [28] Thyroid hormone-responsive genes have been identified that are consistent with these clinical findings. [1, 28] Clinical practice guidelines and product labels for LT_4 products advise careful monitoring and treatment of thyroid disease patients who also suffer from heart failure, as both hypo- and hyperthyroidism can worsen the heart failure. [5-8, 10] As testing of cardiac function becomes more sophisticated, it is evident that even mild thyroid failure has a significant effect on cardiac muscle contractility. [29-31] In the hypothyroid patient, with each heartbeat, less blood is pumped from the heart to the rest of the body and increased backward pressure causes fluid to build up in the lungs and legs. Hyperthyroidism is associated with rapid heartbeat (tachycardia) and atrial fibrillation. [28] Both of these also result in less blood being pumped to the rest of the body with each heartbeat. Atrial fibrillation is also associated with an increased risk of stroke. [32]

4.5 Summary of LT_4 therapy and clinical consequences

In summary, physicians use the TSH levels to judge the adequacy of treatment. To achieve treatment goals, physicians and the 13 million LT_4 treated patients in the U.S. rely on multiple dosage strengths. For titration and maintenance of the desired thyroid status, dosage strengths that differ by only 12 to13 µg are frequently used. Changes in LT_4 treatment or potency, with resulting changes in TSH levels, have significant clinical consequences.

The concerns of the FDA as outlined above and recommendations in the LT_4 product labels further

emphasize the concern that LT_4 product substitution should only be done when LT_4 can be delivered so as not to produce over- or under-treatment. This takes on particular significance for patients who have their TSH monitored every 6 to 12 months. It is possible that LT_4 product substitution could occur between two consecutive TSH assessments and the patient's thyroid status could be changed toward under- or over-treatment. It is these patients who have an increased health risk from a product that is supra- or sub-potent.

5.0 Conclusions

The determination of bioequivalence of LT_4 products should signify that, under all circumstances, these products are truly interchangeable without adverse clinical consequences, and without the need for clinical monitoring, retesting and retitration. The goal of thyroid hormone replacement therapy for hypothyroid patients is to safety titrate the patient to the appropriate dose that achieves and then maintains the euthyroid state. The goal of TSH suppression for the treatment of thyroid cancer is to remove the growth-promoting effect of TSH on thyroid cancer cells such that the patient does not suffer regrowth of the cancer. For these clinical purposes, patients and their physicians rely upon serum TSH levels, the most sensitive and easily measurable parameter of thyroid hormone function. To achieve the optimal TSH levels, physicians titrate individual patients using a wide range dosage forms, routinely using dosage increments in the 12-13 μg range. The clinical evidence presented here demonstrates that small changes in T_4 dosage result in TSH levels that are correlated with undesirable clinical consequences.

The current FDA guidance for the assessment of LT4 bioequivalence does not account for endogenous thyroxine or its biologic regulation. Results from the "bioequivalence" study (M02-417) reveal that LT_4 products approved using the current FDA criterion and based on bioequivalence data without baseline correction for endogenous T_4 levels could differ by as much as 33% from the reference product. Furthermore, simple corrections of the T_4 baseline did not sufficiently solve the problem, because two products that differed by 12.5% in thyroxine content would be declared bioequivalent. Other methodological flaws were also observed that could further reduce the reliability of the current guidance to ensure that products declared bioequivalent will be substitutable in patients without adverse clinical consequences, and without the need to remonitor, retest and retitrate.

In summary, we recommend that the new data be taken into account and careful consideration be given to developing a specific guidance for the assessment of bioequivalence of levothyroxine sodium products. To do so, this guidance must adequately consider the unique nature of the thyroid hormone system and the demonstrated limitations of the current criteria even with baseline correction. Physicians and patients rely on dosage strengths that differ by only 12-13 μg. The concerns of the FDA as outlined in the FDA final action for Synthroid® and recommendations in the LT_4 product labels further emphasize the concern that LT_4 product substitution should only be done when LT_4 can be delivered so as not to produce over- or under-treatment. This needs to be ensured because physicians and patients

alike rely on receiving "the correct dose when filling and refilling their carefully calculated prescriptions." [12] The necessity to deliver bioequivalent LT_4 products assumes that the methodology used to determine bioequivalence is robust and sensitive enough to differentiate doses of LT_4 that are truly different.

6.0 References

1. Anderson GW, Mariash CN, Oppenheimer JH. Molecular actions of thyroid hormone. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text. Philadelphia: Lippincott Williams and Wilkins, 2000:174-195.
2. Bakker O, Hudig F, Meijssen S, Wiersinga WM. Effects of triiodothyronine and amiodarone on the promoter of the human LDL receptor gene. Biochem Biophys Res Commun 1998; 249:517-521.
3. National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease, 2002. Vol. 2003: http://www.nacb.org/lmpg/thyroid_/mpg_pub.stm, 2003.
4. Guidance for Industry. Levothyroxine sodium tablets - *in vivo* pharmacokinetic and bioavailability studies and *in vitro* dissolution testing. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, February 2001.
5. Levoxyl (levothyroxine sodium tablets U. Physician Package Insert. St. Louis, MO: Jones Pharma Incorporated (A wholly owned subsidiary of King Pharmaceuticals, Inc.), Revised Dec, 2001.
6. Synthroid (levothyroxine sodium tablets USP). Physician Package Insert. Abbott Laboratories, North Chicago, IL.,. 03-5195-R1-Rev. July, 2002,.
7. Unithroid (levothyroxine sodium tablets USP). Physician Package Insert. Corona, CA: Watson Pharma, Inc. A Subsidiary of Watson Laboratories, Inc., Revised November, 2000.
8. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA 1995; 273:808-812.
9. Singer PA, Cooper DS, Daniels GH, et al. Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. Arch Intern Med 1996; 156:2165-2172.
10. AACE Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocrine Practice 2002; 8:458-469.
11. Unithroid. Medical Offiver Review, 2000.
12. FDA response. Docket No. 97N-0314/CP2. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, April 2001.
13. Pharmetrics. Synthroid Titration Study (internal report), 2003.
14. Carr D, McLeod DT, Parry G, Thornes HM. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotropin releasing hormone test using a sensitive thyrotropin assay with measurement of free thyroid hormones and clinical assessment. Clin Endocrinol (Oxf) 1988; 28:325-333.
15. Braverman LE, Utiger RD. Introduction to thyrotoxicosis. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text. Philadelphia: Lippincott Williams and Wilkins, 2000:515-517.
16. Braverman LE, Utiger RD. Introduction to hypothyroidism. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text. Philadelphia: Lippincott

Williams and Wilkins, 2000:719-720.

