THE UNIVERSITY OF CHICAGO MEDICAL CENTER
DEPARTMENT OF MEDICINE
THYROID STUDY UNIT
FAX: (773) 702-9241

Graeme I. Bell, Ph.D.	(773) 702-9116
Melissa Cavaghan, M.D.	702-7321
Leslie J. DeGroot, M.D.	702-1470
David A. Ehrmann, M.D.	702-9653
Murray J. Favus, M.D.	702-6227
Louis H. Philipson, M.D.	702-9180
Samuel Refetoff, M.D.	702-6939

Nicholas Sauter, M.D.	702-9179
Janet Tobian, M.D.	702-0746
Eve Van Cauter, Ph.D.	702-0169
Roy E. Weiss, M.D.	702-6939
Outpatient Office	702-6138
New Patient Appointments	702-6138
Endocrinology Laboratory	702-6941
Lipoprotein Core Laboratory	702-1775

Kathleen Reedy, RDH, MS
Executive Secretary
Center for Drug Evaluation and Research, HFD-21
Food and Drug Administration,
5360 Fisher Lane, Rm 1093,
Rockville, MD 20857

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

Dear Ms Reedy-

I write as a physician who has been in active endocrine practice, teaching, and research, for a bit more than 50 years. This period has witnessed profound changes in medical care, including dramatic changes in the precision of diagnosis and treatment of thyroid disease. Many of us caring for patients spend a significant portion of our professional lives adjusting T4 doses to make patients feel their best. As you know, about 6% of all women, and probably 12% of women over 50, are on replacement or suppressive doses of thyroxin, so the effort involves a significant number of people.

Remember firstly that dosage with a replacement hormone such as thyroxin is not at all like giving an antibiotic or chemotherapeutic agent or psychotropic medication where the upward limit is defined by adequate response without toxicity. Instead we are attempting to establish the patients entire metabolic apparatus at a specific narrow set-point that conforms to the bodies own intrinsic recognition system, represented by TSH response. We use TSH to monitor the biochemical response, adjusting the dose to be near the recently determined United States mean of 1.2uU/ml. Most patients tend to feel their best when their dose of thyroxin puts their TSH is in the 0.4-1.5 range. An adjustment of thyroxin dosage from 7-15% is typical, and can move someone from just hypothyroid to a normal level, or mildly hyperthyroid to a normal level. An adjustment of 25% is a very large titration. Naturally we are concerned with the long term effects, including damage to the heart or bones- but at the more immediate level we also

consider subtle but important changes in weight, energy, heart palpitations, altered sleep, irritability, hair thinning, menstrual function, bowel function, and on . And of course in thyroid cancer patients the demand to be just right in dosage is greater, since we commonly try to maintain patients with the dose just high enough to suppress TSH but not cause overt symptoms of hyperthyroidism.

Considering the precision in dosage that we attempt, endocrinologists probably believe that a 100ug thyroxin tablet should not contain as little as 80 ug or as much as 120 ug of thyroxin. That tablets could in fact vary by over 30% and still be with in FDA allowed limits would astound endocrinologists if they thought about it, and probably would be greeted by patients with cries of horror. It would be very interesting, and perhaps appropriate, to add to product labels a statement that "according to current FDA guidelines, dosage variation in thyroxin content of up to 30% is acceptable". This is in fact the case. This is also one of the major concerns that many physicians have about free substitution by pharmacists of one brand for another.

I view the proposals to alter bioequivalence standards for this medication as very positive. In current assays using the AUC of a test dose of 600ug given to healthy subjects, 60-80% of the AUC is contributed by prior days dosages, not the test dose. Correcting the AUC for prior day hormone levels as a baseline is clearly an important step in improving precision. Furthermore, accounting for the normal T4 metabolism will probably further improve precision. It is possible, though uncertain, that precision in this type of assay would be improved significantly by using study subjects who are athyreotic and on T4 replacement.

A second extremely important change would be to reduce allowed variation of potency from a range that encompasses 80-125% confidence limits to a 90-110 percent limit. Probably most products currently in use would actually fall within such tolerances, so institution of this narrower range would not disrupt the market. Such precision is in reality absolutely necessary if we are to provide our patients with the precision in management that they expect. Having all preparations conform to this standard would also go a long way toward allaying concern about substitutibiity of products on the market.

METHODS FOR IMPROVING EVALUATION OF POTENCY AND COMPARABILITY OF T4

1. using current 600 single dose AUC evaluation-
   - -Subtract prior day T4 level to provide baseline.
   - -Include a factor (14%) for decay of prior T4 pool.
   - -Possibly use athyreotic subjects on stable replacement
   - -Consider using athyreotic subjects on T3 replacement so that serum T4 is zero.
   - -Contract with a group of subjects who will do repeated studies.
   - -Reduce the 90% confidence limits from the current 80-125% of the mean, to a tighter level of 90-110% of the mean.
2. Do a real-world comparison in athyreotic subjects maintained on T4, with cross over design, adequate study periods, and TSH as the endpoint.
   - -Do studies on a group of subjects that contract for repeated similar evaluations.

May I also comment on another quite different approach to determining reliability and equivalence of T4 products. In the real world treatment does not consist of 600ug single T4 doses, but therapy with a replacement dose over an extended time. If we really want to compare two products properly, it must be done by replacement studies on athyreotic subjects maintained euthyroid without dosage variation for several months pre-study. The exact design should include a period of at least 5 weeks therapy, a wash out period of at least 5 weeks between treatments, and primary assessment by TSH response. And again, contracting with a group of subjects for continued participation in such evaluations would be advantageous.

Thanks for considering these views. They are not new or unique. Rather, these ideas have been held over a prolonged period of time by endocrinologists who have been using and
reviewing thyroxin therapy.

Sincerely yours,

Leslie J De Groot,MD
Professor of Medicine
Endocrinology Section/University of Chicago