

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 (T_4) 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)

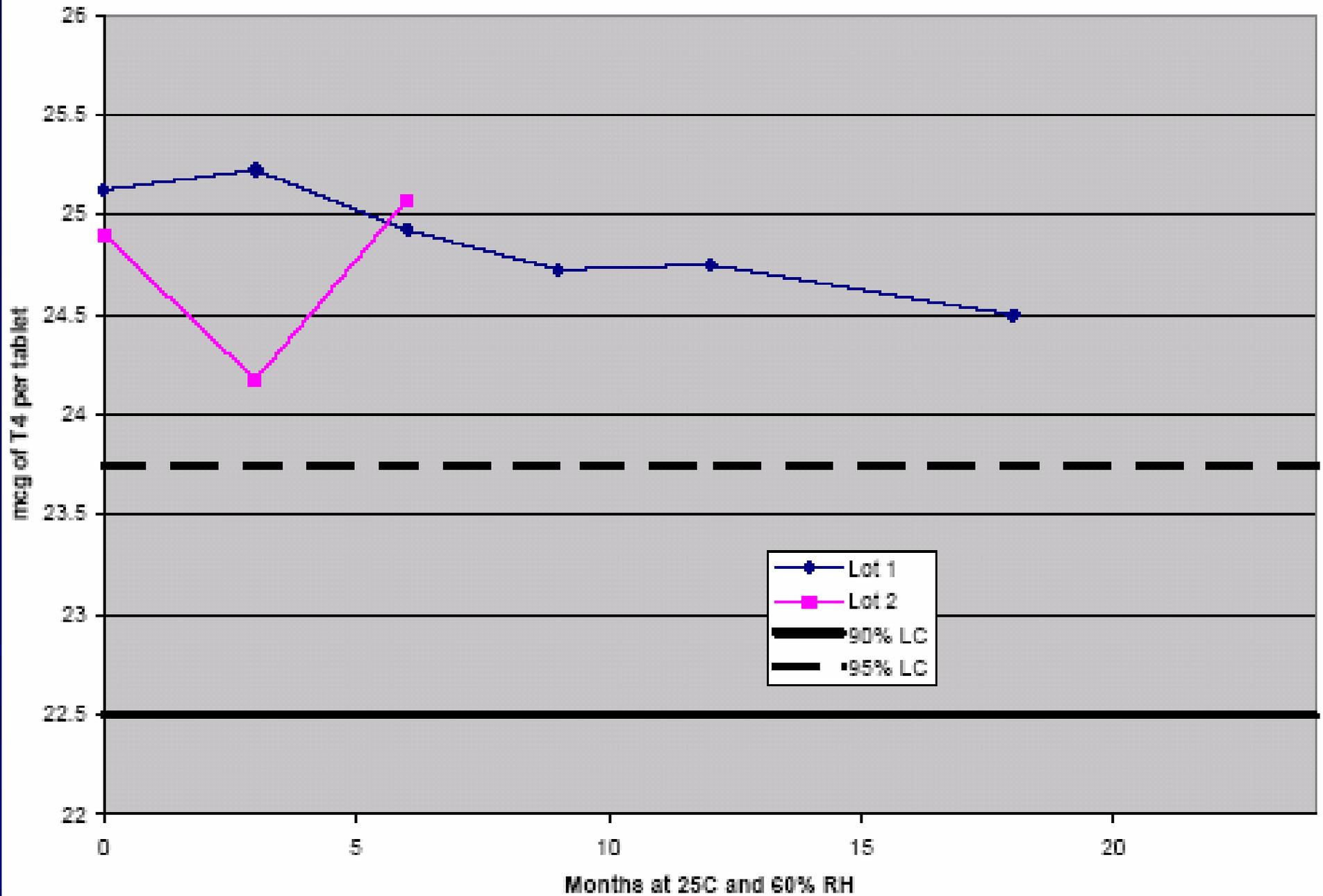
Response to FDA Request for Levothyroxine Tablet Stability Data

- 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)

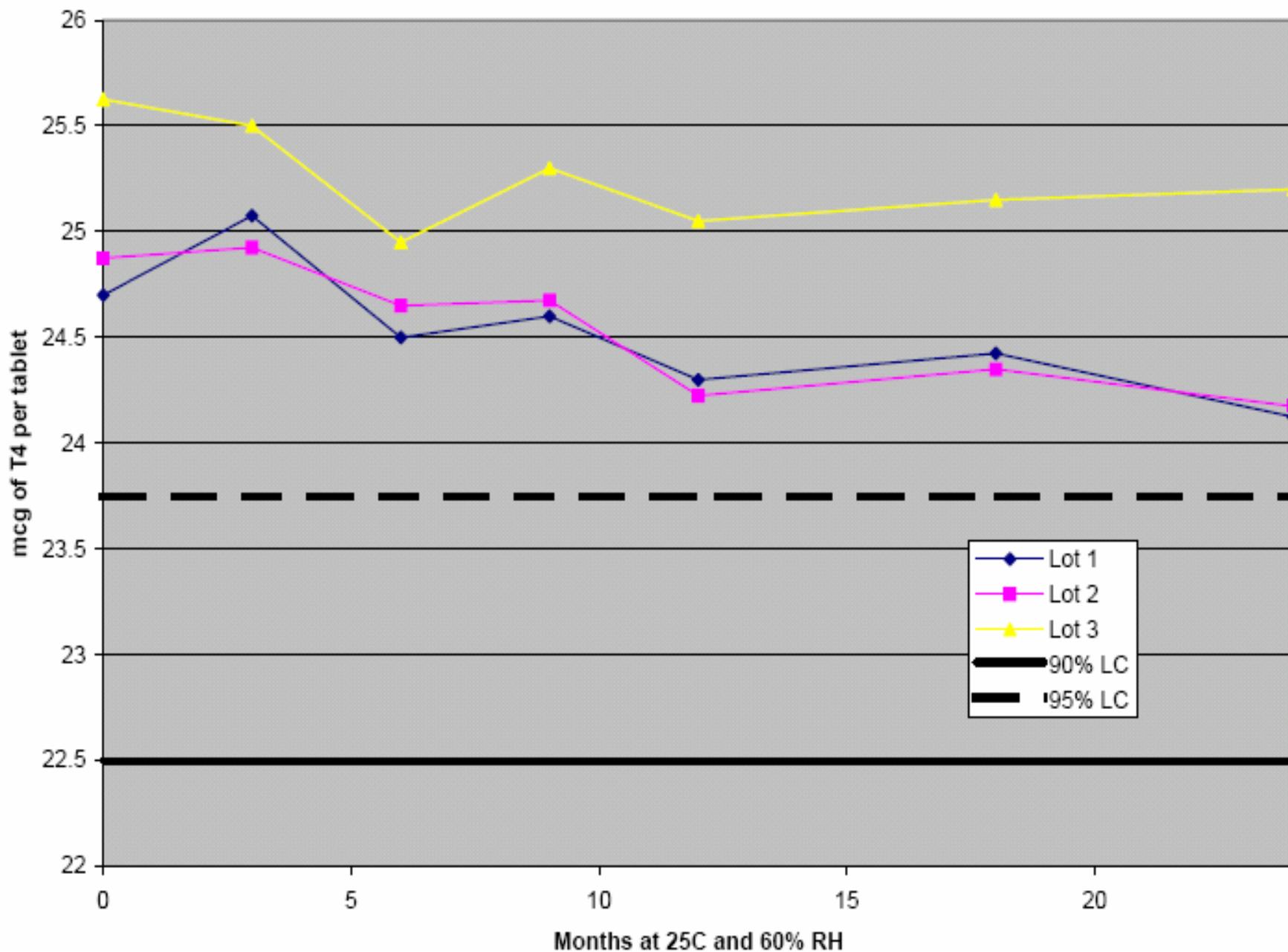
Levothyroxine Stability --- Overview of Submitted Data