17. Canaris GJ, Manowitz NR, Mayor GM, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160:526-534.

18. American Cancer Society. Cancer Facts & Figures 2003. Vol. 2003, 2003.

19. Mazzaferri EL. Carcinoma of follicular epitheliuim - Radioiodine and other treatment and outcomes. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text. Philadelphia: Lippincott Williams and Wilkins, 2000:904-929.

20. Fisher DA, Brown RS. Thyroid physiology in the perinatal period and during childhood. In: Braverman LE, Utiger RD, eds. Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text. Philadelphia: Lippincott Williams and Wilkins, 2000:959-972.

21. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999; 341:549-555.

22. Tanis BC, Westendorp GJ, Smelt AHM. Effect of thyroid substitution on hypercholesterolemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. Clin Endocrinol (Oxf) 1996; 44:643-649.

23. Arem R, Patsch W. Lipoprotein and apolipoprotein levels in subclinical hypothyroidism. Arch Intern Med 1990; 150:2097-2100.

24. Caron PH, Calazel C, Parra JH, Hoff M, Louvet JP. Decreased HDL cholesterol in subclinical hypothyroidism: the effect of L-thyroxine therapy. Clin Endocrinol (Oxf) 1990; 33:519-523.

25. Danese MD, Ladenson PW, Meinert CL, Powe NR. Effect of thyroxine therapy on serum lipoproteins in patients with MTF: a quanitative review of the literature. J Clin Endocrinol Metab 2000; 85:2993-3001.

26. Meier C, Staub J-J, Roth C-B, et al. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double-blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab 2001; 86:4860-4866.

27. Hak AE, Pols HAP, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 2000; 132:270-278.

28. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344:501-509.

29. Biondi B, Fazio S, Palmieri EA, et al. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 1999; 84:2064-2067.

30. Monzani F, Di Bello V, Caraccio N, et al. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. J Clin Endocrinol Metab 2001; 86:1110-1115.

31. Vitale G, Galderisi M, Lupoli GA, et al. Left ventricular myocardial impairment in subclinical hypothyroidism assessed by a new ultrasound tool: pulsed tissue Doppler. J Clin Endocrinol Metab 2002; 87:4350-4355.

32. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994; 331:1249-1252.

Appendix A

Abbott Laboratories
Study M02-417 Synopsis and Discussion

Title of Study

Evaluating the Impact of Correcting for Endogenous T_4 Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers

Objective

The objective of this study was to evaluate the impact of various methods for correcting for endogenous T_4 baseline on the bioequivalence of levothyroxine sodium formulations in healthy volunteers.

Methodology

This Phase 1, single-dose, open-label, study was conducted according to a three-period, randomized crossover design in healthy volunteers. The total dose given was 600 µg levothyroxine sodium for Regimen A, 450 µg levothyroxine sodium for Regimen B and 400 µg levothyroxine sodium for Regimen C. Subjects received one of six sequences of Regimen A (twelve 50 µg Synthroid® tablets), Regimen B (nine 50 µg Synthroid® tablets) or Regimen C (eight 50 µg Synthroid® tablets) under fasting conditions at approximately 0830 on Study Day 1 of each period. A washout interval of at least 44 days separated the doses of the three study periods.

Blood samples (sufficient to provide approximately 2 mL serum) for total levothyroxine (T_4), total triiodothyronine (T_3) and thyroid stimulating hormone (TSH) assay were collected by venipuncture into 5 mL evacuated siliconized collection tubes as follows:

- At approximately 0 hours and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 18 hours after the 0-hour collection on Study Day –1 in each study period.
- At approximately –30 minutes, –15 minutes and at 0 hours prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72 and 96 hours after dosing on Study Day 1 in each study period.

Serum concentrations of T_4 and T_3 were determined using validated radioimmunoassay (RIA) methods. The lower limit of quantification of T_4 was 1.00 μg/dL. The lower limit of quantification of T_3 was 0.25 ng/mL. Serum concentrations of TSH were determined using a validated IRMA assay; lower limit of quantification was 0.250 μIU/mL.

Subjects

Subjects were male and female volunteers between 19 and 50 years of age, inclusive. Subjects were judged to be euthyroid and in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram and laboratory tests. Females were postmenopausal, sterile, or if of childbearing potential, were not pregnant or breast-feeding and were practicing an acceptable method of birth control.

Thirty-six subjects (18 M, 18 F) participated in the study, with mean age of 32.9 years, mean weight of 74.5 kg and mean height of 172 cm. Three subjects received study drug in only one period and thus were not included in any of the pharmacokinetics analyses. Thirty-three subjects (16 M, 17 F) were included in the pharmacokinetic analyses, with mean age of 33.1 years, mean weight of 73.5 kg and mean height of 171 cm.

Pharmacokinetics and Statistical Methods

The pharmacokinetic parameters of total levothyroxine (T_4) were estimated using noncompartmental methods. These included: the maximum serum concentration (C_{max}) and time to C_{max} (T_{max}), the area under the serum concentration-time curve (AUC) from time 0 to 48 hours (AUC_{48}), time 0 to 72 hours (AUC_{72}) and time 0 to 96 hours (AUC_{96}). For T_4, values of these parameters (C_{max}, T_{max}, AUC_{48}, AUC_{72} and AUC_{96}) were determined without correction for endogenous T_4 levels and after correcting all post-dose concentrations using each of following three methods:

Correction Method 1: The predose baseline value on the day of dosing was subtracted from each post-dose concentration. The pre-dose baseline value was calculated as the average of the three concentrations at –0.5, –0.25 and 0 hours prior to dosing in each period.

