Endogenous Substance
Bioavailability and Bioequivalence:
Levothyroxine Sodium Tablets

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FDA / CDER / OPS / OCPB
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Overview

• Background:
  – Why levothyroxine sodium tablets were declared a “new drug”
  – “Guidance for Industry”

• FDA’s decision for bioequivalence evaluation of levothyroxine sodium tablets:
  – Study design
  – Bioequivalence analyses
Introduction

• Prior to August, 2000, levothyroxine sodium was an unapproved marketed drug ("grandfathered")

• Introduced in the 1950s
  (more pure, synthetic form of Thyroid, USP)

• In 1997 at least 37 manufacturers or re-packagers of levothyroxine sodium tablets
Introduction - cont.

- Although the clinical effectiveness of levothyroxine sodium had been established through four decades of clinical use, there was a high degree of uncertainty about all of the products. Namely, issues existed with regard to:
  - Product stability (i.e., shelf-life);
  - Formulation consistency over time within a given “brand;” and
  - Bioequivalence had never established between brands.
Product Stability

• Levothyroxine degrades quickly with exposure to light, moisture, oxygen, and carbohydrate excipients

• Between 1990 and 1997:
  – 10 recalls, 150 lots, and 100 million tablets
    • content uniformity, sub-potency, and stability failures

• Many products were manufactured using an overage

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>% of LABELED CLAIM</th>
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</thead>
<tbody>
<tr>
<td>Flint (Synthroid™)</td>
<td>106% – 109%</td>
</tr>
<tr>
<td>USV</td>
<td>101%</td>
</tr>
<tr>
<td>Geneva – Zenith</td>
<td>93% – 108%</td>
</tr>
<tr>
<td>Rugby</td>
<td>107%</td>
</tr>
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</table>

Fish et al. (1987)
Formulation Consistency

• Significant changes in formulation were occurring over time as firms attempted to improve product stability.

• Case reports in the literature suggesting that therapeutic failures had occurred when patients received a refill of the same product for which they had been previously stable.

• Of the 58 case reports of therapeutic failure received by the Agency, from 1987 - 1994, nearly half occurred when patients received a refill of a product on which they had been stable for years.
Federal Register Notice
(62 FR 43535)

• In an effort to standardize levothyroxine sodium tablets, and to reduce the instances of therapeutic failures, on August 14, 1997, the FDA declared levothyroxine sodium tablets a “new drug”

• Sponsors wishing to continue to market their product needed to submit an NDA or file a citizen’s petition describing why an NDA was not necessary
FDA Guidance for Industry
Levothyroxine Sodium Tablets - *In Vivo* Pharmacokinetic and Bioavailability Studies and *In Vitro* Dissolution Testing -- Feb. 2001

- Introduction and Background
- *In vivo* pharmacokinetic and bioavailability studies
  - Inclusion criteria
  - Single-dose (relative) bioavailability
  - Dosage-form proportionality
- *In vitro* dissolution testing
- Formulation
- Biowaiver
- Assay validation
Relative Bioavailability

**Objective** - determine the relative BA of the proposed formulation to a reference oral solution - fasting

**Design** - single-dose, 2 treatment, 2 sequence crossover design with a washout interval of at least 35 days

**Dose** - a total dose of 600 mcg
  - Treatment 1: 2 x 300 mcg levothyroxine tablets
  - Treatment 2: an oral solution equal to the dose in treatment 1

**Analyses** - AUC and $C_{max}$ without baseline correction ($T_4$)
Dosage-form Proportionality

**Objective** - determine the dosage-form proportionality among the to-be-marketed strengths - fasting

**Design** - single-dose, 3 treatment, 6 sequence crossover design with a washout interval of at least 35 days

**Dose** - multiples to achieve a total dose of 600 mcg
- Treatment 1: 12 x 50 mcg
- Treatment 2: 6 x 100 mcg
- Treatment 3: 2 x 300 mcg

**Analyses** - AUC and $C_{\text{max}}$ without baseline correction ($T_4$)
Formulation

- Must target 100% of label claim
- No unaccountable or “stability” overages
NDAs

• Between June 1999 and July 2001, nine sponsors submitted “stand alone” NDA applications

• The first product was approved in August, 2000

• There are currently six approved levothyroxine sodium tablet NDAs
## Approved Applications

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>IND #</th>
<th>NDA #</th>
<th>IND Filed</th>
<th>NDA Filed</th>
<th>NDA Review</th>
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<tbody>
<tr>
<td>Lloyd, Inc.</td>
<td>57,315</td>
<td>21-116</td>
<td>11-20-98</td>
<td>08-19-99</td>
<td>AP (10-24-02)</td>
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<td>Jerome Stevens</td>
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<td>Genpharm</td>
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<td>06-27-00</td>
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<td>Jones (King)</td>
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<td>10-26-99</td>
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<td>MOVA</td>
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<td>21-342</td>
<td>11-26-97</td>
<td>04-30-01</td>
<td>AP (3-01-02)</td>
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<td>Abbott</td>
<td>62,720</td>
<td>21-402</td>
<td>06-06-01</td>
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</table>
Abbott Laboratories
Endogenous Substance Bioavailability and Bioequivalence: Levothyroxine Sodium Tablets

Steven B. Johnson, Pharm.D.

