American
Medical
Women's
Association, Inc.

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:

This letter outlines the American Medical Women's Association's (AMWA) concerns about current FDA standards for determining bioequivalence for levothyroxine sodium products and other endogenous hormonal drugs. The current method for determining bioequivalence appears to be both insensitive and flawed.

I am Dr. Omega Logan Silva, a past president of the AMWA, a board certified endocrinologist who practiced twenty-nine years at the Veterans Administration Medical Center in Washington, DC, most of the time as the Assistant Chief of The Endocrine Division seeing thyroid patients. Also, I have served on the FDA's Immunology Panel in the 1980's and spent a number of years doing research in endocrinology subsequent to working as a biochemist at the National Institutes of Health. Presently, I am Professor Emeritus of Medicine at the George Washington University.

Firstly, current pharmacokinetic parameters do not take into account the endogenous hormone present in the healthy volunteers tested. Bioequivalence of levothyroxine products may be difficult to assess accurately without the ability to distinguish the administered levothyroxine from the endogenous thyroxine present in the healthy volunteer. The assumption that because of the normal feedback of the hypothalamic-pituitary-thyroid axis that endogenous thyroid hormone is immediately and constantly suppressed by exogenous thyroid administration may not be operable in all circumstances. The FDA needs to determine if baseline correction will be adequate to ensure bioequivalence or if the study design needs to incorporate subjects with no thyroid function to accurately assess the bioequivalence of levothyroxine products.

Secondly, administering a single supraphysiological dose of 600 ug levothyroxine sodium to normal subjects does not provide data appropriate to determine bioequivalence. Unpublished data (submitted to the FDA by Abbott Laboratories) has indicated that

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current bioequivalence standards are unable to distinguish between 600 ug and 400 ug doses of administered levothyroxine.

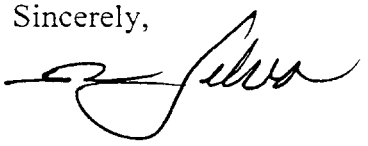
Another concern with the current guidance for bioequivalence with levothyroxine products is not utilizing serum TSH as the clinical marker. Serum TSH is the most sensitive and accurate clinical marker used to evaluate the action of thyroid hormone for the diagnosis of thyroid disease as well as determining the effectiveness of levothyroxine replacement therapy. The relationship between serum TSH and T4 concentrations are closely tied so that small reductions or increases in the dosage of replacement therapy can result in large shifts in serum TSH concentrations. Very significant clinical effects can be seen with levothroxine therapy with as little as a 10% difference in dose, especially in the elderly or thyroid cancer patient. FDA bioequivalence guidelines must take the TSH into account.

It should be emphasized that the treatment of hypothyroidism and hyperthyroidism, as well as thyroid cancer and other thyroid disease states, requires extremely tight control as indicated by serum TSH concentrations. Over-treatment and under-treatment due to the substitution of a preparation of levothyroxine with a variation in potency must be avoided since the consequences of both hypothyroidism and hyperthyroidism are well-known and often serious, both acutely and chronically. Again, this is especially important for the elderly, cardiovascular patients, infants, and patients treated for thyroid cancer. These patients and others may be at increased risk of adverse effects due to the interchange of levothyroxine products that are not therapeutically equivalent.

I would like to insert a personal story here. In the endocrine clinic at the VA where I worked I had several patients, who had been perfectly euthyroid on their levothyroxine doses, suddenly become inadequately controlled both clinically and chemically (according to their TSH). What had happened? Without the knowledge of the Endocrine Division the pharmacy had changed suppliers of levothyroxine. These patients had suffered needlessly and the cost savings the pharmacy realized was more than offset by the increase in laboratory use, more patient visits, and my professional time to say nothing of the cost of the harm to patients.

All of our patients need to be guaranteed that the drug they have been prescribed is not substituted with a product that may not have the same therapeutic response. We look forward to FDA action to ensure that there are stringent guidelines in place for determining the bioequivalence of levothyroxine and all endogenous hormone products.

Sincerely,



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