UNIVERSITY OF CALIFORNIA LOS ANGELES

UCLA

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO

SANTA BARBARA • SANTA CRUZ

DEPARTMENT OF MEDICINE
UCLA SCHOOL OF MEDICINE
CENTER FOR THE HEALTH SCIENCES

ENDOCRINOLOGY 111D
PLEASE REPLY TO: VA GREATER LOS ANGELES HEALTHCARE SYSTEM
11301 WILSHIRE BLVD.
LOS ANGELES, CALIFORNIA 90073

March 6, 2003

Kathleen Reedy, RDH, MS
Executive Secretary
Center for Drug Evaluation and Research, HFD-21
Food and Drug Administration
5630 Fishers Lane, Room 1093
Rockville, MD 20857

Re: Docket Number 3926, OC 200317
FDA Advisory Committee for Pharmaceutical Science
Meeting March 13, 2003

Dear Ms. Reedy:

I wish to comment on the assessment of levothyroxine bioequivalence pertaining to the public hearing on this topic scheduled for March 12, 13, 2003. I have had a sustained interest in this area for many years. I have been a practicing clinical endocrinologist for 35 years with a major interest in thyroid diseases. In addition, I have been a clinical investigator of thyroid disorders with peer-reviewed funding for more than 35 years. I edited the journal *Thyroid* from 1991-2000, the official journal of the American Thyroid Association.

I reviewed the document submitted by Abbott Laboratories concerning their Study M02-417, Evaluating the impact of correcting for endogenous T4 baseline on the bioequivalence of levothyroxine sodium formulations in healthy volunteers. In my opinion, the data show that the current method for establishing bioequivalence can lead to erroneous bioequivalence when doses differ by as much as 33%. Doses that differ by as little as 10% can be significant in various clinical circumstances, including the most common therapeutic use, namely, treatment of hypothyroidism.

A more reasonable standard for bioequivalence is the measurement of serum TSH in hypothyroid patients. Since the development of TSH immunoassays (1,2), studies have shown that the treatment of hypothyroidism with levothyroxine can reduce the serum TSH level to the normal range. Small changes in thyroxine dose, such as 12.5 mcg above or below that which normalizes serum TSH, may elevate serum TSH above the normal range or suppress it below the normal range in some patients (3,4). Elevation of serum TSH occurs when thyroxine is taken with drugs that interfere with its absorption, such as calcium carbonate, even though the fall in serum free T4 is very slight and within the normal range (5). Administration of a large amount of stable iodine can raise serum TSH

without causing a significant fall in serum T4, demonstrating the exquisite sensitivity of the pituitary to very small reduction of circulating thyroid hormone levels (6).

Despite 30 years of attempts to find clinical markers for the action of thyroid hormone that are more sensitive than serum TSH, or equally sensitive, no such test exists. Clinical endocrinologists now use the concept that the serum TSH is the most sensitive and accurate marker of the action of thyroid hormone. The serum TSH is the gold standard for diagnosis of primary hypothyroidism and for determining the ideal replacement dose in the patient with this condition. Overtreatment due to the substitution of a preparation of levothyroxine with increased potency could lead to osteoporosis or atrial fibrillation and cerebral embolic disease. Preparations with reduced potency could lead to unappreciated subclinical hypothyroidism and contribute to hypercholesterolemia, cardiovascular disease, or depression.

Levothyroxine is also used to suppress serum TSH in following patients with thyroid cancer because TSH is a growth factor for thyroid cancer. The sensitive serum TSH methods enable the clinician to set a reasonable goal for the degree of suppression, based on the staging of the cancer and the years of cancer-free survival (8). Precise titration of these patients is necessary in order to suppress serum TSH without causing clinical thyrotoxicosis.

Patients with benign thyroid nodules are treated with TSH suppression of a milder degree to reduce the size of the nodule. Although this therapy is controversial, the most recent work and review of the literature show it is efficacious in over one-half of the patients (9). Again precise dosage of levothyroxine is necessary to avoid overdosage or underdosage.

For the reasons noted above, I urge that you incorporate measurement of serum TSH in hypothyroid subjects as the standard for bioequivalence of levothyroxine sodium preparations. Of course it would have to be done in carefully controlled circumstances consistent with high-quality clinical research.

**References**

1. Hershman JM, Pittman JA: Utility of the radioimmunoassay for serum thyrotropin in man. Ann Internal Med 74:481-490, 1971.

2. Pekary AE, Hershman JM, Parlow AF: A sensitive and precise radioimmunoassay for human thyroid stimulating hormone. J Clin Endocrinol Metab 41:676-684, 1975.

3. Pekary AE, Hershman JM, Sawin CT. Linear modulation of serum thyrotropin by thyroid hormone treatment in hypothyroidism. Acta Endocrinol 95:472-478, 1980.

4. 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) 28:325-333 1988.

5. Singh N, 200 Singh PN, Hershman JM. Effect of calcium carbonate on the absorption of levothyroxine. JAMA 283:2822-5, 2000.

6. Sawin CT, Hershman JM, Azukizawa M: The relationship of the iodide-induced increase in the TSH response to TRH to changes in serum thyroid hormones. Hormone Research 10:20-24, 1979.

7. Hershman JM, Singh N. Hypothyroidism. Conn's Current Therapy. 54th edition. RE Racol (ed). W. B. Saunders, Philadelphia, 2002, pp. 646-648.

8. Hershman JM, Blahd WH, Gordon HE. Thyroid Gland. Cancer Treatment, Haskell CM ed. WB Saunders, Philadelphia, 5th ed, 2001, pages 1054-64.

9. Wémeau JL, Caron P, Schvartz C, et al. Effects of Thyroid-Stimulating Hormone Suppression with Levothyroxine in Reducing the Volume of Solitary Thyroid Nodules and Improving Extranodular Nonpalpable Changes: A Randomized, Double-Blind, Placebo-Controlled Trial by the French Thyroid Research Group. J Clin. Endocrinol. Metab87: 4928-4934, .2002.

Please do not hesitate to call on me if you wish to discuss this issue further.

Sincerely,

Jerome M. Hershman

Jerome M. Hershman, M.D.
Associate Chief, Endocrinology and Diabetes Division
VA Greater Los Angeles Healthcare System
Professor of Medicine, UCLA