Levothyroxine Sodium Regulatory History

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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
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.
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 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.