

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005N-0137]

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Levothyroxine Sodium Therapeutic Equivalence; Public Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public meeting on the therapeutic equivalence of levothyroxine sodium drug products. This will be a workshop involving FDA staff and representatives of three medical societies: The American Thyroid Association (ATA), the Endocrine Society, and the American Association of Clinical Endocrinologists (AACE). The purpose of the public meeting is to discuss FDA's regulatory standards and methodological approaches for determining therapeutic equivalence between levothyroxine sodium drug products. The agency is seeking comments and input from interested constituencies, including patient advocacy and education groups, and pharmaceutical sponsors.

DATES: The public meeting will be held on May 23, 2005, from 8:30 a.m. to 5 p.m. Submit written or electronic comments by July 23, 2005.

ADDRESSES: The public meeting will be held at the National Transportation Safety Board Boardroom and Conference Center, 429 L'Enfant Plaza, SW., Washington, DC 20594, 202-314-6421. The center can be reached by Metro using the L'Enfant Plaza station on the green, yellow, blue, and orange lines. For directions, see <http://ntsb.gov/events/newlocation.htm>. (FDA has verified

the Web site address, but FDA is not responsible for any changes to the Web site after this document publishes in the **Federal Register**.)

Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Rose Cunningham, Center for Drug Evaluation and Research (HFD-006), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852, 301-443-5595, e-mail: cunninghamr@cderr.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of August 14, 1997 (62 FR 43535), FDA declared that oral drug products containing levothyroxine sodium were considered new drugs and subject to regulation as such. The document called for new drug applications (NDAs) for levothyroxine sodium products from sponsors wishing to market such products in the United States after August 14, 2000. This deadline was eventually extended to August 14, 2001.

The NDAs submitted for levothyroxine sodium products included literature references supporting the safety and effectiveness of levothyroxine sodium for the proposed indications and full manufacturing information supporting the purity, potency, and stability of the products. Manufacturers were required to target 100 percent of the labeled levothyroxine sodium content at release. (Some manufacturers had historically added a “stability overage” to give their products a longer shelf-life.) In addition, bioavailability and in vitro dissolution studies were required to establish that the products

were readily and consistently absorbed across the range of dosage strengths proposed to be marketed. To assist manufacturers, in December 2000, FDA published a guidance on the conduct of in vivo pharmacokinetic and bioavailability studies and in vitro dissolution tests on these products.

FDA has approved seven NDAs for levothyroxine sodium products. None were originally rated as interchangeable with any other. Since their approval, FDA has approved supplemental NDAs from some sponsors demonstrating the therapeutic equivalence (interchangeability) of their products to other approved levothyroxine sodium products. The agency has also approved one levothyroxine sodium product under an abbreviated new drug application (ANDA).

ATA, the Endocrine Society, and AACE have questioned FDA's regulatory and scientific standards for determination of therapeutic equivalence of levothyroxine sodium products, particularly FDA's bioequivalence methodology.

II. Scope of the Public Meeting

The public meeting is intended to review FDA's regulatory and scientific approach to levothyroxine sodium products, including manufacturing standards, in vitro dissolution studies, and bioavailability/bioequivalence methods.

The public meeting will also review clinical, scientific, and methodological issues relevant to the possible use of serum thyrotropin concentration as a pharmacodynamic measure of levothyroxine sodium bioequivalence.

The public meeting will include representatives from FDA and from the three medical societies. A series of brief presentations will frame the issues under consideration, followed by panel discussions involving speakers and

moderators, with questions and comments from the audience. Other interested constituencies (e.g., patient advocacy and education groups, pharmaceutical sponsors, general public) will have an opportunity to provide input during the question and comment periods.

III. Registration, Agenda, and Presentations

No registration is required to attend the meeting. Seating will be on a first-come, first-served basis. If you need special accommodations due to a disability, please contact (see **FOR FURTHER INFORMATION CONTACT**).

The agenda for public meeting will be available on FDA's Center for Drug Evaluation and Research Web site at <http://www.fda.gov/cder/meeting/levothyroxine.htm> and at the meeting. After the meeting, the agenda, presentations, and transcript will be placed on file in the Division of Dockets Management under the docket number found in the heading of this document and on CDER's Web site identified previously.

IV. Comments

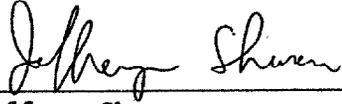
Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments on the topics discussed in this document. Submit two copies of mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments are available for public examination in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

V. Transcripts

Copies of the transcript may be requested in writing from the Freedom of Information Office (HFI-35), Food and Drug Administration, 5600 Fishers Lane, rm. 12A-16, Rockville, MD 20857, approximately 20 working days after

the meeting at a cost of 10 cents per page or on compact disc at a cost of \$14.25 each. You may also examine the transcript at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: 4-14-05
April 14, 2005.



Jeffrey Shuren,
Assistant Commissioner for Policy.

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