American Association of Colleges of Pharmacy AACP

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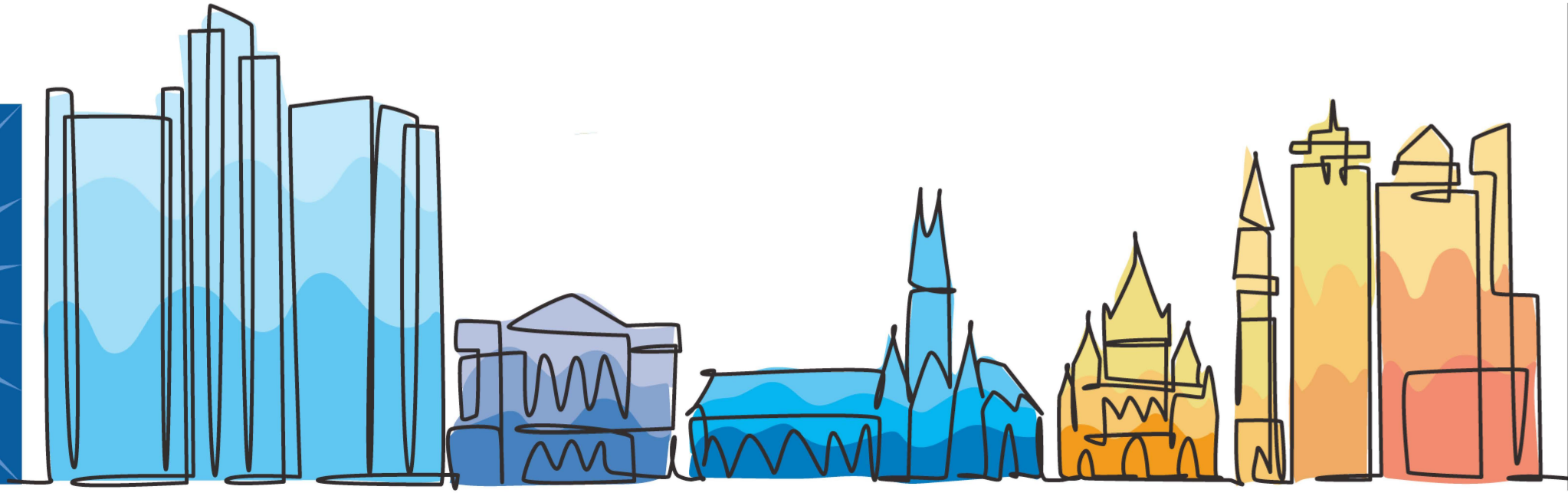
AACP Annual Meeting

July 20–23 Boston

Hynes Convention Center

PHARMACY EDUCATION 2024



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Generic Drugs and Bioequivalence: What Every Pharmacy Student Should Know!

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Generic Drugs and Bioequivalence: What Every Pharmacy Student Should Know!

Agenda for Session

- Introduction to Session (Kathy Giacomini)
- Overview of the Generic Drug Approval Process (Rob Lionberger)
- Case Studies for Pharmacy Students (Kathy Giacomini)
- Q&A (Rob Lionberger and Kathy Giacomini)

Requirements for a Generic Drug

- Generic drugs and the RLD (Reference Listed Drug) have the **same**
  - Active Ingredient
  - Route of Administration
  - Dosage Form
  - Strength
  - Labeling
  - Conditions of Use/Patient Population
- Generic drugs and the RLD may have **different**
  - Inactive Ingredients
  - Formulation Design or Drug Release Mechanism
  - Manufacturing Process

Generic Drug Scientific Review

- Bioequivalence
  - Human studies (healthy subjects) that verify that the generic and RLD provide an equivalence rate and extent of drug delivery to the site of action, OR
  - Waivers or in vitro studies that ensure the same delivery to the site of action
- Quality (same standards as for brand products)
  - Identity, strength, quality, and purity
  - Formulation
  - Manufacturing process
  - Manufacturing site
  - Microbiology
    - Sterile products
- Clinical Review
  - Bioequivalence studies with clinical endpoints
  - Irritation/adhesion studies for transdermal systems
  - User interface of drug device combination product (inhalers, auto-injectors)
- Labeling
  - Label for the generic product

