

Levothyroxine Sodium Regulatory History

Jane A. Axelrad, J.D.
Associate Director for Policy
Center for Drug Evaluation and Research

Presentation at Joint Advisory Committee Meeting
October 4, 2006

Overview

- Early history of levothyroxine use and regulation
- FDA concerns
- FDA regulatory actions
- Results
- Remaining issues

Early History

- Late 1800s, treatments developed from thyroid hormone obtained from animals
- Synthetic levothyroxine products (T4) became commercially available in the 1950s without approved new drug applications
- By 1997, at least 37 manufacturers or repackers of marketed levothyroxine sodium products

Regulatory Concerns

- Between 1987 and 1997, FDA received reports of adverse drug reactions associated with levothyroxine products and the agency became aware of multiple recalls due to:
 - Sub-potency
 - Stability failures
 - Super-potency
- Products routinely released with a stability “overage” (more than 100% of labeled claim of T4) to “address” rapid degradation of product

Regulatory Action

- August 14, 1997, FDA announced in Federal Register that oral drug products containing levothyroxine sodium products were considered new drugs subject to approval under the Food, Drug, and Cosmetic Act
- Because of medical necessity, set deadline of August 14, 2000 (later extended to August 14, 2001) for companies to submit applications and get products approved

Regulatory Action, cont'd

- FDA issued a guidance that established a gradual phase-out of unapproved products to allow for manufacturers of approved products to scale up their production and for patients and health care providers to make a reasonable transition from unapproved to approved products (7/2001)

Results

- FDA has approved under section 505(b)(2) of the Act 5 NDAs for levothyroxine sodium products that are currently marketed.
- FDA approved 2 ANDAs under section 505(j) for products currently marketed.
- Several products have demonstrated bioequivalence to another product and received an AB rating to that referenced drug (i.e., they are therapeutically equivalent).

Results, cont'd

- Higher quality products than pre-1997
 - All products have established content uniformity (tablets contain reasonably uniform quantity of T4)
 - Have to target 100% potency at release (eliminates super-potency)
 - Some products were reformulated to improve stability profiles
 - Labeled expiry based on products meeting standard USP potency specification (not less than 90% of labeled amount of T4 during shelf-life)

But issues remain. . .

- Clinicians have expressed concerns about substitution of one product for another
- FDA denied two citizen petitions expressing concerns about FDA's bioequivalence methodology for these products, and a petition for reconsideration is currently pending
- FDA cosponsored a meeting with the American Thyroid Association, the Endocrine Society, and the American Association of Clinical Endocrinologists in May 2005 to discuss concerns
- Although the focus of the meeting was on interchangeability of products, bioequivalence methodology and therapeutic equivalence ratings, FDA believes the significance of within product variability is not well understood