The FDA’s decision for the evaluation of levothyroxine sodium tablet bioequivalence

Study design

Bioequivalence analyses
Data Limitations

• Their data was confirmatory and useful when the FDA adopted a baseline correction method for evaluating levothyroxine sodium tablet bioequivalence

• However, baseline correction has some drawbacks related to the lower doses used in the study:
  – 400 mcg and 450 mcg doses yield concentrations that are closer to the baseline
  – prevents an accurate evaluation of the true differences between the 400 mcg and 450 mcg doses
  – doses of 600 mcg or greater should be utilized, as suggested in the bioequivalence study protocol
Protocol for Evaluating BE

**Objective** - determine if bioequivalence can be conferred between Product A and Product B - fasting

**Design** - single-dose, 2 treatment, 2 sequence crossover design with a washout interval of at least 35 days

**Subjects** - healthy male and female subjects

**Dose** - multiples to achieve a total dose of 600 mcg
- Test Product: 2 x 300 mcg tablets
- Reference Product: 2 x 300 mcg tablets

**Analyses** - AUC and $C_{\text{max}}$ with a baseline correction ($T_4$)

**Biowaiver** - strengths not studied *in vivo*
Healthy Volunteers

• Allows for the use of a single dose study
• More sensitive evaluation of true formulation differences between products
• Single-dose study cannot be conducted in patients
Dose

• The 600 mcg dose in healthy subjects provides concentrations that are significantly higher than the individual subject’s baseline T₄ value

• The issue of non-linearity is not an issue since the subject is receiving the same amount of drug in each treatment period
T₄, T₃, and TSH

- T₄ (LT₄) is the preferred measure for demonstrating bioequivalence - it can be accurately measured *in vivo* and is the drug that is being administered to the subject.

- T₃ is an active metabolite.

- TSH is a biomarker that is an indirect measure and is “downstream” from what is being administered and is considerably more variable than T₄.
Hypothalamus

Thyrotropin Releasing Hormone (TRH)

Anterior Pituitary

Thyroid Stimulating Hormone (TSH)

Thyroid Gland

LT$_4$ → → → → 

T$_4$ → inhibitory → T$_3$

LT$_4$
21 CFR 320.24(b)

• ... descending order of accuracy, sensitivity, and reproducibility, ... for determining bioavailability and bioequivalence of a drug product.

  – (1)(i) ... concentration of the active ingredient ... in blood, plasma, serum, ... (T₄)
  – (2) ... urinary excretion of the active moiety ...
  – (3) ... acute pharmacological effect of the active moiety ... (TSH)
  – (4) Well controlled clinical trial ... (TSH)
  – (5) ... in vitro testing
  – (6) Any other approach deemed adequate by FDA
Bioequivalence Analysis

• Using total T₄, without a baseline correction, is insensitive for bioequivalence analysis

• A baseline correction, whereby the mean of 3 pre-dose samples are subtracted from all subsequent post-dose values *, is preferred

* data provided by Abbott Laboratories
Total $T_4$ Adjusted for Baseline (Ratios of LSM – 90% Confidence Intervals)

[data from dosage-form equivalence studies]

<table>
<thead>
<tr>
<th>Product</th>
<th>$\text{AUC}_{0-48 \text{ hrs}}$</th>
<th>$\text{C vs. B}$</th>
<th>$\text{C max}$</th>
<th>$\text{C vs. B}$</th>
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<tr>
<td></td>
<td>$\text{A vs. B}$</td>
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<td>$\text{A vs. B}$</td>
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<tr>
<td>1</td>
<td>102.4%</td>
<td>100.2%</td>
<td>103.5%</td>
<td>97.7%</td>
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<tr>
<td></td>
<td>(94.7% - 110.8%)</td>
<td>(92.6% - 108.4%)</td>
<td>(97.3% - 110.0%)</td>
<td>(91.8% - 103.8%)</td>
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<tr>
<td>2</td>
<td>103.72%</td>
<td>91.45%</td>
<td>103.12%</td>
<td>95.05%</td>
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<td></td>
<td>(95.98% - 112.09%)</td>
<td>(84.70% - 98.74%)</td>
<td>(96.87% - 109.76%)</td>
<td>(89.36% - 109.76%)</td>
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<tr>
<td>3</td>
<td>104%</td>
<td>98%</td>
<td>102%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>(97.09% - 110.35%)</td>
<td>(92.36% - 104.92%)</td>
<td>(94.94% - 108.57%)</td>
<td>(92.79% - 106.04%)</td>
</tr>
<tr>
<td>4</td>
<td>97%</td>
<td>114%</td>
<td>94%</td>
<td>104%</td>
</tr>
<tr>
<td></td>
<td>(90% - 105%)</td>
<td>(106% - 123%)</td>
<td>(87% - 101%)</td>
<td>(97% - 111%)</td>
</tr>
</tbody>
</table>

Treatment A = 12 x 50 mcg; Treatment B = 6 x 100 mcg; Treatment C = 2 x 300 mcg
Conclusion

- The FDA has thoroughly reviewed each NDA submission, the literature, and the recent “correction method” study and concludes the following:
  - Levothyroxine can be evaluated in healthy subjects
  - A single-dose crossover study design is preferred
  - $T_4$ is an appropriate and sensitive measure
  - A baseline correction using the mean of 3 pre-dose samples is adequate when determining equivalence between two levothyroxine sodium products
Dr. Barbara Davit