DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

MEMORANDUM

From: Center for Drug Evaluation and Research

To: Members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and the Advisory Committee for Pharmaceutical Science (ACPS)

Subject: Joint Advisory Committee meeting on levothyroxine sodium drug products

Date of Meeting: October 4, 2006

EXECUTIVE SUMMARY

The purpose of the joint advisory committee meeting is to discuss the stability profiles of FDA-approved levothyroxine sodium drug products and whether the stability profile of any of these products leads to a loss of potency that has clinical implications. If there are clinical implications, then FDA must consider whether it should take additional regulatory actions.

The diagnosis and management of thyroid disorders have advanced significantly over the past century. As a result of FDA's regulatory actions, the quality and consistency of levothyroxine sodium products have improved significantly compared to those that were historically available. Nonetheless, manufacturers of certain approved levothyroxine sodium products and some clinicians have expressed concerns about potential variability between levothyroxine sodium products that FDA has reviewed and approved as interchangeable with one another.

Levothyroxine sodium is considered a drug with a narrow therapeutic index in which suboptimal dosing may result in untoward adverse effects. FDA acknowledges that substantial variability in potency between levothyroxine sodium products (interproduct variability) could raise clinical concerns. However, the agency believes that if variability is a concern, it is fundamental to first understand and to properly control consistency of dosing within a given product over time from prescription to prescription (intraproduct variability) before contemplating any action related to relationships between products.

As a result, the agency requested product stability data from manufacturers of all approved and marketed levothyroxine sodium drug products, manufactured between July 2003 and June 2005. Current potency specifications for approved products allow for a loss of 10% potency over the expiration dating period (a 90-110% potency specification). FDA's evaluation of the stability data reveal that some of the approved, marketed levothyroxine sodium formulations lose up to 10% potency within a 8 to 12 month time period. This means that a patient dispensed fresh product would receive 100% of the labeled claim for LT4, but within 8 months the product could be only 90% potent.

The questions before the committee relate to whether the approved, currently marketed products retain sufficient clinically relevant potency over a reasonable period of time to ensure consistent safe and effective long-term management of the underlying thyroid condition, particularly when the patient receives therapy from only one levothyroxine sodium product over time.

QUESTIONS PRESENTED

1. Does a 10% loss in potency over shelf life raise clinically significant concerns?

2. If there are clinically significant concerns, should the potency specifications for levothyroxine sodium products be narrowed (e.g., from a minimum potency loss of 10% (a 90-110% potency specification) to a minimum loss of 5% (e.g., 95-105% potency specification))?

ATTACHMENTS

- Attachment 1 provides the regulatory history of how these products have been made available to the American public and a discussion of current regulatory issues.

- Attachment 2 provides the clinical background for the use of oral levothyroxine sodium products.

- Attachment 3 provides regulatory background on potency and stability, a discussion of the stability data that we requested from manufacturers of levothyroxine sodium products, and a presentation of the data provided to the agency.