December 4 - 8 ■ Philadelphia, PA
69TH ANNUAL MEETING

FDA Town Hall Update
Generic Antiepileptic Drug Bioequivalence in Epilepsy Patients: From Anecdotes to Evidence

Symposium Chair:
Michael Privitera, M.D.

Monday, December 7, 2015
Convention Center – Room 204

3:00 – 5:00 p.m.

GENERAL INFORMATION

Accreditation

The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

Physicians

The American Epilepsy Society designates this live activity for a maximum of 30.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistant

AAPA accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 30.75 hours of Category 1 credit for completing this program.

Jointly provided by AKH Inc., Advancing Knowledge in Healthcare and the American Epilepsy Society.

Nursing

AKH Inc., Advancing Knowledge in Healthcare is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 30.75 contact hours.

Nurse Practitioners

AKH Inc., Advancing Knowledge in Healthcare is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider Number: 030803. This program is accredited for 30.75 contact hours which includes 8 hours of pharmacology. Program ID #21547

This program was planned in accordance with AANP CE Standards and Policies and AANP Commercial Support Standards.

Pharmacy

AKH Inc., Advancing Knowledge in Healthcare is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Select portions of this Annual Meeting are approved for pharmacy CE credit. Specific hours of credit for approved presentations and Universal Activity Numbers assigned to those presentations are found in the educational schedules. Criteria for success: nursing and pharmacy credit is based on program attendance and online completion of a program evaluation/assessment.

If you have any questions about this CE activity, please contact AKH Inc. at service@akhcme.com.

International Credits

The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for *AMA PRA Category 1 Credits*™.

CME/CE Certificates

For those attendees who wish to claim CME or CE, there is an additional fee. Registrants can pay this fee as part of the registration process. Those who do not pre-purchase the credit will also have the ability to pay this fee at the time they attempt to claim credit. Fees for CME increase after January 16 and are a one-time charge per annual meeting.

The evaluation system will remain open through Friday, February 26, 2016. Evaluations must be completed by this date in order to record and receive your CME/CE certificate.

Member Fees:	$50 through January 15, 2016 $75 January 16 – February 26, 2016
Non-member Fees:	$75 through January 15, 2016 $100 January 16 – February 26, 2016

Attendance Certificate/International Attendees

A meeting attendance certificate will be available at the registration desk for international meeting attendees on Tuesday, December 8.

Policy on Commercial Support and Conflict of Interest

The AES maintains a policy on the use of commercial support, which assures that all educational activities sponsored by the AES provide in-depth presentations that are fair, balanced, independent and scientifically rigorous. All faculty, planning committee members, moderators, panel members, editors, and other individuals who are in a position to control content are required to disclose relevant relationships with commercial interests whose products relate to the content of the educational activity. All educational materials are reviewed for fair balance, scientific objectivity and levels of evidence. Disclosure of these relationships to the learners will be made through syllabus materials and the meeting app.

Disclosure of Unlabeled/Unapproved Uses

This educational program may include references to the use of products for indications not approved by the FDA. Faculty have been instructed to disclose to the learners when discussing the off-label, experimental or investigational use of a product. Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the AES.

OVERVIEW
Uncontrolled studies suggested lack of efficacy or increased adverse events when people with epilepsy switched from brand to generic AEDs. Some neurologists, patients and patient advocacy groups questioned the FDA whether product bioequivalence established in healthy volunteers can ensure AED bioequivalence in people with epilepsy receiving concomitant medications. To address the epilepsy community's concern, the FDA Office of Generic Drugs (OGD) has funded a series of prospective brand-to-generic AED switching studies in epilepsy patients starting in 2010, including the bioequivalence in Epilepsy Patients (BEEP) study and Equivalence in Generic Drugs (EQUIGEN) study. The research findings from BEEP and EQUGEN studies will be presented. Some other factors which may affect AED clinical outcomes, including pill appearance, patient adherence and patient/physician perception about generic drugs, will be discussed. FDA OGD's continued efforts on generic AEDs including narrow therapeutic index (NTI) drug classification and modified release products will be updated.

LEARNING OBJECTIVES
Following participation in this symposium, learners should be able to:

- Describe results and conclusions from current single- and multiple-dose AED bioequivalence trials in epilepsy patients
- List factors which may impact AED clinical outcomes
- Delineate NTI drug classification process

TARGET AUDIENCE
Basic: Those new to epilepsy treatment or whose background in the specialty is limited, e.g., students, residents, general physicians, general neurologists and neurosurgeons, other professionals in epilepsy care, administrators.

Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, and other providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques or advanced treatment modalities, including surgery.)

Agenda
Chair: Michael Privitera, M.D.

Introduction
Michael Privitera, M.D.

BEEP Study Findings
Tricia Ting, M.D.

EQUIGEN Single Dose Study Update
Michael Privitera, M.D.