- 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

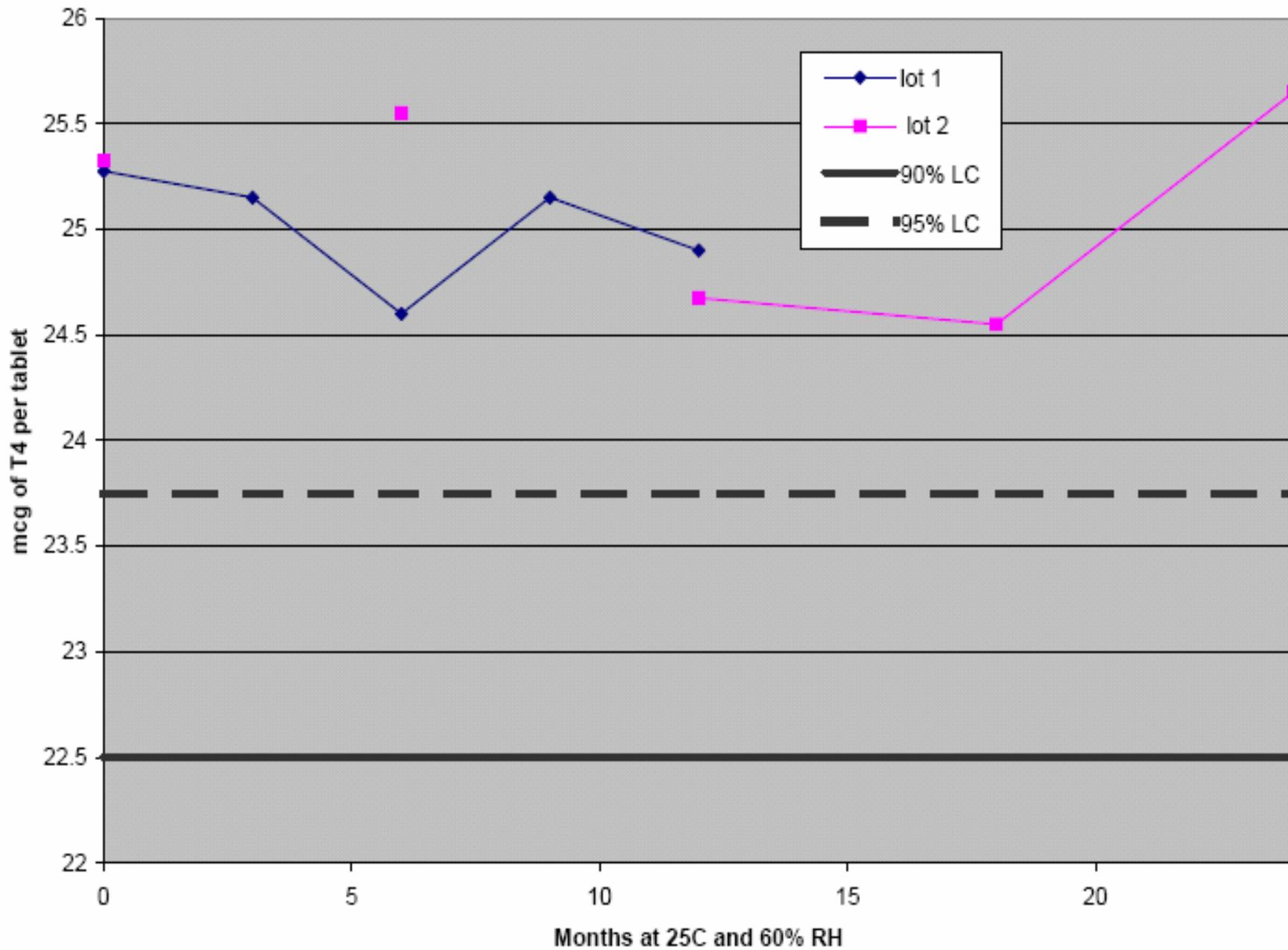
Brand "E" 25-mcg tablets in 100-ct bottles



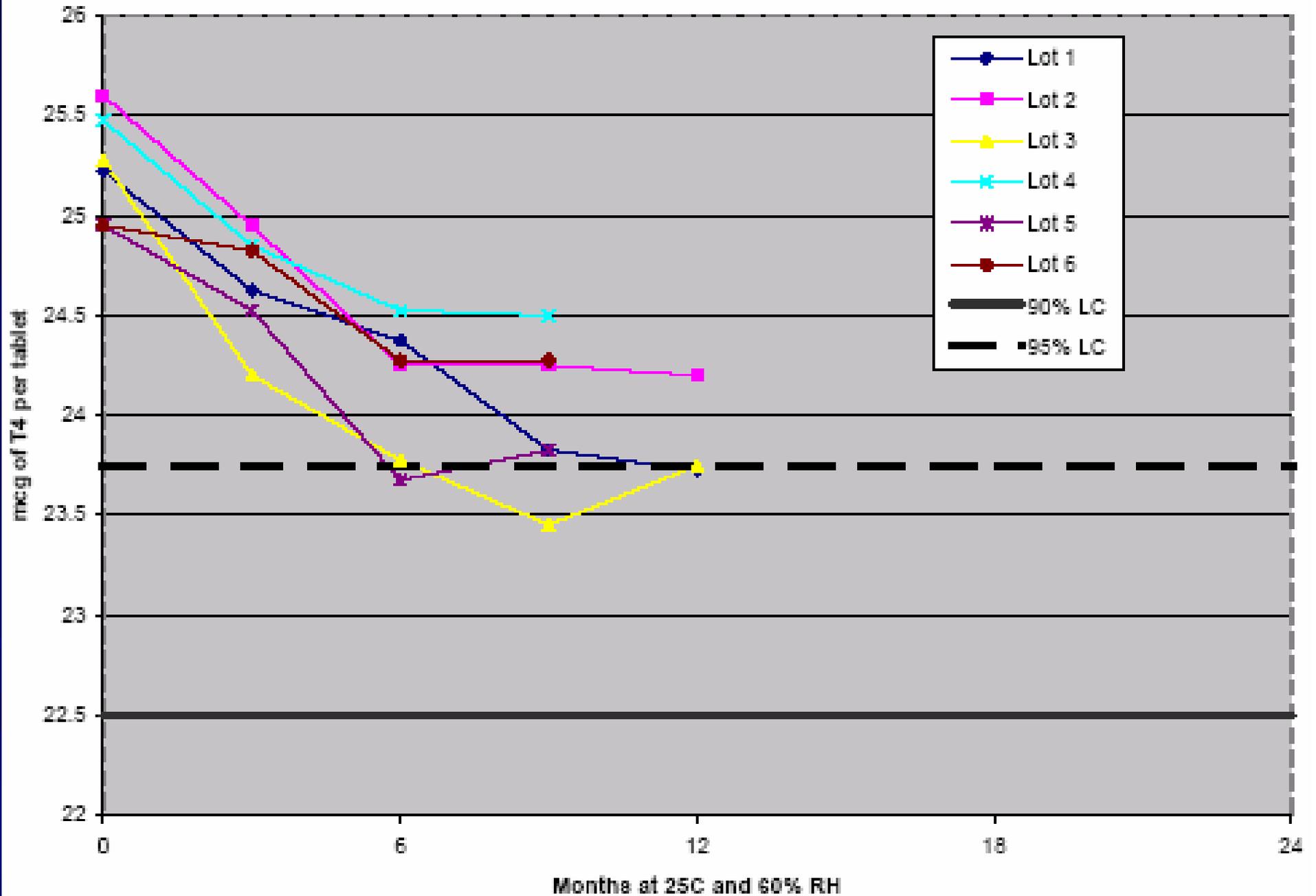
Brand "B" 25-mcg tablets in 100-ct bottles



