Stability Of Levothyroxine Sodium Products

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Stability Of Levothyroxine Sodium Products

- Stability overview
- Levothyroxine Stability – History
- Levothyroxine Stability – Present
- Levothyroxine Stability Data
- Conclusion
Potency

- Potency = the strength of a drug product, expressed as the quantity of active ingredient per dosage unit
- Potency determined by assay (chromatographic, chemical determination or biological assay)
- Can be expressed as percent labeled claim (e.g., 96%), or as amount of active ingredient per dosage unit (e.g., 24 mcg per tablet)
Introduction - Stability

A measure of how a pharmaceutical article maintains its quality attributes over time

– Stability testing is used to:
  - Provide evidence as to how the quality of a drug product varies with time
  - Establish shelf life for drug product
  - Determine recommended storage conditions
  - Determine container closure system suitability
Stability Overview

- A drug must conform to standards for strength, quality, and purity throughout its labeled shelf life.
- Drug is tested according to an approved stability protocol.
- Each package presentation and strength is tested separately.
Stability Protocol

- Specifications
  - Tests
  - Analytical methods (validated)
  - Acceptance criteria

- Packaging (type, composition, size)

- Testing schedule

- Storage conditions

- Expiration dating period
Stability Specification

Stability specification
- Ensures maintenance of product quality through expiry to maintain safety and efficacy

Typical tests
- **Assay** *(potency determination)*
- Dissolution (oral dosage forms)
- Identification
- Impurities/degradation products
- Content uniformity
- Physical characteristics
Levothyroxine Tablet Stability

Levothyroxine sodium (T₄) is labile to the following:
- Heat, moisture, oxidative conditions, chemical reactions
- *These conditions typically occur during levothyroxine formulation, tableting, packaging, and storage.*

Many levothyroxine drug products have exhibited:
- History of sub-optimal stability profile
- Significant loss of potency over shelf life
- Inconsistent stability profiles within an individual manufacturer’s drug product line
Current levothyroxine potency requirements (A/NDA products)

Agency requires product formulated at a target of 100% of labeled claim, e.g., **no “stability overage”**

– However, the current NDA/ANDA Specifications permit assay of 90 to 110% labeled claim based upon current USP monograph.

Potency range takes into account **analytical variability** and **manufacturing variability**.

Not intended to allow for release with overage
FDA Request for Levothyroxine Tablet Stability Data

**Purpose:** To further evaluate stability data for all marketed levothyroxine drug products

Request sent to seven applicants (5 NDA and 2 ANDA)

All available stability data for lots manufactured between July 2003 and June 2005 (all strengths and packaging)
Response to FDA Request for Levothyroxine Tablet Stability Data

- Agency received stability data from all 7 applicants
- Quantity of data varied between applicants
- Agency focused evaluation on potency
- Agency focused on room-temperature stability studies (25°C and 60% RH)
Levothyroxine Stability --- Overview of Submitted Data

- Received data for all 12 tablet strengths
- Data charts are presented for three strengths: 25, 100, and 150-mcg
  - 25-mcg (lowest dose, used for pediatric patients)
  - 100-mcg (most prescribed, expressions of strength same number for label claim and for mcg T4 per tablet)
  - 150-mcg (example of overlapping dose)
    - Degraded 150-mcg tablets can contain < T4 than fresh 137-mcg tablets
Brand "A" 25-mcg tablets in 100-count bottles

- **Lot 1**
- **Lot 2**
- **90% LC**
- **95% LC**

**mcg of T4 per tablet**
- 22.5
- 23
- 23.5
- 24
- 24.5
- 25
- 25.5
- 26

**Months at 25C and 60% RH**
- 0
- 5
- 10
- 15
- 20
Brand "F" 25-mcg tablets in 100-ct bottles

- Lot 1
- Lot 2
- Lot 3
- Lot 4
- Lot 5
- Lot 6
- 90% LC
- 95% LC

mcg of T4 per tablet vs. Months at 25°C and 60% RH
Brand "G" 100-mcg tablets in 1000-count bottles

Months at 25C and 60% RH

mcg of T4 per tablet
Brand "D" 100-mcg tablets in 1000-ct bottles

- Lot 1
- Lot 2
- Lot 3
- 90% LC
- 95% LC

mcg of 14 per tablet vs. Months at 25C and 60% RH
Some stability studies indicated loss of potency between 5 and 10% during labeled expiration dating period (expiry).

Expiry varied widely between *products*, *dosage strengths*, and *packaging*
- Shortest expiry = 8 months
- Longest expiry = 24 months
- Expiry was based upon meeting the requirement that potency $\geq 90.0\%$ labeled claim through expiry
Stability Data vs. Current Potency Specification Limits

- Current regulatory requirements allows for 10% loss of potency from initial release (100.0 to 90.0%)
- Intermediate tablet strengths (112-150 mcg) are separated by ≤ 10 % of levothyroxine dose
- Theoretically, a tablet can degrade to contain less $T_4$ than a lower strength tablet!
  - **Example**: 150 mcg tab losing 10% potency contains 135 mcg $T_4$ (< fresh 137-mcg tab) OVERLAPPING DOSE
  - **This situation actually occurred in 2 stability studies**
Brand "F" 150-mcg tablets in 1000-ct bottles

![Graph showing the decrease in mcg of T4 per tablet over months at 25C and 60% RH for different lots and conditions.]
Brand "C" 150-mcg tablets in 100-count bottles

- Lot 1
- Lot 2
- Lot 3
- Lot 4
- Lot 5
- 137-mcg tabs LC
- 150-mcg tabs 90% LC

mcg of T4 per tablet vs. Months at 25C and 60% RH
Levothyroxine Stability Studies – Comparison to “Real Life” situations

- Stability studies utilize controlled conditions of temperature and humidity
- Represent “idealized” storage conditions
  - Temperature/humidity per ICH (controlled)
    - 25°C ± 5°C and 60% RH ± 5% RH (room temperature)
  - Closed containers (containing desiccants and inner seals)
    - Open fresh container(s) for each test station
“Real-life” Situation for Storage of Levothyroxine Tablets

- Storage conditions typically not controlled
- Shipped from manufacturer to holding center
- Shipped from holding center to warehouse
- Mail order (can be up to a 3-month supply)
- Shipped from warehouse to pharmacy
  - Store in opened stock bottles
  - Baker cells for dispensing
  - Filled into prescription bottles + dispensed
- Stored in various ways by patient (often in warm, moist environment)
Compare Stability Studies With Real-Life Conditions

Can assume that real-life stability profile of the drug product is NOT BETTER than that observed from stability studies
Conclusions

Based Upon Best Stability Testing Conditions:

- Observed Inter-product variability of potency
- Observed Intra-product variability of potency
  - Overlapping doses
  - There has observed potency loss through expiry

-Potential Impact of Potency Change on Patients?