Promises About Generic Drugs

- FDA-approved generic drugs are **Therapeutically Equivalent**
- They can be freely interchanged or substituted for the RLD (brand) or other generics to that RLD
- Generic and RLD will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling
- Approved generic drugs have therapeutic equivalence ratings in the Orange Book (https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book)
  - AB rating indicates the product is substitutable with its RLD

Key Knowledge for Pharmacists About Generic Drugs and Their Reference List Drug

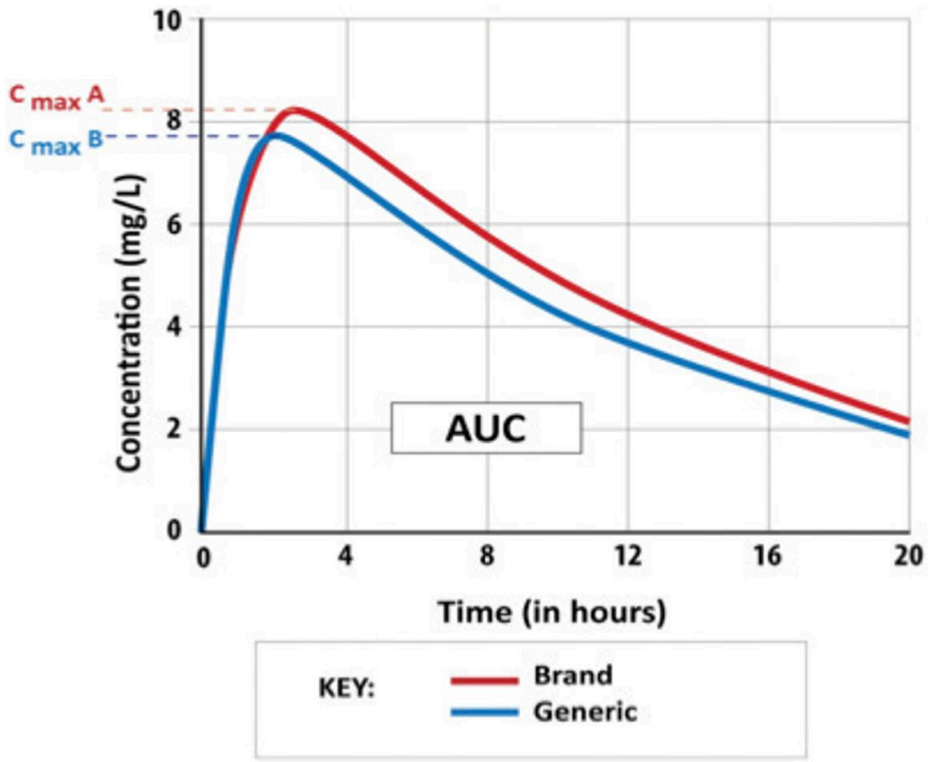
Things that are the same

- The same dosage form
- The same route of administration
- The same clinical indication
- The same active ingredient
- The same drug availability at the site of action

Things that can differ

- Appearance
- Inactive Ingredients
- Device or container

Bioequivalence Evaluation and Biowaivers



M9 Biopharmaceutics Classification System-Based Biowaivers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
ICH

https://www.cadth.ca/sites/default/files/pdf/What_Are_Bioavailability_and_Bioequivalence_e.pdf

Can Bioequivalent Products Have Different Therapeutic Outcomes?