Correction Method 2: For each time of post-dose sampling, the observed concentration was corrected assuming that the endogenous T_4 baseline level at 0 hours declines according to a half-life of 7 days.

Correction Method 3: The T_4 concentration for each time of post-dose sampling was corrected by the concentration observed at the same time of day during the 24 hours preceding the dose.

For all three methods of correction, the corrected 0-hour concentration was assumed to be 0.

For uncorrected and corrected T_4 an analysis of variance (ANOVA) with fixed effects for sex, sequence, sex-by-sequence interaction, period, regimen and the interaction of sex with each of period and regimen, and with random effects for subjects nested within sex-by-sequence combination was performed for T_{max}, and the natural logarithms of C_{max} AUC_{48}, AUC_{72} and AUC_{96}. A significance level of 0.05 was used for all tests.

The bioavailability of each of Regimen B (450 µg dose) and Regimen C (400 µg dose) relative to that of Regimen A (600 µg dose) for uncorrected and corrected T_4 was assessed by the two one-sided tests procedure[1] *via* 90% confidence intervals obtained from the analysis of the natural logarithms of AUC_{48} and C_{max}. Bioequivalence was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUC_{48} and C_{max} were within the 0.80 to 1.25 range. Likewise, the bioavailability of Regimen B (450 µg dose) relative to that of Regimen C (400 µg dose) was assessed. The same was done using each of AUC_{72} and AUC_{96} in place of AUC_{48}.

A repeated measures analysis was performed on the T_4 concentration data of Study Day –1 for each period. To investigate the possibility of carryover effects, an ANOVA was performed on the logarithms of the Study Day –1 AUC_{24}.

Pharmacokinetic Results

Levothyroxine (T_4) Without Correcting for Endogenous T_4 Baseline Concentrations

The mean serum concentration-time plots for uncorrected T_4 after administration of levothyroxine sodium on Study Day 1 are presented in Figure 1. The mean T_4 serum concentrations-time profiles are fairly consistent after administration of the three regimens. Mean T_4 concentrations prior to dosing are approximately 7.5 µg/dL and increase to about 13 to 14 µg/dL at maximum before declining. The mean T_4 concentrations remain at approximately 9 µg/dL at 96 hours after administration of these large doses of levothyroxine sodium to the healthy volunteers.

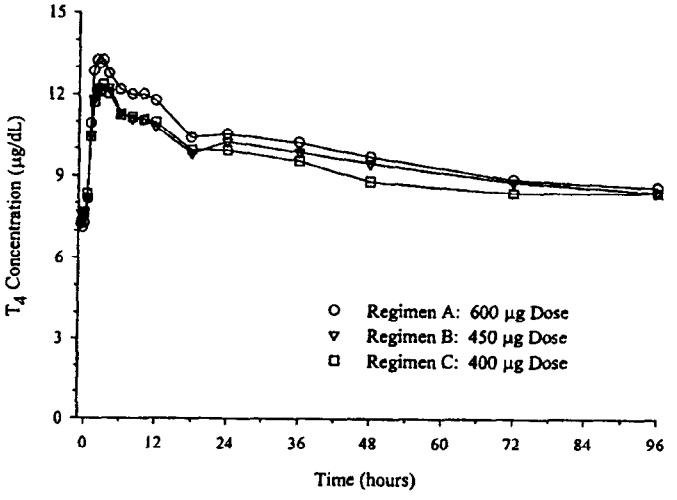


Figure 1. Mean Levothyroxine (T_4) Concentration-Time Profiles on Study Day 1 Following Single Dose Administration of Levothyroxine Sodium – Uncorrected for Endogenous T_4 Baseline Concentrations

Mean ± standard deviation (SD) pharmacokinetic parameters of T_4 after administration of the three regimens without correcting for endogenous T_4 baseline concentrations are listed in Table 1.

Table 1. Mean ± SD Pharmacokinetic Parameters of Levothyroxine (T_4) Without Correcting for Endogenous T_4 Baseline Concentrations

Pharmacokinetic Parameters (units)		Regimens A: 600 µg Dose (N = 31)	B: 450 µg Dose (N = 33)	C: 400 µg Dose (N = 33)
T_{max}	(h)	3.1 ± 2.4	3.2 ± 2.1	3.5 ± 3.3
C_{max}	(µg/dL)	14.3 ± 2.14	13.2 ± 2.05*	13.2 ± 2.45*
AUC_{48}	(µg•h/dL)	518 ± 71.8	493 ± 72.7*	484 ± 73.6*
AUC_{72}	(µg•h/dL)	741 ± 102	712 ± 108*	691 ± 102*,+
AUC_{96}	(µg•h/dL)	951 ± 133	919 ± 139	892 ± 133*,+

* Statistically significantly different from Regimen A (ANOVA, $p < 0.05$).
\+ Statistically significantly different from Regimen B (ANOVA, $p < 0.05$).

The bioequivalence/bioavailability results for uncorrected T_4 are listed in Table 2.

Table 2. Bioequivalence and Relative Bioavailability–Uncorrected Levothyroxine (T_4)

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value* Test	Central Value* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
450 µg *vs.*600 µg	C_{max}	13.0	14.0	0.928	0.890 – 0.968
	AUC_{48}	481.7	504.8	0.954	0.927 – 0.982
	AUC_{72}	694.9	721.9	0.963	0.936 – 0.990
	AUC_{96}	896.2	925.6	0.968	0.941 – 0.996
400 µg *vs.* 600 µg	C_{max}	12.9	14.0	0.921	0.883 – 0.960
	AUC_{48}	469.6	504.8	0.930	0.904 – 0.958
	AUC_{72}	670.4	721.9	0.929	0.903 – 0.955
	AUC_{96}	865.7	925.6	0.935	0.909 – 0.962
450 µg *vs.* 400 µg	C_{max}	13.0	12.9	1.007	0.967 – 1.050
	AUC_{48}	481.7	469.6	1.026	0.997 – 1.055
	AUC_{72}	694.9	670.4	1.037	1.009 – 1.065
	AUC_{96}	896.2	865.7	1.035	1.007 – 1.064