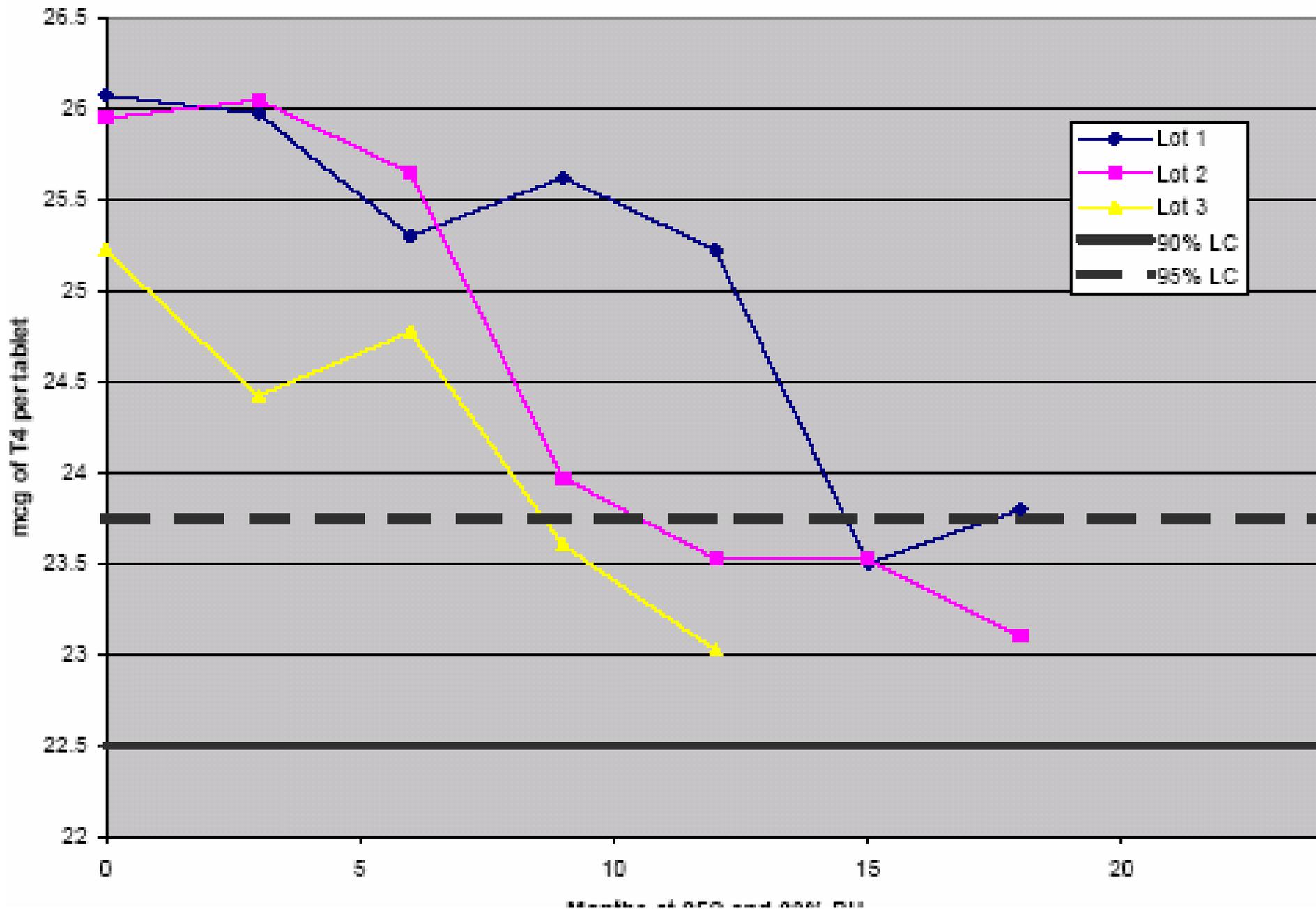
Brand "A" 25-mcg tablets in 100-count bottles



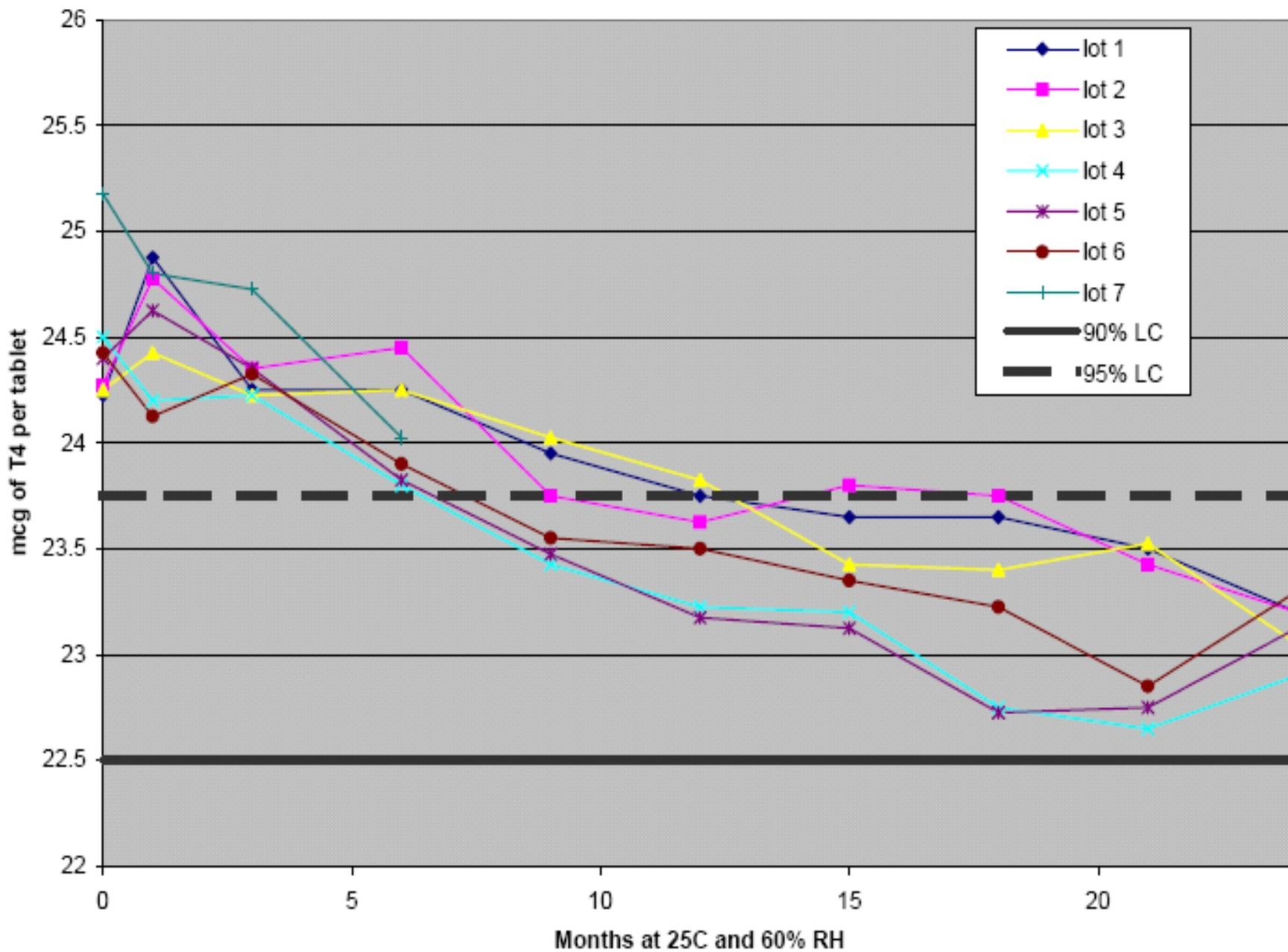
Brand "F" 25-mcg tablets in 100-ct bottles