- There continue to be anecdotal reports that generic drugs do not work the same as the brand product (Bottle of Lies book)
- Over the past 10 years FDA has conducted a series of studies in patients to address questions related to generic substitution
- The goal of these studies was to produce a set of evidence FDA could use to discuss this issues. Without these studies in the literature, the discussion is driven by
  - Anecdotal reports => not evidence
  - Bad epidemiology => not evidence
  - Testing non-U.S. approved products => not evidence

FDA-funded Generic Drug Substitution Studies

- Randomized trial approach
  - Two independent studies on anti-epileptic drugs (patients with multiple switches between brand and generics)
    - doi:10.1001/jamaneurol.2017.0497 and doi:10.1111/epi.13095
  - Study on tacrolimus in liver and kidney transplant patients
    - doi:10.1371/journal.pmed.1002428
  - Study on bupropion in patients with depression
    - doi:10.1002/cpt.1309
  - All measured pharmacokinetic (PK) intensively, no difference in drug exposure in patients, no observed clinical differences but were smaller studies (N <100)
- Real world data approach (using electronic health records)
  - Studies on levothyroxine substitution (cover N>10,000)
  - doi:10.1001/jamanetworkopen.2020.17645 and doi:10.1007/s12020-021-02779-x and doi:10.1001/jamainternmed.2022.0045
  - This is the future of how we will monitor and evaluate generic substitution (the patient studies above each cost about $2M each)

Why can my pills look different each time I fill the same prescription?

Why do my pills look different each time I fill the same prescription?

Consumer Reports News: May 25, 2012 04:58 PM

Patients May Respond to Changes in Appearance

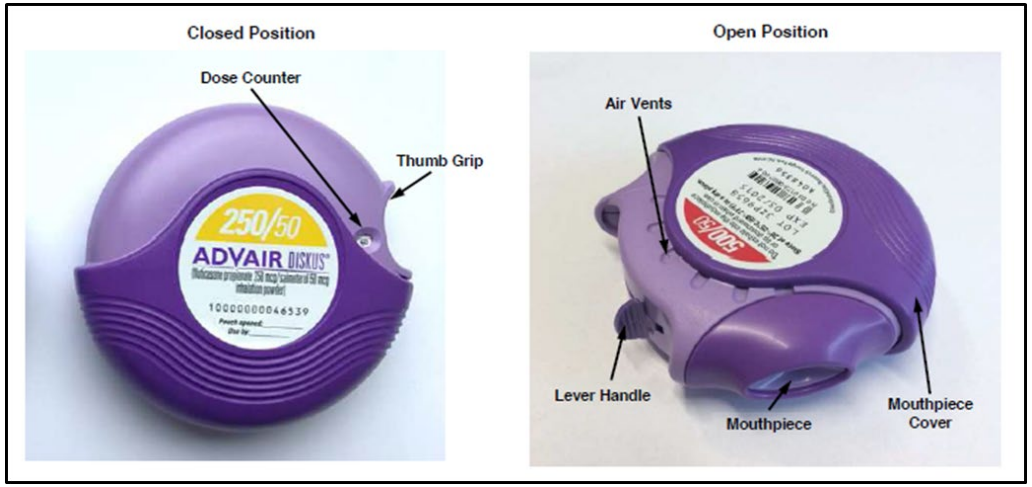
- Literature studies suggest real impact
- Not possible for FDA to mandate similar appearance
- Falls on the pharmacist to be prepared for patient concerns
- Switches between different generic manufactures may happen at any time

