Discussion with EMA PKWG and CVSWP: Levothyroxine NTI Classification and BE Approach

Slides prepared by:

Mark Donnelly, Ph.D.,
Lanyan (Lucy) Fang, Ph.D.,

Division of Quantitative Methods and Modeling
Office of Research and Standards
Office of Generic Drugs
CDER, FDA

3/20/2019

Outline

- NTI assessment of levothyroxine
- Recommended BE approach in product-specific guidance
- Comparison of levothyroxine guidances
- BE study case example
- Alternative BE approaches under evaluation

NTI Assessment

- **FDA considers levothyroxine sodium as NTI**
  - RLD label[1]

5.4 Prevention of Hyperthyroidism or Incomplete Treatment of Hypothyroidism

SYNTHROID has a narrow therapeutic index. Over- or undertreatment with SYNTHROID may have negative effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and glucose and lipid metabolism. Titrate the dose of SYNTHROID carefully and monitor response to titration to avoid these effects *[see Dosage and Administration (2.4)]*. Monitor for the presence of drug or food interactions when using SYNTHROID and adjust the dose as necessary *[see Drug Interactions (7.9) and Clinical Pharmacology (12.3)]*.

  - FDA Product-Specific Guidance (ANDA)[2,3]

Explanation: FDA has concluded that levothyroxine sodium is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between serum levothyroxine therapeutic and toxic concentrations is narrow;
- Some levothyroxine-associated toxicities are serious and/or irreversible;
- Sub-therapeutic levothyroxine concentrations result in inadequate treatment and lead to poor clinical outcomes;
- Levothyroxine sodium requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity;
- Therapeutic drug monitoring based on serum TSH and total or free-T_4 levels is routinely employed to facilitate levothyroxine dose titration; and
- Levothyroxine has small-to-medium within-subject variability.

Product Specific Guidance[2]

Active Ingredient: Levothyroxine sodium

Dosage Form; Route: Tablet; oral

Recommended Studies: One study

1. Type of study: Fasting
   Design: Single-dose, four-way, fully replicated crossover in vivo
   Strength: 0.3 mg
   Subjects: Healthy males and non-pregnant females, general population
   Additional comments:
   1. Females should not be pregnant or lactating, and should practice abstention or use appropriate forms of contraception during the study.
   2. Levothyroxine has a long elimination half-life, hence adequate washout periods should be ensured between treatments in the crossover study. Measurement of levothyroxine may be truncated to 48 h post-dose.
   3. The dose for R and T administered during the study should be 0.6 mg to ensure adequate measurement of the analyte.
   4. Given the numerous drug-drug interactions for levothyroxine sodium, caution should be exercised in administering concomitant medications during the study.
   5. Post-dose levothyroxine measurements by the baseline levothyroxine value should be corrected in each period for each subject. The baseline value should be obtained from the average of three levothyroxine measurements taken before dosing (i.e., at 0.5 h, 0.25 h, and 0 h pre-dose).
   6. Applicant may consider using the reference-scaled average bioequivalence approach for levothyroxine sodium.

Analytes to measure (in appropriate biological fluid): Levothyroxine in serum

Bioequivalence based on (90% CI): Baseline-corrected levothyroxine

Recommended BE Approach in PSG

- BE approach for NTI drugs
  - Single-dose, four-way, fully-replicated crossover BE study
  - Reference-scaled average BE (RSABE) approach

- Baseline-correction of concentration
  - Baseline-correction improves ability to differentiate formulation differences[4-7]
  - Baseline-correction may inflate WSV (within-subject variability) and thus widen RSABE limits

- Dose of 600 mcg administered to ensure adequate measurement of analyte[4-7]
  - Doses of 400 or 450 mcg show concentrations closer to baseline[4-7]

- Analyte measured for BE is levothyroxine (T4) in serum
  - FDA guidance recommends using parent drug unless metabolite is formed substantially through pre-systemic metabolism and contributes to safety and efficacy[8]
  - FDA disagreed with citizen petition requests to include T3 and TSH in BE approach[6,7]
    - T3 is produced endogenously and thus does not directly indicate T4 absorption from products
    - TSH levels are more variable than T4 and thus less accurate for BE
    - TSH levels are considered a secondary response and change slowly after T4 administration

Comparison of Levothyroxine Guidances

- Relative BA study and dosage-form proportionality study recommended in the guidance for new drug products (Dec 2000)[9]
  - Uncorrected total levothyroxine (T4) and triiodothyronine (T3) concentration
  - Waiver of strengths not used in dosage-form proportionality study
  - Does not provide recommendation on "BE"