* Antilogarithm of the least squares means for logarithms.
\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Levothyroxine (T_4) After Correction for Endogenous T_4 Baseline Concentrations

The mean serum concentration-time plots for T_4, after correction for endogenous baseline levels of levothyroxine using each of the correction methods, are presented in Figure 2 for Correction Method 1, Figure 3 for Correction Method 2, and Figure 4 for Correction Method 3. The mean T_4 serum concentrations after correcting for endogenous baseline levels by any of the three methods of correction were higher after administration of Regimen A (600 µg dose) than after administration of Regimens B (450 µg dose) and C (400 µg dose) throughout the 96-hour sampling period. The mean baseline corrected T_4 concentrations for Regimens B (450 µg dose) and C (400 µg dose) were comparable throughout the 96-hour sampling period. The baseline corrected T_4 concentrations prior to dosing were assigned a value of zero for each of the three methods of correction. However, 96 hours after administration of these large doses of levothyroxine sodium to healthy volunteers the mean baseline corrected T_4 concentrations remain at

approximately 1 to 2 µg/dL for Correction Methods 1 and 3 and approximately 3 to 4 µg/dL for Correction Method 2.

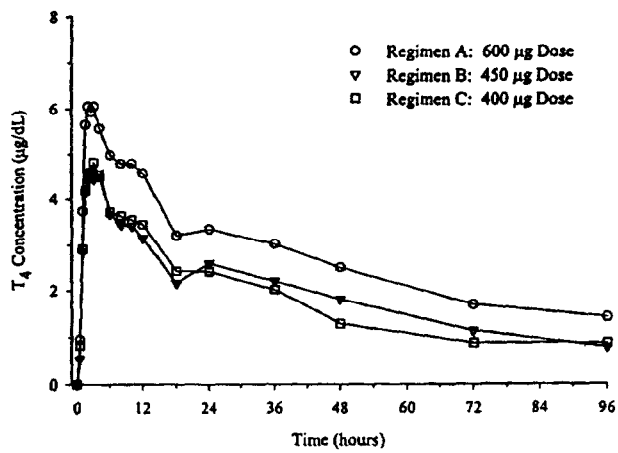


Figure 2. Mean Levothyroxine (T_4) Concentration-Time Profiles after Correction for Endogenous Baseline Levels of T_4 Using Correction Method 1

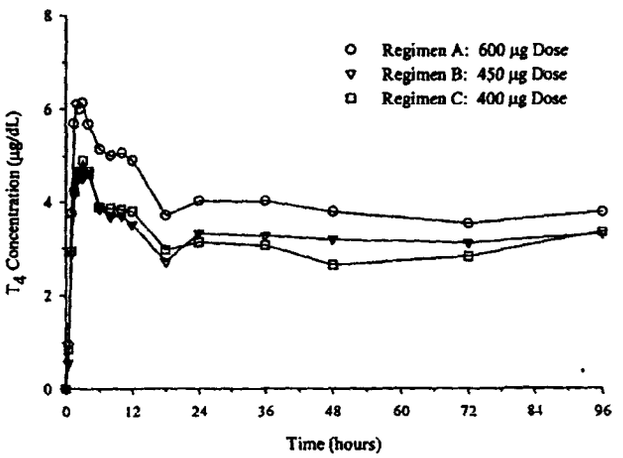


Figure 3. Mean Levothyroxine (T_4) Concentration-Time Profiles after Correction for Endogenous Baseline Levels of T_4 Using Correction Method 2

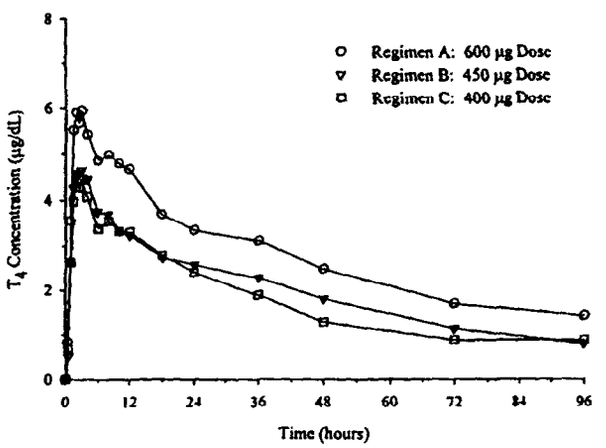


Figure 4. Mean Levothyroxine (T_4) Concentration-Time Profiles after Correction for Endogenous Baseline Levels of T_4 Using Correction Method 3

Mean ± SD pharmacokinetic parameters of T_4 after administration of the three regimens after correcting for endogenous T_4 baseline concentrations are listed in Table 3.

Table 3. Mean ± SD Pharmacokinetic Parameters of Levothyroxine (T_4) after Correcting for Endogenous T_4 Baseline Concentrations

Pharmacokinetic Parameters (units)		Regimens A: 600 µg Dose (N = 31)	B: 450 µg Dose (N = 33)	C: 400 µg Dose (N = 33)
Correction Method 1				
T_{max}	(h)	3.1 ± 2.4	3.2 ± 2.1	3.5 ± 3.3
C_{max}	(µg/dL)	7.05 ± 1.66	5.54 ± 1.53*	5.72 ± 1.44*
AUC_{48}	(µg•h/dL)	172 ± 40.4	126 ± 39.0*	123 ± 45.4*
AUC_{72}	(µg•h/dL)	222 ± 56.0	161 ± 55.5*	149 ± 68.6*
AUC_{96}	(µg•h/dL)	259 ± 72.5	184 ± 69.9*	169 ± 92.5*
Correction Method 2				
T_{max}	(h)	3.3 ± 2.8	5.8 ± 9.3	3.7 ± 3.5
C_{max}	(µg/dL)	7.15 ± 1.64	5.68 ± 1.50*	5.83 ± 1.45*
AUC_{48}	(µg•h/dL)	204 ± 40.9	160 ± 40.1*	156 ± 43.4*
AUC_{72}	(µg•h/dL)	292 ± 56.9	235 ± 58.2*	221 ± 62.7*
AUC_{96}	(µg•h/dL)	379 ± 74.0	312 ± 74.6*	295 ± 82.2*
Correction Method 3				
T_{max}	(h)	3.5 ± 3.1	3.6 ± 2.3	3.6 ± 4.0
C_{max}	(µg/dL)	7.03 ± 1.64	5.85 ± 1.78*	5.56 ± 1.69*
AUC_{48}	(µg•h/dL)	176 ± 36.9	131 ± 39.2*	120 ± 28.4*
AUC_{72}	(µg•h/dL)	226 ± 49.4	166 ± 52.9*	146 ± 45.4*,+
AUC_{96}	(µg•h/dL)	263 ± 64.8	189 ± 65.6*	167 ± 67.2*