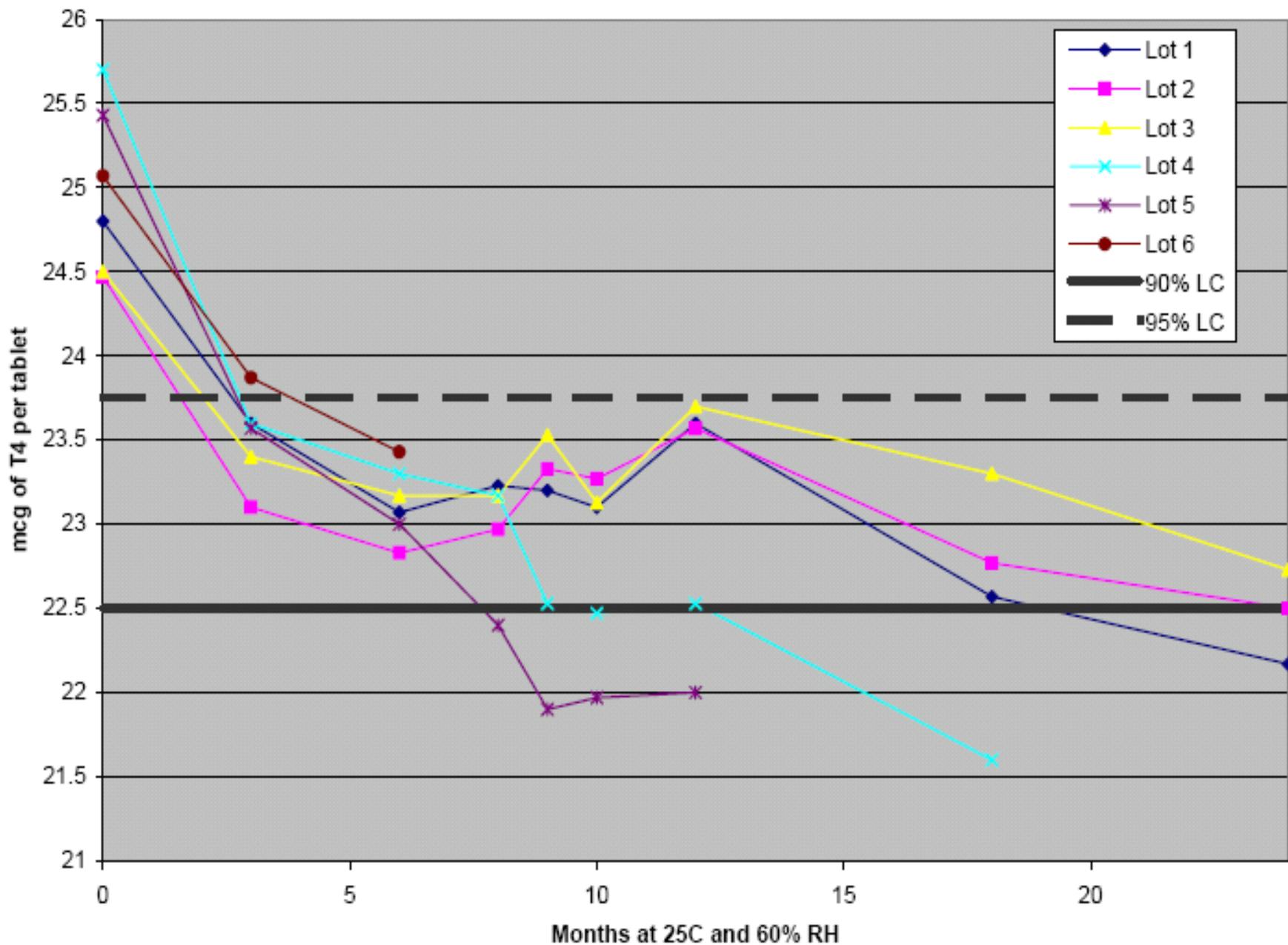
Brand "D" 25-mcg tablets in 100-ct bottles



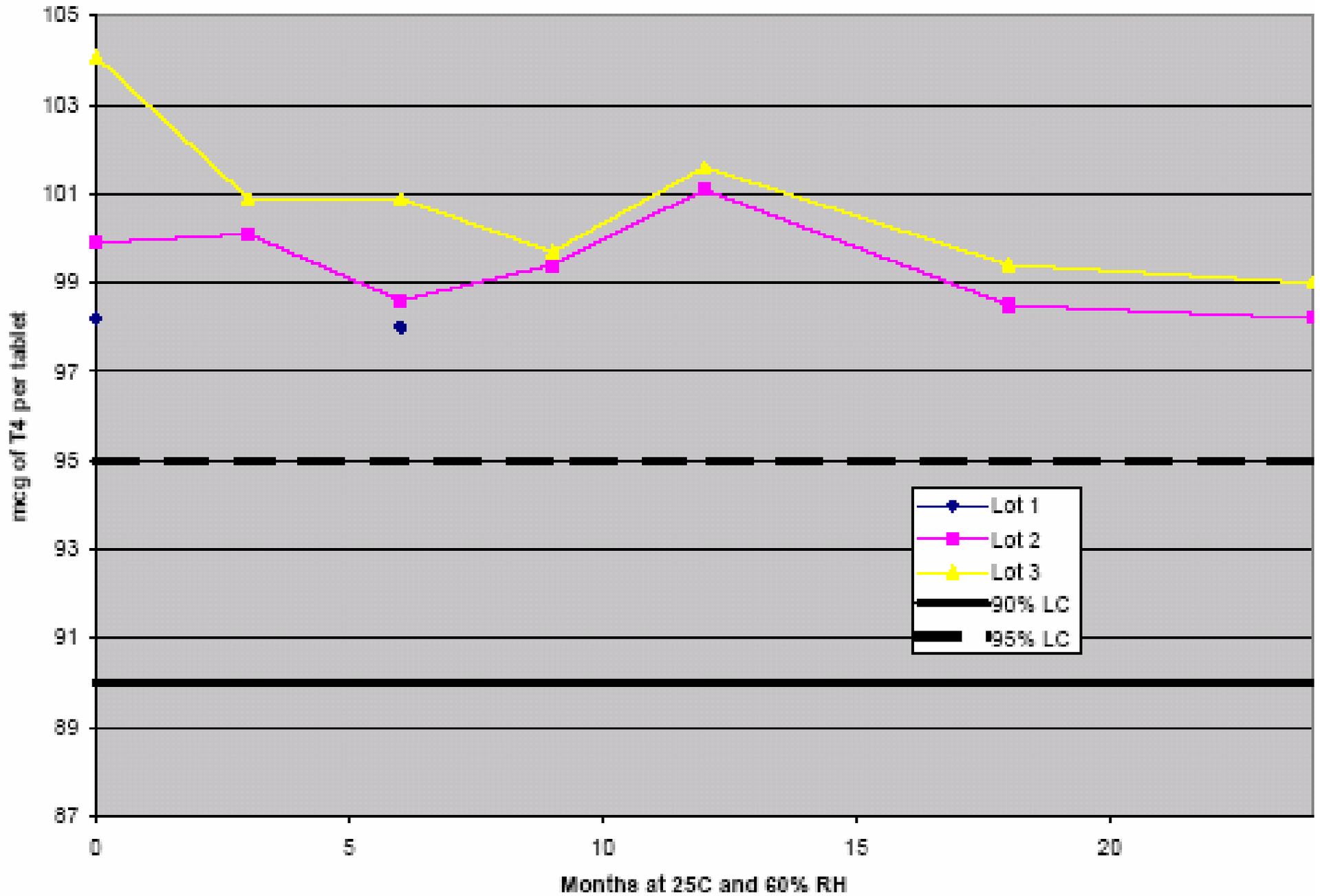
Brand "C" 25-mcg tablets in 100-ct bottles