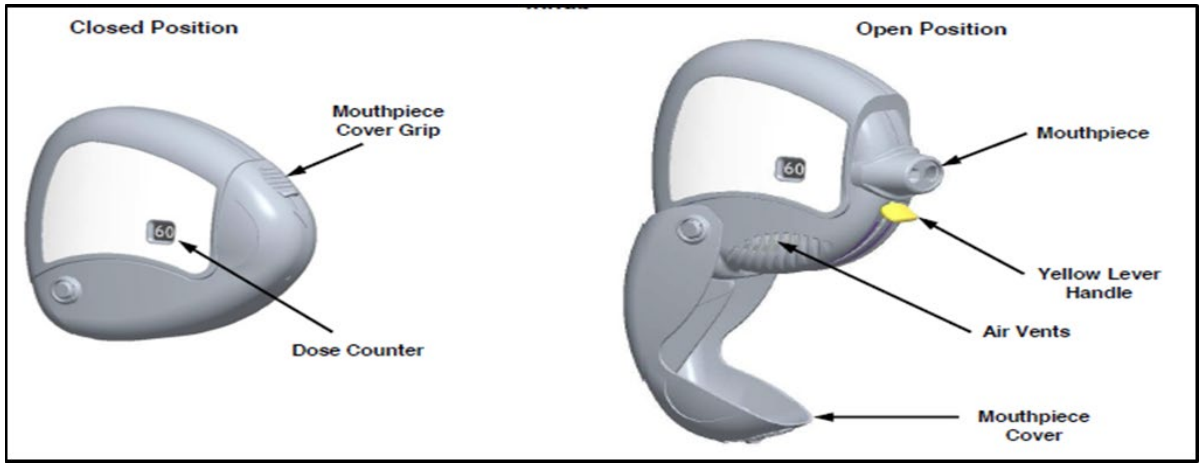
Inactive Ingredients May Be Different

- Inactive ingredient differences do not impact drug delivery
- Inactive ingredients used in generic products follow FDA's Inactive Ingredient Database (IID) and equal or lower than amounts used previously for the same route of administration
- Individuals may have reactions to specific inactive ingredients
  - The inactive ingredients are found in the drug label

Devices May Appear Different

Brand Product





Approved Generic Product

Pharmacists' Role in Generic Substitution

- Utilization of generic products is critical to the health care sector
- FDA's focus is on drug delivery and product quality
- Allowing variations in the appearance accelerated access to generics
  - Patents and trademarks do not block competition
- But the consequence is that equivalent products may appear different
- Pharmacists are the first line of communicating products that look different perform the same

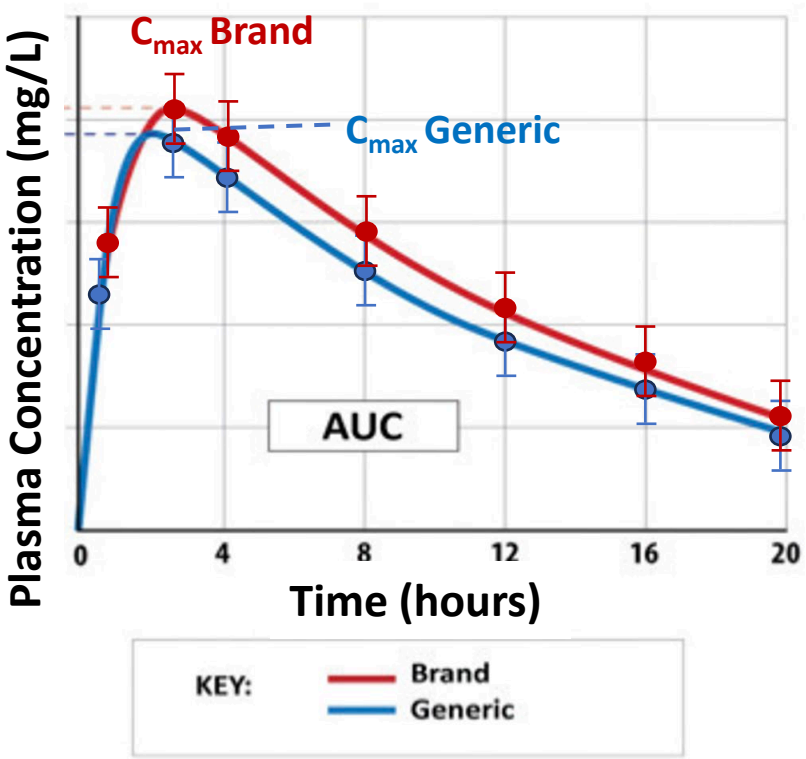
Bioequivalence of Lamotrigine

1. Read the manuscript by Tricia Ting et al.

2. Prepare a PowerPoint to teach the class about how bioequivalence studies based on pharmacokinetics are conducted in healthy volunteers and how this field study showed that bioequivalence standards of FDA may be reasonable in actual patients.

