DEPARTMENT OF HEALTH & HUMAN SERVICES

OCT 3 2007

Food and Drug Administration
Rockville MD 20857

Ms. Angela G. Long
Executive Secretariat
The United States Pharmacopeial
Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 10-07-001-O

Dear Ms. Long:

This letter proposes revisions to the monograph for Levothyroxine Sodium Tablets in USP 30, pages 2470-2471.

We propose that the assay range specification in the USP monograph for Levothyroxine Sodium Tablets be narrowed from the current 90 percent to 110 percent of label claim to 95 percent to 105 percent of label claim. This proposal is part of an ongoing effort to address concerns expressed about the performance of approved levothyroxine sodium products and to help ensure that levothyroxine sodium drug products maintain their quality throughout their shelf-lives.

In response to physician and patient concerns about product performance, particularly for patients taking different levothyroxine sodium products after prescription refills that may involve products from different manufacturers, we requested product stability data from manufacturers of all the approved, marketed levothyroxine sodium drug products manufactured between July 2003 and June 2005 to obtain a stability profile for each marketed levothyroxine sodium product. Although all approved levothyroxine sodium products meet the current potency specifications, it is evident from these data that there is a trend of potency loss in levothyroxine sodium products, with some formulations showing potency amounts approaching 90 percent of labeled potency by the established expiration date.

In October 2006 we presented the data and analyses concerning the potency loss of levothyroxine sodium products to a joint meeting of the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) and Advisory Committee for the Pharmaceutical Sciences (ACPS) (see transcript at http://www.fda.gov/ohrms/dockets/ac/cder06.html#.) FDA asked at the meeting whether this loss of potency could raise clinical concerns for patients. The vast majority of the joint advisory committee panel voted that a 10 percent loss in potency over shelf life raises clinically significant concerns and recommended that the potency specifications for human levothyroxine sodium products be narrowed from 90 to 110 percent to 95 to 105 percent. FDA proposes a revision to the USP monograph based on our evaluation of stability data submitted as part of the drug approval process, evaluation of stability data provided by applicants in the spring of 2006, evaluation of available clinical data and literature, discussions and opinions expressed at an October 2006 joint meeting of the EMDAC and the ACPS, and further evaluation of the joint advisory committee panel's recommendation.

We are notifying the holders of approved NDAs and ANDAs for levothyroxine sodium drug products that we have decided to require that all approved levothyroxine sodium drug products meet a 95 percent to 105 percent range of label claim throughout their labeled shelf-lives. We are directing them to incorporate these revised potency specifications in their applications and to begin meeting these specifications no later than 24 months after notification (October 3, 2007). In addition, we are informing the application holders that FDA will work with the USP to revise the potency specification indicated in the USP monograph for levothyroxine sodium tablets.

We propose that the USP monograph revision to the assay range also include a provision for a delayed implementation to correspond as closely as possible to the above date provided to the application holders. In this way, implementation of the USP monograph revision can be contemporaneous with the date when all approved products will be expected to meet the revised potency specifications.

We hope these comments will be helpful to USP and the Monograph Development – Gastrointestinal, Renal, and Endocrine Expert Committee. Please feel free to contact me at 301-796-1585 if there are any questions. Please use the reference number provided above on any ensuing correspondence.

As a final note, we would like to advise you that due to public interest in this matter, we will be placing a copy of this letter, a sample copy of the letter sent to application holders, and additional explanatory information, including question and answers, on the following CDER Internet website:
http://www.fda.gov/cder/drug/infopage/levothyroxine/default.htm.

Sincerely,

Larry A. Ouderkirk

Larry A. Ouderkirk
Director
Compendial Operations Staff
Office of Pharmaceutical Science
Center for Drug Evaluation & Research