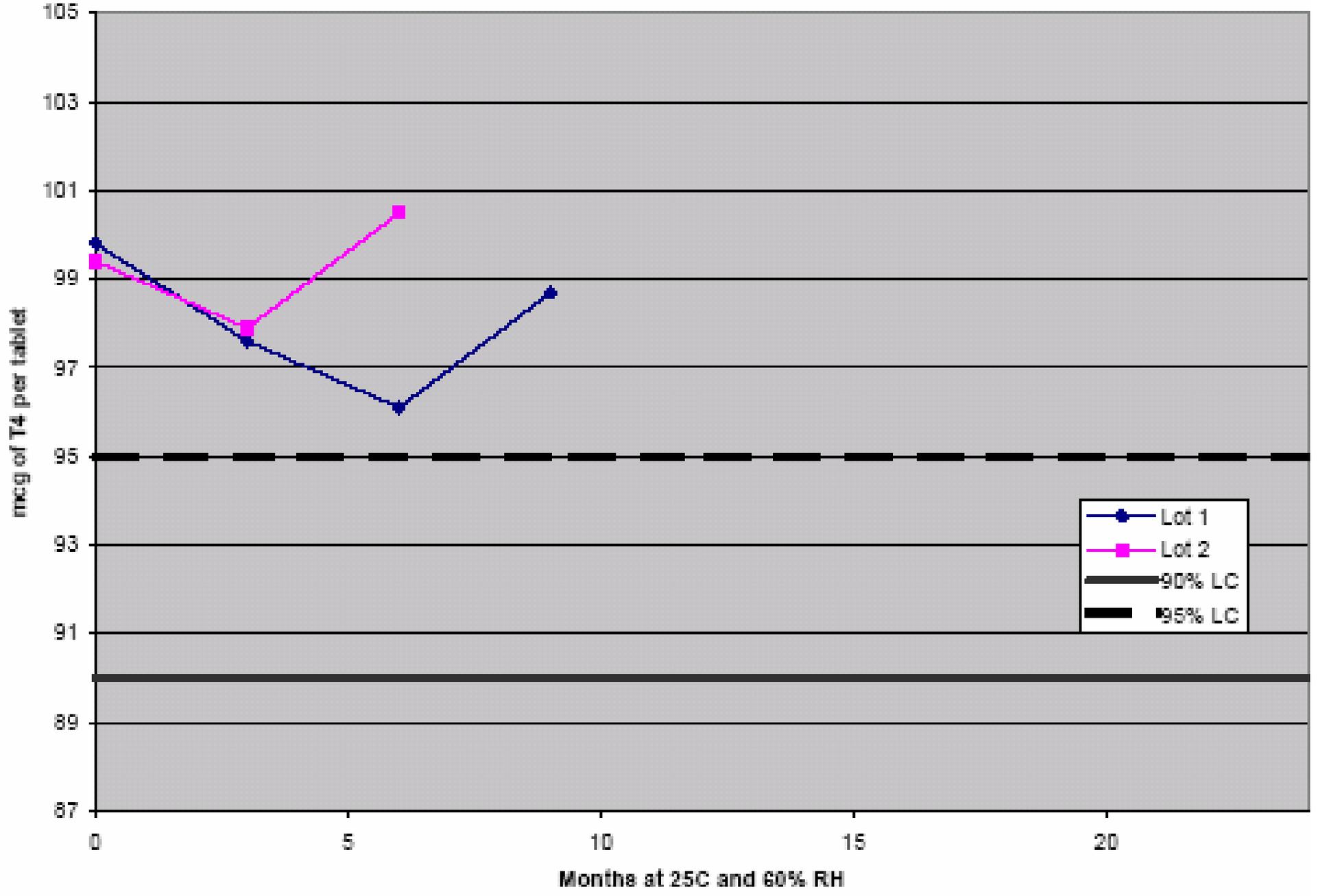
Brand "G" 25-mcg tablets in 100-ct bottles