* Statistically significantly different from Regimen A (ANOVA, $p < 0.05$).
\+ Statistically significantly different from Regimen B (ANOVA, $p < 0.05$).

The bioequivalence/bioavailability results for T_4 using Correction Method 1, Correction Method 2, and Correction Method 3 are listed in Tables 4, 5, and 6, respectively.

Table 4. Bioequivalence and Relative Bioavailability for T_4 (Correction Method 1)

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value* Test	Central Value* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
450 µg *vs.*600 µg	C_{max}	5.4	6.9	0.783	0.727 – 0.844
	AUC_{48}	119.7	167.3	0.715	0.658 – 0.778
	AUC_{72}	151.4	215.7	0.702	0.636 – 0.774
	AUC_{96}	170.2	250.2	0.680	0.602 – 0.768
400 µg *vs.* 600 µg	C_{max}	5.6	6.9	0.803	0.745 – 0.865
	AUC_{48}	118.9	167.3	0.711	0.653 – 0.773
	AUC_{72}	144.9	215.7	0.672	0.609 – 0.741
	AUC_{96}	165.1	250.2	0.660	0.584 – 0.746
450 µg *vs.* 400 µg	C_{max}	5.4	5.6	0.975	0.906 – 1.049
	AUC_{48}	119.7	118.9	1.007	0.926 – 1.094
	AUC_{72}	151.4	144.9	1.044	0.948 – 1.150
	AUC_{96}	170.2	165.1	1.031	0.914 – 1.163

* Antilogarithm of the least squares means for logarithms.
\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Table 5. Bioequivalence and Relative Bioavailability for T_4 (Correction Method 2)

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value* Test	Central Value* Reference	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
450 µg *vs.*600 µg	C_{max}	5.6	7.0	0.793	0.739 – 0.850
	AUC_{48}	154.5	199.1	0.776	0.721 – 0.835
	AUC_{72}	227.5	284.9	0.799	0.729 – 0.875
	AUC_{96}	301.6	369.5	0.816	0.743 – 0.897
400 µg *vs.* 600 µg	C_{max}	5.7	7.0	0.807	0.753 – 0.866
	AUC_{48}	148.4	199.1	0.745	0.693 – 0.802
	AUC_{72}	207.9	284.9	0.730	0.666 – 0.800
	AUC_{96}	277.3	369.5	0.750	0.683 – 0.824
450 µg *vs.* 400 µg	C_{max}	5.6	5.7	0.982	0.916 – 1.051
	AUC_{48}	154.5	148.4	1.041	0.969 – 1.119
	AUC_{72}	227.5	207.9	1.094	1.001 – 1.197
	AUC_{96}	301.6	277.3	1.088	0.992 – 1.192

* Antilogarithm of the least squares means for logarithms.
\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Table 6. Bioequivalence and Relative Bioavailability for T_4 (Correction Method 3)

Regimens Test *vs.* Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate+	90% Confidence Interval
450 µg *vs.*600 µg	C_{max}	5.7	6.9	0.820	0.757 – 0.888
	AUC_{48}	125.1	172.9	0.723	0.672 – 0.779
	AUC_{72}	158.7	222.0	0.715	0.645 – 0.792
	AUC_{96}	177.7	256.6	0.693	0.631 – 0.760
400 µg *vs.* 600 µg	C_{max}	5.3	6.9	0.775	0.715 – 0.839
	AUC_{48}	115.4	172.9	0.667	0.620 – 0.718
	AUC_{72}	135.9	222.0	0.612	0.553 – 0.678
	AUC_{96}	164.0	256.6	0.639	0.582 – 0.702
450 µg *vs.* 400 µg	C_{max}	5.7	5.3	1.058	0.979 – 1.145
	AUC_{48}	125.1	115.4	1.084	1.008 – 1.165
	AUC_{72}	158.9	135.9	1.168	1.057 – 1.291
	AUC_{96}	177.7	164.0	1.084	0.989 – 1.188

* Antilogarithm of the least squares means for logarithms.
\+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Baseline Levothyroxine (T_4) Prior to Dosing (Study Day –1)

The mean serum concentration-time plots for baseline T_4 on Study Day –1 prior to dosing with levothyroxine sodium in each Period are presented in Figure 5. Analysis of the T_4 concentration data obtained during the 24 hours of Study Day –1 of each period confirmed that T_4 has a diurnal cycle with statistically significant differences across time. The diurnal variation in baseline T_4 concentrations prior to dosing are consistent with the observed diurnal variation in the serum concentrations of TSH (Figure 6).

Analysis of the 24-hour AUC for Study Day –1 revealed that the regimens (dose levels) had statistically significantly different carryover effects from one period to the next (first-order carryover) and from Period 1 to Period 3 (second-order carryover).

