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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NOV 26 2002

Hogan & Hartson  
Attention: David M. Fox  
Columbia Square  
555 Thirteenth Street, NW  
Washington, DC 20004-1109

Reference Number: OGD #02-413

Dear Mr. Fox:

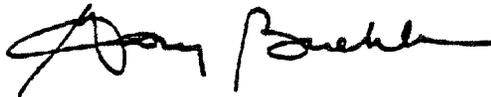
This is in reply to your letter dated July 10, 2002 written on behalf of Abbott Laboratories, sponsor of NDA No. 21-402 for Synthroid® (levothyroxine sodium, USP). The letter provided comments regarding the appropriate reference listed drug for bioequivalence (BE) studies to establish an "AB" rating for product applications submitted under section 505(b)(2) or 505(j) of the Federal Food, Drug, and Cosmetic Act referencing Synthroid®.

Detailed background was provided about the August 1997 Federal Register notice that reaffirmed the new drug status of levothyroxine sodium tablets and the required FDA approval to be legally marketed. The letter pointed out that the notice was based on concerns that marketed, unapproved levothyroxine sodium tablets may not be consistent in potency and bioavailability and that stability was not necessarily assured. The letter also stated that since levothyroxine sodium tablets have a narrow therapeutic index, precise dosing is essential and patients could not be assured that they were receiving a consistent therapeutic dose from any of the marketed products.

Rationale was provided for the opinion that a BE study performed on a pre-NDA version of Synthroid® tablets should not be used to establish a therapeutic equivalence rating of "AB" for an already approved and marketed 505(b)(2) application for levothyroxine sodium tablets or to secure market approval for an application accepted pursuant to section 505(j).

The Office of Generic Drugs agrees with your conclusion that it would be inappropriate for FDA to accept any BE study that used the previous, unapproved version of Synthroid® tablets as the reference products in such a study. Therefore, FDA would not expect to assign an "AB" therapeutic equivalence code to an already approved 505(b)(2) application for levothyroxine sodium tablets that used the previous version of Synthroid® tablets in its study. Neither would FDA accept an abbreviated new drug application that contains a BE study that used the previous version of Synthroid® tablets.

Sincerely,



Gary J. Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research