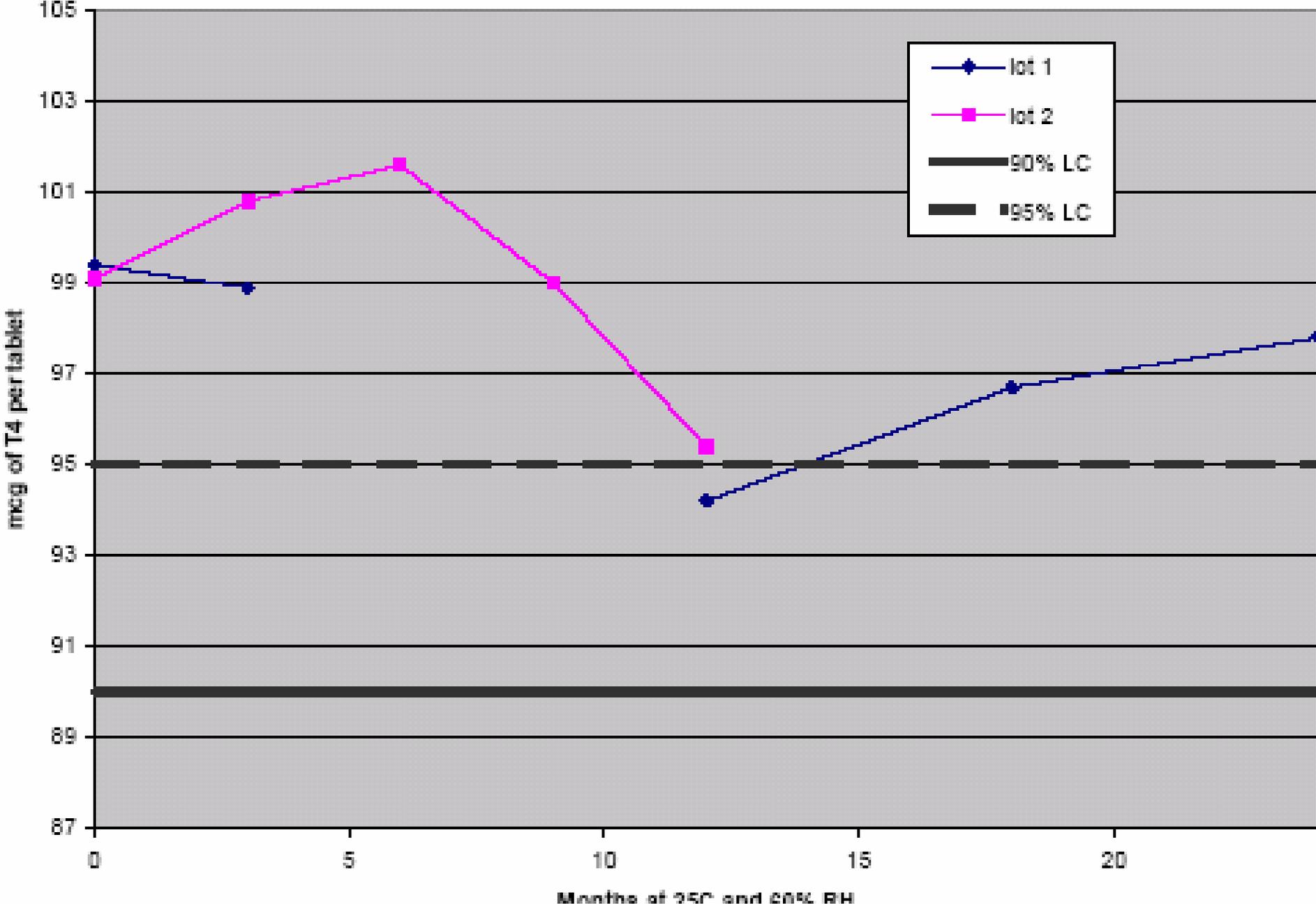
Brand "B" 100-mcg tablets in 1000-ct bottles



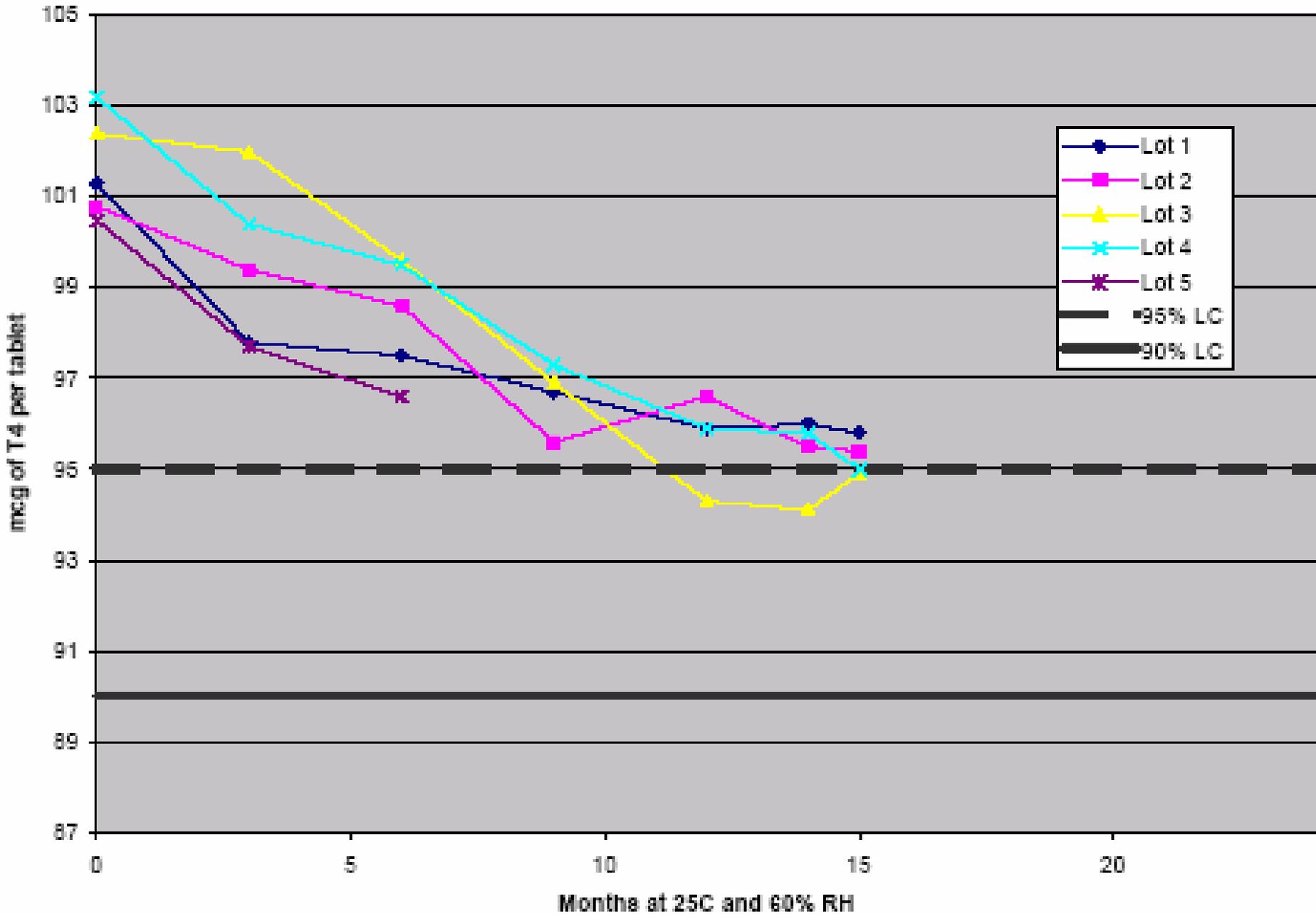
Brand "E" 100-mcg tablets in 1000-ct bottles