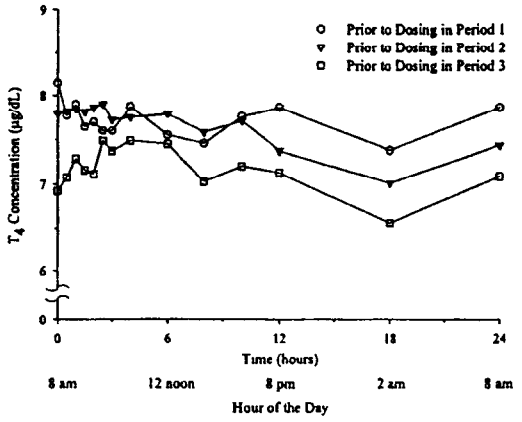


Figure 5. Mean Levothyroxine (T_4) Concentration-Time Profiles on Study Day –1 Prior to Dosing with Levothyroxine Sodium by Period

Thyroid-Stimulating Hormone (TSH)

The mean serum concentration-time plots for TSH for the 24 hours prior to and 96 hours after administration of levothyroxine sodium on Study Day 1 are presented in Figure 6. The serum concentrations of TSH appear to clearly show diurnal variation, prior to dosing. During the 24-hour period prior to dosing, the concentrations of TSH decline during the morning hours until reaching the lowest levels at approximately 1200 before starting to increase to maximum values at 0200 the next morning, *i.e.*, the morning of Study Day 1 (18 hour sample on Study Day –1).

Administration of any of the three large doses of levothyroxine sodium substantially, but not completely, suppressed the TSH serum concentrations throughout the 24-hour period after dosing on Study Day 1. TSH serum concentrations continued to be suppressed throughout the 96-hour sampling period after dosing; the concentrations did not return to baseline values even after 96 hours. The rank order of suppression of the TSH serum concentrations was consistent with the rank order of the size of levothyroxine sodium dose administered in each of the three regimens with the greatest suppression of TSH serum concentrations associated with administration of the largest dose (Regimen A, 600 µg).

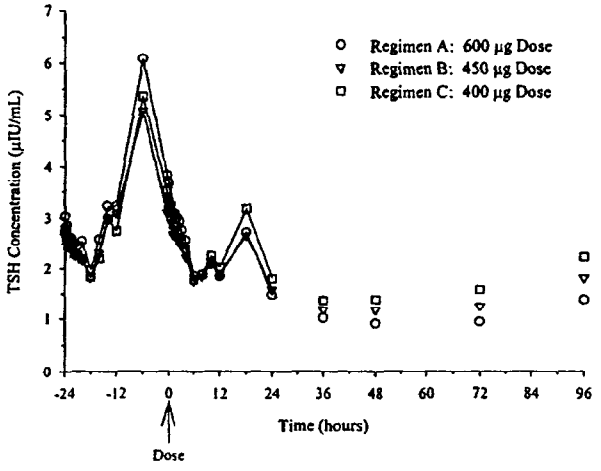


Figure 6. Mean TSH Concentration-Time Profiles for the 24 Hours Prior to (Study Day –1) and for the 96 Hours after Administration of Levothyroxine Sodium on Study Day 1

Triiodothyronine (T_3) Concentrations

The mean T_3 concentration for the 24-hour period prior to dosing and throughout the 96-hour period after dosing were in the very narrow range of 1.1 to 1.3 ng/mL after administration of the large doses of levothyroxine sodium to healthy volunteers.

Discussion

Determination of the bioavailability of levothyroxine sodium products in healthy volunteers presents significant challenging issues. Levothyroxine is naturally present in the blood, with total endogenous baseline T_4 levels ranging from 4 to 14 µg/dL. Thus, to compare the bioavailabilities of levothyroxine sodium formulations after a single dose in healthy volunteers, FDA Guidance[2] recommends administration of 600 µg, several times the normal clinical dose, to raise the levels of the drug significantly above baseline and to hopefully reduce the influence of endogenous levels. However, results from several bioavailability studies and a stochastic simulation study with levothyroxine products suggested that, given very reasonable assumptions about endogenous levothyroxine behavior in healthy subjects, the use of baseline uncorrected C_{max} and AUC_{48} values

would result in a high probability of declaring two products bioequivalent when they actually differ by as much as 35%.[3]

The current study was designed to evaluate how much two formulations could differ and still pass the bioequivalence criteria specified in the current guidance when not correcting for endogenous T_4 baseline levels. The results from this study clearly indicate that the use of baseline uncorrected C_{max}, AUC_{48}, AUC_{72} and AUC_{96} values would result in declaring two products bioequivalent when they actually differ by as much as 25% to 33% (450 µg and 400 µg *versus* 600 µg). Utilizing the criteria specified in FDA Guidance,[2] both the 450 µg dose (Regimen B) and the 400 µg dose (Regimen C) would be declared bioequivalent to the 600 µg dose (Regimen A) because the 90% confidence intervals for evaluating bioequivalence obtained without correcting for endogenous T_4 baseline levels were contained within the 0.80 to 1.25 range. Furthermore, the 450 µg dose would be declared bioequivalent to the 400 µg dose because the 90% confidence intervals for evaluating bioequivalence without correcting for endogenous T_4 baseline levels were contained within the 0.80 to 1.25 range. Considering the margin by which the conditions for declaring bioequivalence were passed in this study, products that differ by more than 33% would have a good chance of being declared bioequivalent on the basis of uncorrected data. The results of this study clearly demonstrate the significant limitations and problems with the current methodology and criteria for assessing the bioequivalence of levothyroxine sodium products in healthy volunteers without correcting for endogenous T_4 baseline levels.

Several mathematical and statistical methods can be used to correct for the contribution of T_4 baseline levels, based on different biologic assumptions about the behavior of endogenous T_4 following administration of exogenous levothyroxine. When a single dose of exogenous levothyroxine sodium is given to healthy subjects, one could assume that endogenous levothyroxine levels remain constant if there is no suppression of endogenous production (Correction Method 1). If production were completely suppressed, *via* feedback through the hypothalamic-pituitary axis, the endogenous levothyroxine would decline at an average rate defined by its half-life, which is approximately 7 days (Correction Method 2). Thus, a constant baseline of endogenous levothyroxine (Correction Method 1) *versus* a baseline that decays exponentially with a 7-day half-life (Correction Method 2) defines the limits for endogenous levothyroxine following a dose of exogenous levothyroxine sodium. This assumes that no other

components of the thyroid system would impact the turnover of T_4 and T_3. The third method of baseline correction (Correction Method 3) employed in this study corrected the T_4 concentration for each time of post-dose sampling by the baseline T_4 concentration observed at the same time of day during the 24 hours preceding the dose, *i.e.,* on Study Day –1.