Epilepsia, 56(9):1415–1424, 2015
doi: 10.1111/epi.13095

Typical Bioequivalence Evaluation Based on Pharmacokinetics

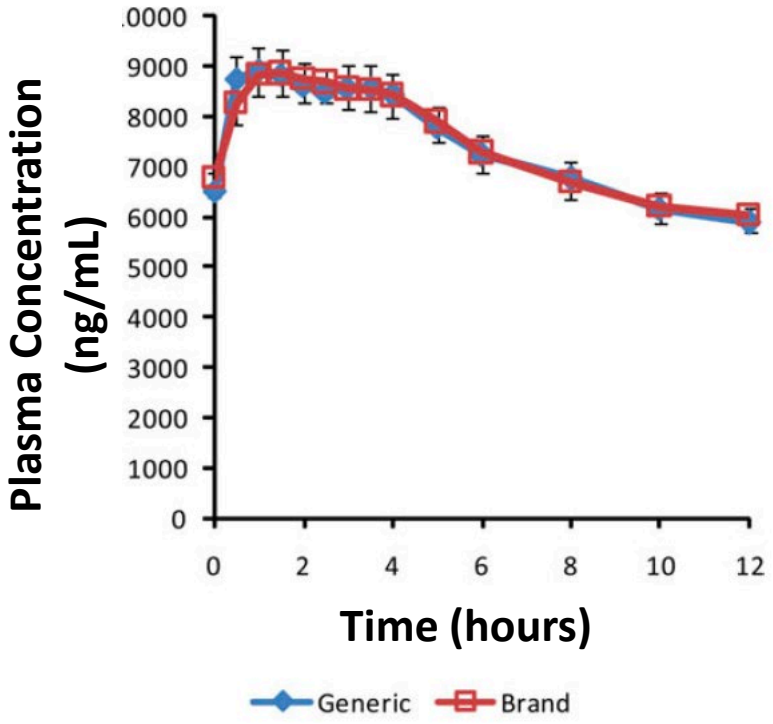


Typical Requirements for Bioequivalence (PK)

- **Single dose randomized crossover study of generic product and brand-name product in healthy volunteers under fasting**
- **90% confidence intervals of the Cmax and AUC ratios must fall between 80 % and 125%**

https://www.cadth.ca/sites/default/files/pdf/What_Are_Bioavailability_and_Bioequivalence_e.pdf

Generic Lamotrigine Versus Brand Name Lamictal Bioequivalence In Patients with Epilepsy: A Field Test of the FDA Bioequivalence Standard



FULL-LENGTH ORIGINAL RESEARCH

Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: A field test of the FDA bioequivalence standard

*Tricia Y. Ting, †Wenlei Jiang, †Robert Lionberger, ‡Jessica Wong, ‡Jace W. Jones, ‡Maureen A. Kane, *Allan Krumholz, †Robert Temple, and ‡James E. Polli

Epilepsia, 56(9):1415–1424, 2015
doi: 10.1111/epi.13095

Conclusion: Bioequivalence results in "generic-brittle" patients with epilepsy under clinical conditions support the soundness of the FDA bioequivalence standards

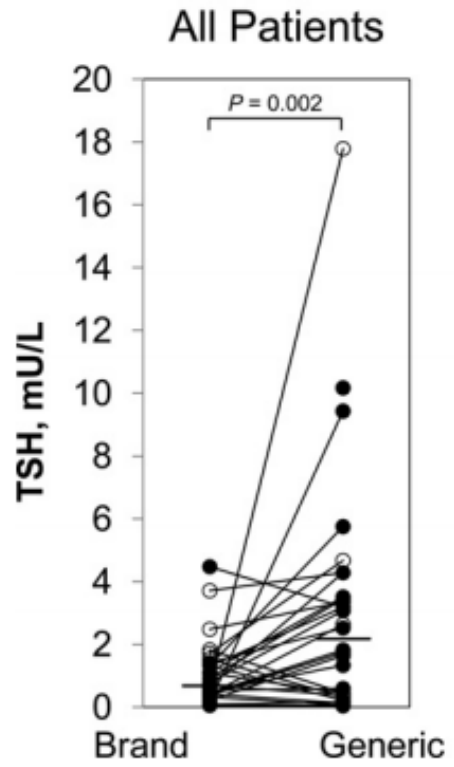
Epilepsia, 56(9):1415–1424, 2015
doi: 10.1111/epi.13095