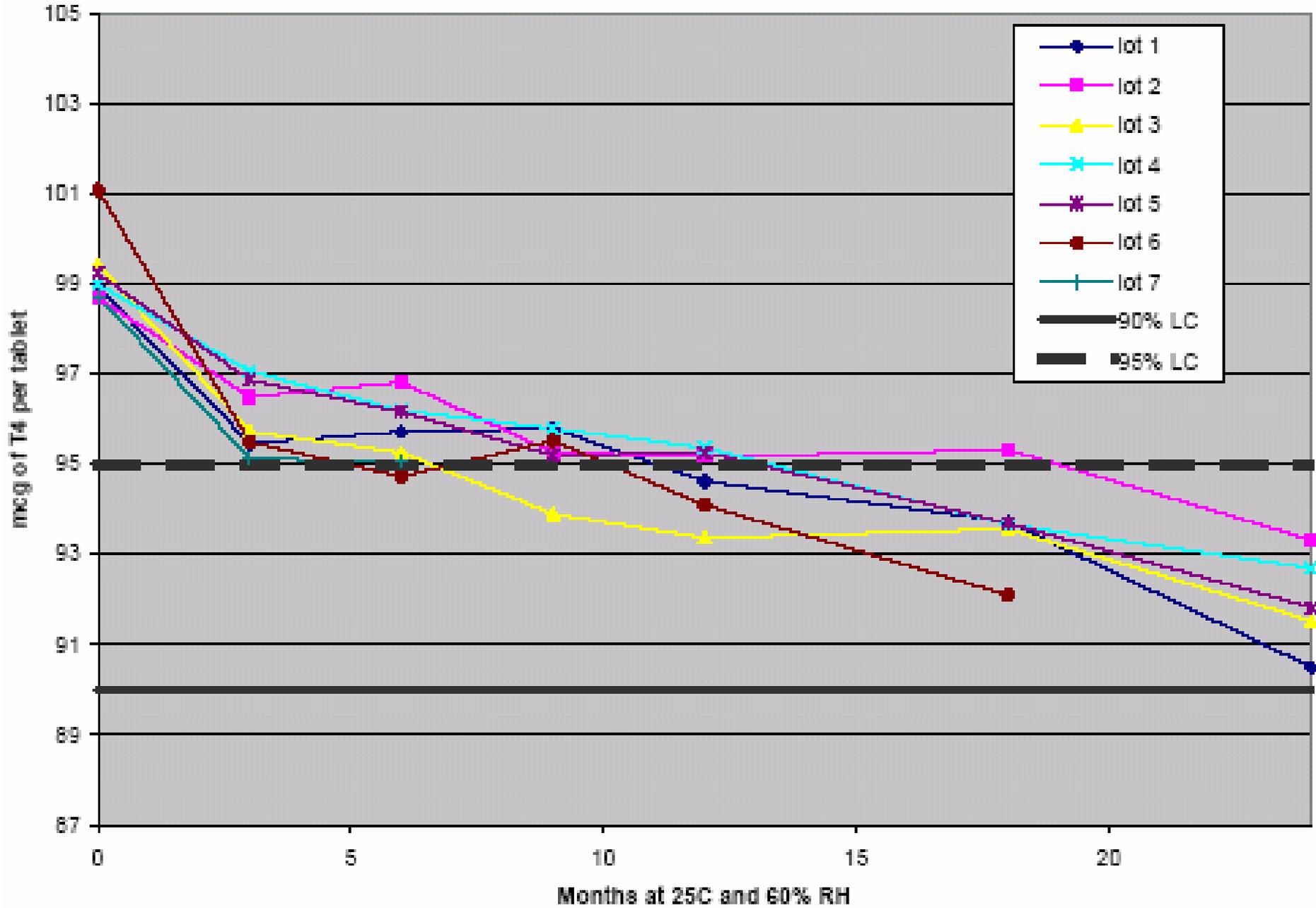
Brand "A" 100-mcg tablets in 1000-count bottles



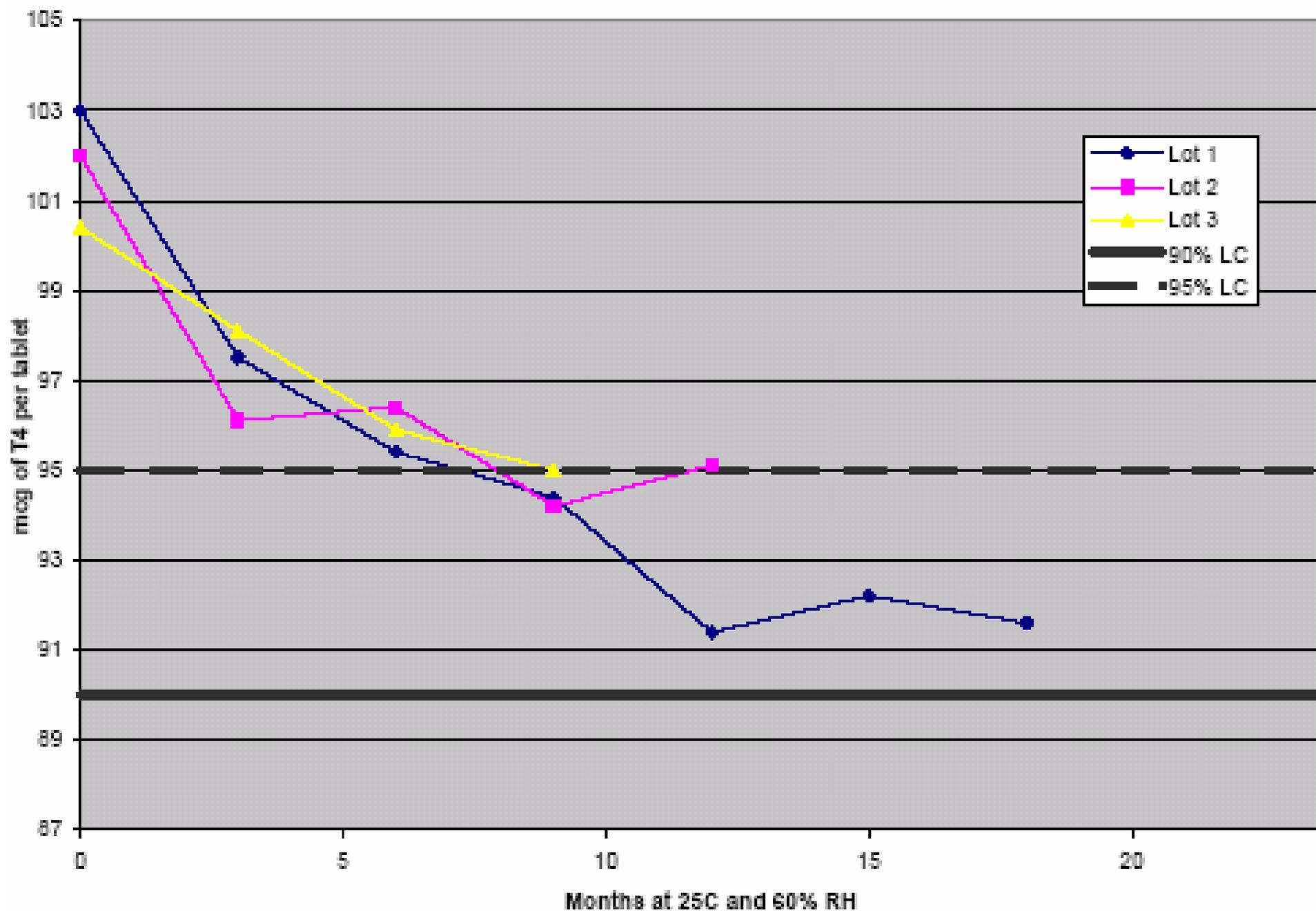
Brand "F" 100-mcg tablets in 1000-ct bottles