One of the objectives of the current study was to better understand the impact of three different methods of correction for endogenous T_4 baseline on the bioequivalence evaluation of levothyroxine sodium formulations in healthy volunteers. In contrast to the results with uncorrected data, for all three correction methods for endogenous T_4 baseline, neither the 450 μg dose nor the 400 μg dose would be declared bioequivalent to the 600 μg dose. However, as with the uncorrected data, the 450 μg dose would continue to be declared bioequivalent to the 400 μg dose after correcting for endogenous T_4 baseline levels using any of the three correction methods because the 90% confidence intervals for evaluating bioequivalence after correcting for endogenous T_4 baseline continue to be contained within the 0.80 to 1.25 range. The 50μg difference between the 450 μg dose and the 400 μg dose represents a 12.5% difference.

Correction Method 1 relies on the assumption that there is no suppression of endogenous production when a single large dose of exogenous levothyroxine sodium is given to healthy subjects, thus assuming a constant baseline of endogenous levothyroxine. This assumption is clearly not true since TSH levels after dosing with levothyroxine sodium in the study were definitely suppressed, though not completely. Thus, it is very unlikely that endogenous T_4 production would be constant after administration of large doses of levothyroxine sodium to healthy volunteers. This method of correction has also several undesirable characteristics. The method will sometimes produce a negative value for AUC as was observed with one of the subjects in this study. Furthermore, the method relies completely upon the results from only three samples obtained during an interval of only 30 minutes just prior to dosing. Just from a consideration of randomness alone, the influence of the average of these three concentrations could be significant. More troubling than the small number of observations is the brief time span from which they are taken. It is known that there is a circadian effect on hormone levels, and the Day –1 data from this study clearly confirmed the presence of the circadian effect. Therefore, unless a subject's expected T_4 levels during the 30 minute time frame just prior to dosing

happens also to be the expected average for a 24-hour cycle, the corrected AUC by this method is in error.

Correction Method 2 depends upon the assumption that endogenous production of levothyroxine is completely suppressed when a single large dose of exogenous levothyroxine sodium is given to healthy subjects. Therefore, already available endogenous levothyroxine will decline at rate defined by its half-life, which is assumed to be 7 days. This method also has several undesirable characteristics. Method 2 gives a reasonable correction only if production of endogenous T_4 abruptly and completely stops when study drug is administered and does not resume during the sampling period. Even if this unlikely assumption is true, the correction will be in error for a given subject, with the size of the error depending on how much the given subject's elimination half-life differs from 7 days. The half-life of levothyroxine is not very well documented in healthy volunteers and the 7-day half-life is an approximation based on data from isotope studies with levothyroxine. As previously noted, TSH levels after dosing with levothyroxine sodium were definitely suppressed, but not completely. Thus, it seems very unlikely that endogenous T_4 production would be reduced to zero, with an accompanying 7-day half-life. The use of a single value for levothyroxine half-life for all healthy subjects (regardless of gender, race, and age) at all times is clearly a significant oversimplification. However, estimation of a levothyroxine half-life for each subject in each period is not possible using the currently recommended design in healthy volunteers. Moreover, as with Method 1, Method 2 relies heavily on the average of three concentrations taken immediately before dosing. In particular, for the case in which a subject randomly has a pre-dose average considerably higher than typical for that subject, the corrected AUC is more likely to be negative.

The third method of baseline correction (Method 3) employed in this study corrected the T_4 concentration at each time of post-dose sampling by the corresponding baseline T_4 concentration observed at the same time of day during the 24-hour period preceding the dose, *i.e.,* on Study Day –1. This method provides some advantages in comparison to Methods 1 and 2. The obvious advantages for this method are a) it does not rely on just three samples collected over a very short time period prior to dosing for the correction, and b) the post-dose T_4 concentration is adjusted based on the actual baseline T_4 concentration at the same clock time of the day before dosing in the same subject in the same period, and thus, this method takes into account the diurnal variation in the baseline

T_4 concentration throughout the day in each subject, which is ignored by Methods 1 and 2.

In contrast to Method 2, for Method 3, endogenous T_4 production is not assumed to abruptly stop following study drug administration and a constant value for the elimination half-life across subjects is not assumed. However, similar to Method 1, Method 3 relies on the assumption that there is no suppression of endogenous production when a single dose of exogenous levothyroxine sodium is given to healthy volunteers. Furthermore, Method 3 requires the assumption that the circadian pattern in the endogenous T_4 production does not change when a single large dose of exogenous levothyroxine is administered to healthy subjects.

The impact of administration of large doses of levothyroxine sodium (*e.g.*, 600 μg) on the endogenous production of T_4 is not known. However, the TSH levels are clearly, but not completely, suppressed after administration of the large doses of levothyroxine sodium to the healthy volunteers in this study. The large exogenous dose may also affect the clearance of total T_4 *via* numerous feedback mechanisms. The TSH serum concentration-time data provide clear evidence of the limitations for each of the three methods of correction utilized in this study. Method 2 assumes that endogenous T_4 production is abruptly and completely stopped after study drug administration while Methods 1 and 3 assume that there is no suppression of endogenous production when a single dose of exogenous levothyroxine sodium is given to healthy volunteers.

The FDA Guidance[2] recommended a minimum 35-day washout period between the doses of levothyroxine sodium to minimize carryover. The 24-hour profiles of the baseline T_4 serum concentrations on the day before dosing were clearly not the same for the three study periods even though the washout periods between the doses of levothyroxine sodium in this study were 44 days between Periods 1 and 2 and 53 days between Periods 2 and 3. The Day –1 baseline T_4 data from this study provide convincing evidence that there are carryover effects from the successive study doses, even from the Period 1 dose to the Period 3 dose, and that the carryover effects of the dose levels differ. Carryover effect from the 600 μg dose resulted in higher T_4 levels than carryover effects of the two lower doses. Exploratory analyses of post-dose uncorrected C_{max} and AUC give additional strong evidence of these carryover effects. Also, such unequal carryover effects are present for C_{max} with all three methods of correction. Another component of the period effect may be the presence of seasonal and annual variations in hypothalamic-

pituitary-thyroid hormone concentrations in humans. Significant seasonal and annual rhythms in serum TSH and T_3 levels have been reported in the literature.[4] However, the amplitude of the circannual rhythm is probably not as large as that of the daily circadian variation.[4] Therefore, the results from our studies suggest that a much longer washout period between dosing would be required to truly reduce the impact of carryover between dosing periods.