Bioequivalence of Thyroid Preparations

1. Read the manuscripts of Jeremi Carswell et al. and Juan Brito et al.

2. The class should discuss the contrast between controlled clinical trials and comparative effectiveness studies using real world data on assessment of thyroid bioequivalence.

Bioequivalence of Thyroid Preparations



Objective: We aimed to evaluate the bioequivalence of a brand-name L-T4 (Synthroid) and an AB-rated generic formulation (Sandoz, Princeton, NJ) in children with severe hypothyroidism.

Design: This was a prospective randomized crossover study in which patients received 8 weeks of one L-T4 formulation followed by 8 weeks of the other.

Setting: The setting was an academic medical center.

Patients: Of 31 children with an initial serum TSH concentration 100 mU/L, 20 had congenital hypothyroidism (CH), and 11 had autoimmune thyroiditis.

Main Outcome Measures: The primary endpoint was the serum TSH concentration. Secondary endpoints were the free T4 and total T3 concentrations.

Results: The serum TSH concentration was significantly lower after 8 weeks of Synthroid than after generic drug (P .002), but thyroid hormone levels did not differ significantly. Subgroup analysis revealed that the difference in TSH was restricted to patients with CH (P .0005). Patients with CH required a higher L-T4 dose(P .0004) and were younger (P .003) but were not resistant to thyroid hormone; 15 of 16 CH patients had severe thyroid dysgenesis or agenesis on imaging. The response to generic vs brand-name preparation remained significant when adjusted for age.

Conclusions: Synthroid and an AB-rated generic L-T4 are not bioequivalent for patients with severe hypothyroidism due to CH, probably because of diminished thyroid reserve. It would therefore seem prudent not to substitute L-T4 formulations in patients with severe CH, particularly in those 3 yr of age. Our results may have important implications for other severely hypothyroid patients in whom precise titration of L-T4 is necessary.

J Clin Endocrinol Metab 98: 610–617, 2013

Comparative Effectiveness Studies to Evaluate Bioequivalence

JAMA Internal Medicine | Original Investigation

Association Between Generic-to-Generic Levothyroxine Switching and Thyrotropin Levels Among US Adults

Juan P. Brito, MD, MSc; Yihong Deng, PhD; Joseph S. Ross, MD, MHS; Nam Hee Choi, PhD; David J. Graham, MD, MPH; Yandong Qiang, MD, PhD; Elena Rantou, PhD; Zhong Wang, PhD; Liang Zhao, PhD; Nilay D. Shah, PhD; Kasia J. Lipska, MD, MHS

- **15,829 Levothyroxine Users**
  - **2780 Switchers**
  - **2780 Non-switchers**

TSH Levels

Switchers: 2.7 ± 3.3 mIU/L

Non-switchers: 2.7 ± 2.3 mIU/L

- Results of this comparative effectiveness research study suggest that switching among different generic levothyroxine products was not associated with clinically significant changes in TSH level.
- These findings conflict with the current guideline recommendation that warns clinicians about potential changes in TSH level associated with switching among levothyroxine products sourced from different manufacturers.

Brito JP et al., JAMA Intern Med. 2022 Apr 1;182(4):418-425

Conclusions

- Pharmacists are often the first line of communicating with patients about generic drug substitution.
- A field study in patients with epilepsy showed no bioequivalence difference between generic and branded products, suggesting that FDA standards of using healthy volunteers is effective.
- Real-world data is an emerging tool for monitoring bioequivalence of products.

Questions?