Brand "G" 100-mcg tablets in 1000-count bottles



Brand "D" 100-mcg tablets in 1000-ct bottles



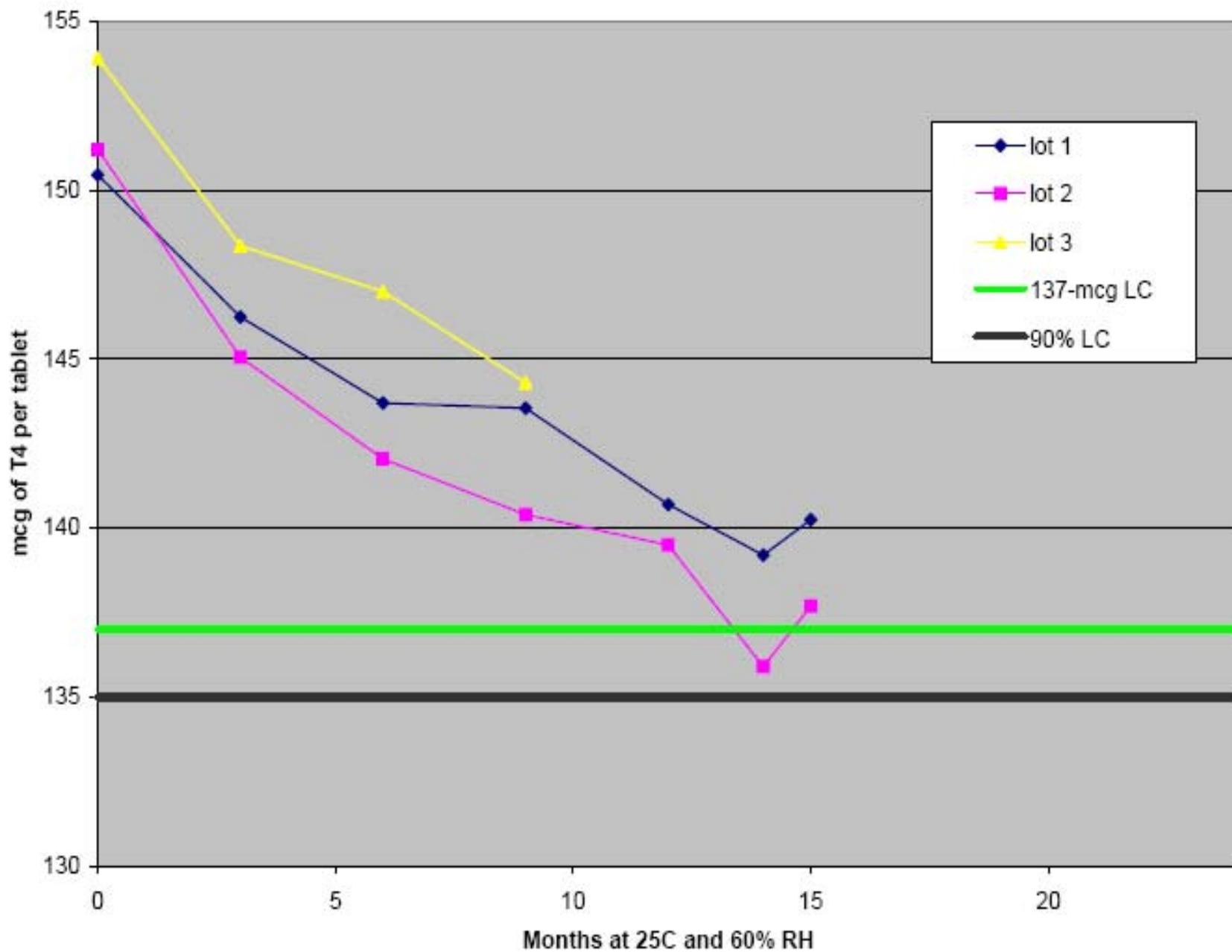
FDA Evaluation of Submitted Levothyroxine Tablet Stability Data

- 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

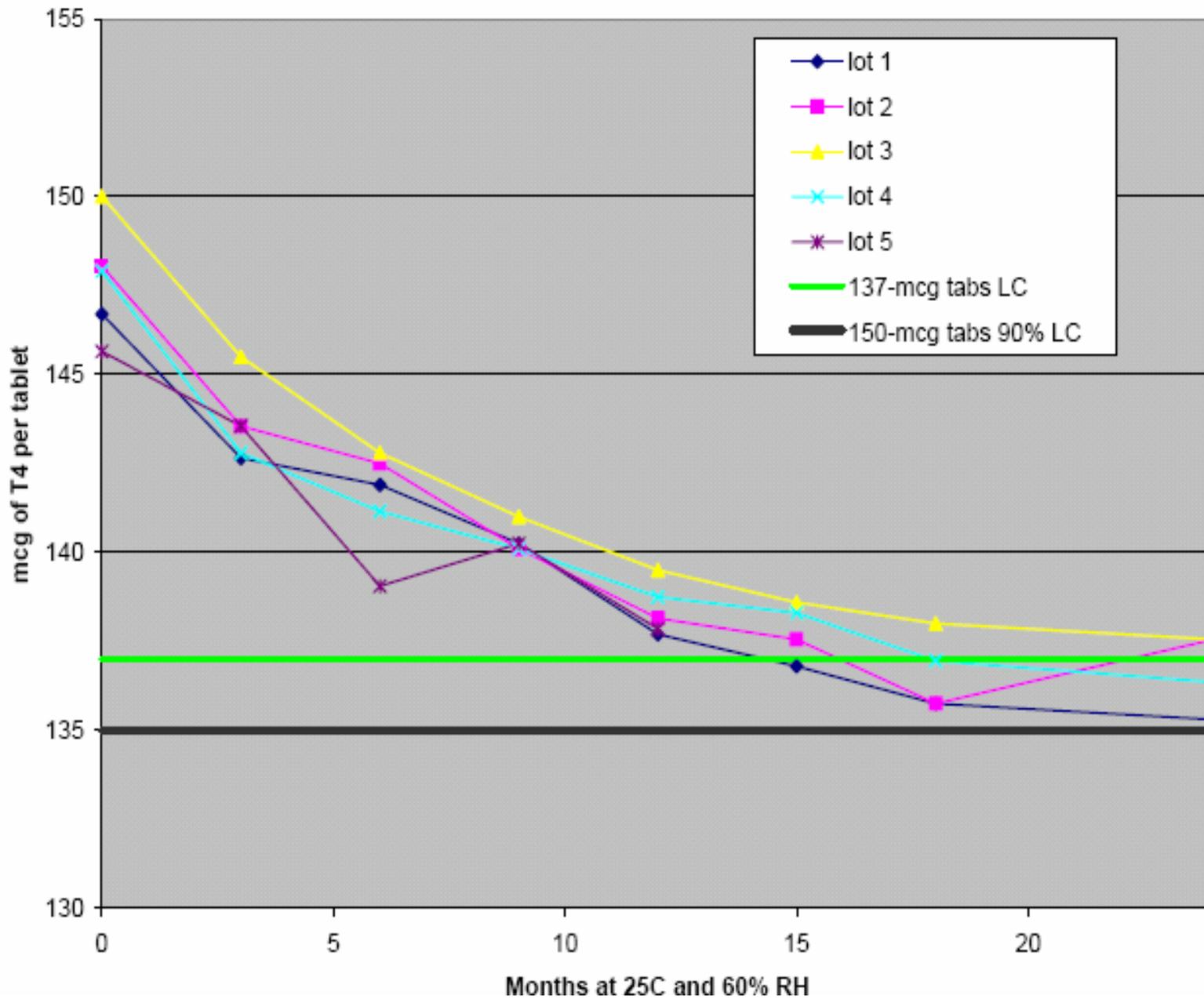
Stability Data vs. Current Potency Specification Limits

- 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 $\leq 10\%$ 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



Brand "C" 150-mcg tablets in 100-count bottles



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*)
 - $25^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and $60\% \text{ RH} \pm 5\% \text{ RH}$ (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?**