Evaluation of the Efficacy of Different L-thyroxine Preparations in the Treatment of Human Thyroid Disease

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By way of introduction I am Dr. Irwin Klein, Professor of Medicine and Cell Biology, New York University School of Medicine and Chief of the Division of Endocrinology at North Shore University Hospital the largest hospital network in the New York tri-state area. I am here today as a concerned Endocrinologist and Thyroidologist and as a consultant to King Pharmaceutical. For the past 25 years I have been interested in the clinical and scientific aspects of thyroid disease specifically the effects of thyroid hormone on the heart. I have published over 150 articles on the subject including chapters on Thyroid Disease in Stein's Textbook of Medicine, chapters on Thyroid Hormone and the Heart in Thyroid Text and the chapter on Cardiovascular Endocrinology for the upcoming edition of Braunwalds Heart Disease.

The issue that I would like to address deals specifically with the assessment of therapeutic efficacy of different L-thyroxine sodium preparations when used in the treatment of hypothyroidism. As you are well aware L-thyroxine is a narrow therapeutic index drug. After a diagnosis of hypothyroidism is established, treatment is initiated and the L-thyroxine replacement dose is titrated to the proper level based upon a combination of both laboratory and clinical parameters. The former includes specifically the TSH level which is targeted to return to a relatively narrow normal range. This is because the effects of under-treatment and

over-treatment are both potentially harmful. Specifically excess T_4 replacement producing suppression of serum TSH as reported by Sawin in The New England Journal of Medicine in 1994 and reviewed by us in that journal in February 2001 can produce atrial fibrillation in as many as 30% of patients above the age of 60. Since hypothyroid patients are committed to lifelong thyroid hormone treatment, the issue with regard to selection of appropriate treatment formulations with reliable and reproducible therapeutic efficacy is obviously important to the clinician.

My review of the FDA guidance for bioequivalence indicated that it is possible to consider two drugs bioequivalent based upon T4 pharmacokinetics which fall between –80 to +125% of the reference compound.

As a physician who cares for over 2,000 patients with hypothyroidism I am concerned that the application of the existing FDA guidelines for bioequivalence when applied to different thyroid hormone preparations will yield results which do not properly reflect therapeutic equivalence. It has been well documented that even with a normal blood level of T4, a low TSH level predicts increased cardiovascular risk. This leads to the opinion that any study of bioequivalence must include serum TSH levels measured at steady state. We have provided a review to the committee which further outlines the basis for this conclusion. If the

guidelines are not amended the resulting effect may be that substitution of non-therapeutically equivalent L-thyroxine preparations will produce potentially unwanted effects among a significant number of the over 8 million patients currently treated for hypothyroidism in the United States. Switching a patient from one formulation of L-thyroxine sodium to another approved under the current guidelines would require at a minimum repeat TSH testing and dosage adjustment to assure that these patients remain euthyroid. Otherwise it could be expected that as many as 20% of the substituted patients would experience a significant fall in TSH and for the over 60 year old segment of the population that would put a minimum of 10,000 patients each year at risk for iatrogenic atrial fibrillation. Since the cost of treatment of those patients is conservatively estimated at $7,000, the increased health care cost as a result of these actions could be well in excess of $70 million yearly. I would be happy to discuss these opinions further with you.