- BE study design and criteria recommended in PSG for generic drugs (Dec 2014 and Nov 2018)[1,2]
  - Reference-scaled average BE approach for NTI drugs
  - Baseline-corrected T4 concentration in serum
  - Biowaiver of lower strengths not evaluated in BE studies

Efforts to bring consistency in BA/BE approach between new drug and generic drugs are in-progress

Biowaiver Criteria for Generic Drugs[8]

- For IR tablet and capsule products, the in vivo BE requirement for one or more strength can be waived based on:
  - Acceptable BE study on the designated strength,
  - Acceptable in vitro dissolution testing of all the strengths, and
  - Proportional similarity of the formulation across all strengths

This guidance defines *proportionally similar* in the following ways:

- All active and inactive ingredients are in similar proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients—almost exactly half that of a tablet of 100-mg strength, and almost twice that of a tablet of 25-mg strength).

- For high-potency drug substances (where the amount of active drug substance in the dosage form is relatively low): (1) the total weight of the dosage form remains nearly the same for all strengths (within ± 10 % of the total weight of the strength on which a biostudy was performed), (2) the same inactive ingredients are used for all strengths, and (3) the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients.

- Active and inactive ingredients that are not in similar proportion between different strengths can be considered proportionally similar with adequate justification (such as dosage form proportionality studies that demonstrate equivalent in vivo bioavailability).

Formulations of levothyroxine may be considered proportionally similar if the conditions above are met

2013 Draft ANDA BE guidance (FDA):
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf

BE Study Case Example

ANDA sponsor conducted a fasting BE study comparing its Levothyroxine Sodium Tablet, USP, 300 mcg to Abbvie's Synthroid® Tablets, 300 mcg

The study was found unacceptable (quoted from Complete Response Letter):

"…Your fasting study fails to meet the acceptance criteria…. In addition, greater than 15% difference is observed in AUC and Cmax between the test and reference product. On October 4, 2006, a joint meeting between the Endocrinologic and Metabolic Drugs Advisory Committee and the Advisory Committee for Pharmaceutical Sciences was held. The committee concluded that a 10% difference in potency is clinically significant; therefore this conclusion would also apply to the 10% difference in bioavailability.

Your fasting bioequivalence study is unacceptable. Please conduct and submit a new bioequivalence study conducted on a reformulated test product which shows considerably less differences in AUC and Cmax between the test and reference products. We suggest that you submit a detailed protocol for bioequivalence study prior to conducting the study."

BE criteria for NTI drugs was met for AUC despite >15% difference in the point estimate

CDER NTI Drug Working Group

Purpose:

1. Develop a science- and risk-based regulatory approach to identify NTI drugs based on the relevant information from new drug development programs and elsewhere

2. Establish a consistent process to resolve key NTI-related scientific and regulatory issues in a transparent and collaborative manner

3. Create (or develop) a consistent process for monitoring and re-evaluating NTI drugs in the early post-marketing stage to support timely availability of product-specific recommendations for generic drug development

Currently, NTI Drug Working Group is investigating concerns with BE approach for levothyroxine sodium tablet and evaluating alternative approaches

Alternative BE approaches

- Evaluating BE approach for NTI drugs with additional constraints
  - 10% **P**oint **E**stimate constraint (90.0-111.1%)
  - 5% **P**oint **E**stimate constraint (95.0-105.3%)
  - 90% **C**onfidence **I**nterval within 90.0-111.1%

- Assessment strategy
  - Defined type I/II error rates
    - Type I error: pass BIE product, defined as GMR ≥ 111% or ≤ 90%
    - Type II error: fail BE product, defined as 95% ≤ GMR ≤ 105%
  - Evaluated type I/II error rates under different scenarios
    - Impact of N, WSV, and variability ratio on type I/II error rates
  - Performed extensive simulations
  - **Results are currently under evaluation and discussion**

Acknowledgments

Office of Generic Drugs (OGD)

- Office of Research and Standards (ORS)
  - Robert Lionberger (ORS)
  - Lei Zhang (ORS)
  - Liang Zhao (DQMM)
  - MJ Kim (DQMM)
- Office of Bioequivalence (OB)
  - Dale Conner (OB)
  - Ethan Stier (DBII)
  - Xiaojian Jiang (DBII)
  - Utpal Munshi (DBI)

Office of Translational Sciences (OTS)

- Office of Clinical Pharmacology (OCP)
  - Mehul Mehta (DCPI)
  - Jaya Vaidyanathan (DCPII)
  - Chandrahas Sahajwalla (DCPII)
  - Rajnikanth Madabushi (IO)
- Office of Biostatistics (OB)
  - Fairouz Makhlouf (DBVIII)
  - Wanjie Sun (DBVIII)
  - Donald Schuirmann (DBVIII)

Office of New Drugs (OND)

- Office of Drug Evaluation II (ODEII)
  - William Chong (DMEP)
  - Marina Zemskova (DMEP)
  - Shannon Sullivan (DMEP)

References

1. SYNTHROID® (levothyroxine sodium) tablets for oral use, product label, revised 02/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021402s024s028lbl.pdf

2. Draft Product Specific Guidance for Oral Tablet (Dec 2014). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428208.pdf

3. Draft Product Specific Guidance for Oral Capsule (Nov 2018). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM626514.pdf

4. Blakesley VA. Current methodology to assess bioequivalence of levothyroxine sodium products is inadequate. AAPS J. 2005 Mar 30;7(1):E42-6.