The results of this study strongly suggest that obtaining additional blood samples on Study Day –1 provided data that improved the method of correction for endogenous levels of T_4, accounting for the possibility of a circadian pattern. Additional samples during the afternoon and night hours on the day before dosing and on the days after dosing may provide further benefits to this method of correcting for the endogenous baseline.

It is widely recognized that dose initiation and titration need to be done in susceptible groups with the 12.5 µg dosage strength. In the package insert of levothyroxine sodium products,[5] it states under 'DOSAGE AND ADMINISTRATION – Specific Patient Populations' "the recommended starting dose of levothyroxine sodium in elderly patients with cardiac disease is 12.5 – 25 µg/day, with gradual dose increments at 4 to 6 week intervals. The levothyroxine sodium dose is generally adjusted in 12.5 to 25 µg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized." NDA approved levothyroxine sodium tablets are available in strengths that differ from their nearest doses by 12 to 13 µg/tablet: that is 75, 88, 100, 112, 125, 137 and 150 µg tablet strengths. The 88 and 112 µg strengths are 12% less or greater, respectively, than the 100 µg strength.

Even though the three methods of correction for endogenous T_4 baseline improve the ability to distinguish between products that are truly different in dose by 25% to 33%, none of the three correction methods were able to distinguish between two products that differ by 12.5%. As stated earlier and similar to the findings with the uncorrected data, the 450 µg dose would continue to be declared bioequivalent to the 400 µg dose after correcting for endogenous T_4 baseline using any of the three correction methods. Narrowing the 90% confidence intervals for evaluating bioequivalence after correcting for endogenous T_4 baseline from the standard range of 0.80 to 1.25 would reduce the chance that two products that differ by 12.5% would be declared bioequivalent.

The potential for conducting bioequivalence trials in athyreotic subjects, a model that minimizes confounding effects from endogenous T_4 due to the absence of residual endogenous hormone, must also be considered. A study in athyreotic subjects would presumably be a multiple-dose study and long enough to properly address the issue of carryover effect. Such a study in athyreotic subjects would utilize therapeutic doses of levothyroxine sodium and remove the need for a method of baseline correction.

Conclusions

This study illustrates some important flaws in the design and analysis of single-dose crossover studies in healthy volunteers to assess bioequivalence of levothyroxine sodium products, stemming from the significant and complex contribution of endogenous T_4. First, the results indicate that the use of baseline uncorrected T_4 C_{max}, AUC_{48}, AUC_{72} and AUC_{96} values would result in declaring two products bioequivalent when they actually differ by as much as 25% to 33% (450 µg and 400 µg *versus* 600 µg). The 450 µg dose and the 400 µg dose would both be declared bioequivalent to the 600 µg dose because the 90% confidence intervals for evaluating bioequivalence without correction for endogenous T_4 baseline were contained within the 0.80 to 1.25 range. Considering the margin by which the conditions for declaring bioequivalence were passed in this study, products that differ by even more than 33% would also have a high likelihood of being declared bioequivalent.

Second, the results from this study indicate that the use of baseline corrected C_{max}, AUC_{48}, AUC_{72} and AUC_{96} values would reduce the likelihood that two products would be declared bioequivalent when they actually differ by 25% to 33%. After correcting for endogenous T_4 levels using each of the three correction methods employed in this study, neither the 450 µg dose nor the 400 µg dose would be declared bioequivalent to the 600 µg dose because the 90% confidence intervals for evaluating bioequivalence were not contained within the 0.80 to 1.25 range for C_{max}, AUC_{48}, AUC_{72} and AUC_{96}.

Third, the 450 µg dose would continue to be declared bioequivalent to the 400 µg dose utilizing the C_{max}, AUC_{48}, and AUC_{96} values for the baseline corrected T_4 data by any of the three methods of correction. A 12.5% difference (400 µg *versus* 450 µg) in levothyroxine sodium products may have a clinically relevant adverse impact on patients. Thus, it is apparent that simple methods of correction for endogenous T_4 concentrations in healthy volunteers are inadequate since these concentrations not only fluctuate on a

diurnal cycle but may also be differentially affected by products with different rates and extents of absorption. Additionally, there is evidence of significant carryover from one dosing period to subsequent periods even with washout periods up to 53 days.

The potential for conducting multiple-dose bioequivalence trials in athyreotic subjects, a model that minimizes confounding effects from endogenous T_4 due to the absence of residual endogenous hormone, must also be considered. Such a study in athyreotic subjects would utilize therapeutic doses of levothyroxine sodium and remove the need for a method of baseline correction.

Reference List for AppendixA

1. Schuirman DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinetics Biopharm.* 1987;15:657-80.

2. Guidance for Industry: Levothyroxine sodium tablets – *in vivo* pharmacokinetic and bioavailability studies and *in vitro* dissolution testing. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, December 2000.

3. Riley S, Ludden TM, Simulation study to assess alternative bioavailability calculations, study designs and acceptance criteria for determining the bioequivalence of levothyroxine sodium tablets. GloboMax Technical Report, Project #KNP00500, April 2002.

4. Maes M, Mommen K, Hendrickx D, Peeters D, D'Hondt P, Ranjan R, *et. al.* Components of biological variation, including seasonality, in blood concentrations of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers. *Clin Endocrinol.* 1997;46:587-598.

5. Synthroid (levothyroxine sodium tablets, USP). Physician Package Insert. Abbott Laboratories, Inc., North Chicago, IL. 03-5195-R1-Rev. July, 2002.