American Thyroid Association Statement
Review of Bioequivalence for levo-thyroxine products

The American Thyroid Association (ATA) is a professional society of 900 U.S. and international physicians and scientists who specialize in the research and treatment of thyroid diseases. In fair disclosure, the ATA acknowledges having received unrestricted financial support from companies which produce levo-thyroxine: Abbott Labs and Jones-Pharma.

Today's review of bioequivalence for levo-thyroxine products by the FDA's ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE very much interests the members of the ATA. Whenever L-T4 is used for the treatment of thyroid disease it is essential that the patient receive an accurate and predictable amount of hormone with each dose, along with a reproducible biologic effect. In the clinical setting, the dose for an individual on thyroxine is determined by a combination of the presence or absence of thyroid related symptoms as well as results from thyroid blood tests, especially TSH. Multiple factors affect the final dose of levo-thyroxine to include body mass, drug absorption and metabolism, the amount of residual functioning thyroid tissue, interference on absorption or metabolism by other medications or food, and patient compliance.

Hormones under control by a biofeedback mechanism provide a unique situation in which the body provides an indication as to whether or not the dosage is appropriate in a given patient. Close monitoring of TSH concentrations enables practitioners to provide patients with an appropriate amount of medication to ensure that hormone levels fall within a narrow optimal physiologic window.

It is our understanding that the bioequivalence for levo-thyroxine products is based on a Berg-Mayor type study design which requires the administration of 600 ug of levo-thyroxine orally to normal subjects followed by measurement of total thyroxine in the blood over 24-96 hours from which the AUC and C_{max} for the preparation is determined. For many oral medications this method may be very appropriate for determining pharmacologic bioequivalence, acting as a surrogate for therapeutic equivalence.

However, in the case of a hormone like thyroxine, this pharmacologic bioequivalence only provides a portion of the story since absorption of the product is only one component of the

equation; the biologic effect of the medication must also be assessed. TSH secretion by the pituitary provides measurable and critical feedback for assessing the biologic effect of a particular dose of L-T4. Thus, in clinical circumstances, determination of the serum level of TSH is a more appropriate method to assess T4 action on a biologic tissue.

Another important distinguishing factor of L-T4 is that it has a prolonged half-life of approximately one week. Presently measures of bioequivalence are done after an acute supraphysiologic dose of L-T4. This does not take into account the time required for the hormone to equilibrate in the patient's tissues. In addition, one can question the comparability of bioequivalence from a supraphysiologic dose of L-T4 in a normal person with an intact thyroid versus a patient with reduced or even no endogenous thyroid hormone production. Also, this technique does not allow discrimination between smaller dosages of L-T4.

In summary, in the case of hormone therapy, particularly with oral L-T4, we have an instance where one can actually measure true biological equivalence (i.e., the effect on a tissue of the body) which is what in reality "bioequivalence" should truly mean. Measurement of serum TSH should be done following an appropriate length of time (4-6 weeks) to account for the long half-life of L-T4. This would allow the medication's true biological equivalence to be assessed under clinically relevant conditions.

The ATA recognizes the complex nature of the issues being discussed today. Again, our main interest is to ensure that all L-T4 preparations are reliable sources of thyroxine replacement, and that any determination of bioequivalence for such preparations be based on both pharmacologic and therapeutic bioequivalence. Therefore, we feel it is imperative that the biologic effect of L-T4 as measured by TSH be a part of any method the FDA considers for evaluating equivalency of such preparations.