5. Bolton S. Bioequivalence studies for levothyroxine. AAPS J. 2005 Mar 30;7(1):E47-53.

6. Citizen's Petition #2003P-0387. FDA OC to Abbott Laboratories et al Petition Denial, posted Jun 29, 2004. https://www.regulations.gov/document?D=FDA-2003-P-0364-0006

7. Citizen's Petition # 2003P-0126. FDA OC to Covington and Burling et al Petition Denial, posted Jun 29, 2004. https://www.regulations.gov/document?D=FDA-2003-P-0227-0002

8. FDA's Draft Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA (December 2013). https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm377465.pdf

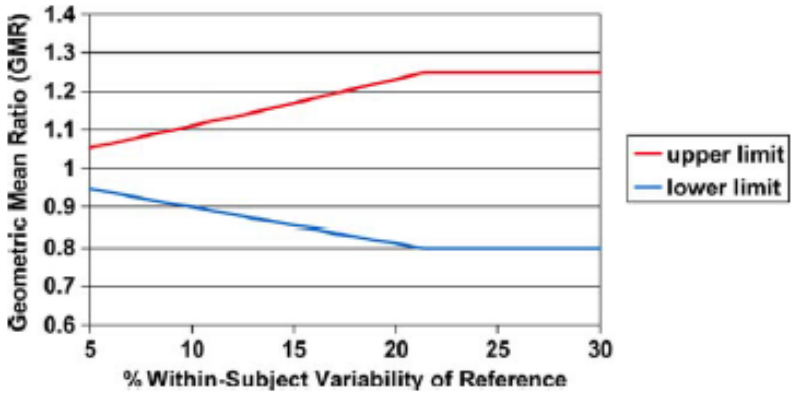
9. FDA's Guidance for Industry: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing (Dec 2000) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071946.pdf


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Classification and BE Criteria for NTI Drugs

- Criteria for NTI classification
  1. Little separation between therapeutic and toxic doses or the associated blood/plasma/serum concentrations
  2. Sub-therapeutic concentrations may lead to serious therapeutic failure
  3. Subject to therapeutic monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures
  4. Low-to-moderate (NMT 30%) within-subject variability
  5. Doses are often adjusted in small increments (<20%) in clinical practice

- BE criteria for NTI drugs
  1. Unscaled average BE limits
  2. Reference scaled average BE limits (scaled to the variability of the reference product)
  3. Comparison of test-to-reference within-subject variability



Clin Pharmacol Ther. 2015 Mar;97(3):286-91. doi: 10.1002/cpt.28. Epub 2014 Dec 15.

NTIDWG Membership

Office of Generic Drugs (OGD)

- Office of Research and Standards (ORS)
  - **Liang Zhao (DQMM) [Chair]**
  - Lanyan (Lucy) Fang (DQMM)
  - Mark Donnelly (DQMM)
  - Karen Bengtson (IO) [PM]
  - Markham Luke (DTP)
  - Xiaohui (Jeff) Jiang (DTP)
- Office of Bioequivalence (OB)
  - Xiaojian Jiang (DBII)
  - Ethan Stier (DBII)
- Office of Generic Drug Policy (OGDP)
  - Philip Bonforte

Office of Surveillance and Epidemiology (OSE)

- Office of Pharmacovigilance and Epidemiology (OPE)
  - Anne Tobenkin (DPVI)

Office of Translational Sciences (OTS)

- Office of Clinical Pharmacology (OCP)
  - **Mehul Mehta (DCPI) [Co-Chair]**
  - Yaning Wang (DPM)
  - Rajnikanth Madabushi (IO)
- Office of Biostatistics (OB)
  - Fairouz Makhlouf (DBVIII)
  - Wanjie Sun (DBVIII)

Office of New Drugs (OND)

- Office of Drug Evaluation I (ODEI)
  - Martin Rose (DCRP)
  - Steven Dinsmore (DNP)
- Office of Hematology and Oncology Products (OHOP)
  - Dow-Chung Chi (DOPI)