Authorized Generics, Pill Appearance and Patient Adherence
Joshua Gagne, Pharm.D., Sc.D.

FDA OGD Updates on Generic AEDs and NTI Designation
Wenlei Jiang, Ph.D.

Panel Discussion

Moderators: Michel Berg, M.D. and Xiaohui Jiang, Ph.D.
Panel members: Tricia Ting, M.D., James Polli, Ph.D., Michael Privitera, M.D., Michel Berg, M.D., Joshua Gagne, Pharm.D., Sc.D., Xiaohui Jiang, Ph.D. and Wenlei Jiang, Ph.D.

Education Credit
2.0 CME Credits

Nurses may claim up to 2.0 contact hours for this session.

Nurse Practitioners may claim 2.0 hours of pharmacology for this session.

Pharmacy Credit
AKH Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 2.0 contact hours (0.2 CEUs). UAN 0077-9999-15-039-L01-P. Initial Release Date: 12/7/2015.

The American Board of Psychiatry and Neurology has reviewed the FDA Town Hall Update Generic Antiepileptic Drug Bioequivalence in Epilepsy Patients: From Anecdotes to Evidence Symposium and has approved this program as part of a comprehensive program, which is mandated by the ABMS as a necessary component of maintenance of certification.

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME's Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
Michael Privitera, M.D. (Chair)
Dr. Michael Privitera is Professor of Neurology and Director of the Epilepsy Center at the University of Cincinnati Neuroscience Institute. Dr. Privitera is an expert on advanced treatments for epilepsy, with a research focus on new antiepileptic drugs, generic equivalence of AEDs, and stress as a seizure precipitant. He has over 140 scientific publications. He has served as a reviewer for NIH and FDA, and earned many honors and awards. He is a member of the Board of Directors for the Epilepsy Foundation of Greater Cincinnati and Columbus, and Vice President of the American Epilepsy Society.

Dr. Privitera discloses receiving support for Consulting from Upsher Smith (DSMB), Astellas (DSMB); for Contract Research from UCB (clinical trial; indirect) Neuren (clinical trial; indirect).

Michel Berg, M.D.
Dr. Michel J. Berg is a Professor of Neurology at the University of Rochester School of Medicine and Dentistry. Dr. Berg received a B.S. in Physics from Miami University in Oxford, Ohio, then his M.D. from the University of Cincinnati College of Medicine. He completed a residency in Internal Medicine at SUNY Health Science Center in Syracuse and then completed a residency in Neurology and a fellowship in Epilepsy at the University of Rochester and subsequently joined the Strong Epilepsy Center faculty in 1993. Dr. Berg is involved in projects on enhancing medication adherence with smart

medication dispensers, automating MRI analysis and seizure prediction from EEG. He is co-PI on the EQUIGEN studies examining bioequivalence of AEDs.

Dr. Berg discloses receiving support for Receipt Of Intellectual Property Rights/Patent Holder from Pharmadva - Automated Home Medication Dispener - prerevenue; Jemsico-illuminated electrical outlet - pre-revenue; for Contract Research from Site investigator on studies from NeuroPace, Eisai, Sunovioun, Pfizer, Lundbeck, Acorda, FDA grant, Equivalence among Generic AEDs- All payments indirect to institution.; for Ownership (i.e. stocks, stock options or other ownership) from Pharmadva - Automated Home Medication Dispener - prerevenue; Jemsico-illuminated electrical outlet - pre-revenue; for Other Services from Up to several per year expert medicolegal cases.; from EPI - local Epilepsy Foundation affiliate - volunteer member of Board of Directors - no compensation

Joshua Gagne, Pharm.D., Sc.D.
Joshua J. Gagne, PharmD, ScD, is an Assistant Professor of Medicine at Harvard Medical School, a pharmacoepidemiologist in the Division of Pharmacoepidemiology and Pharmacoeconomics at the Brigham and Women's Hospital and an Assistant Professor in the Department of Medicine at the Harvard T.H. Chan School of Public Health. His current research centers on methods for generating post-marketing comparative safety and effectiveness evidence for new medical products. He is Co-Lead of the methods core of the FDA's Sentinel program. Dr. Gagne's research is funded by FDA, AHRQ, PCORI, and IMEDS. He serves on the editorial boards of Drug Safety and of Pharmacoepidemiology and Drug Safety.

Dr. Gagne discloses receiving support for Contract Research from Novartis Pharmaceuticals Corporation (previously PI of grants, paid to the Brigham and Women's Hospital.) These grants indirectly supported my salary.

Wenlei Jiang
Dr. Wenlei Jiang is the Acting Deputy Director of the Office of Research and Standards in the Office of Generic Drugs. She provides oversight on Generic Drug User Fee Act (GDUFA) regulatory science research activities to help develop ANDA review standards and ensure the therapeutic equivalence of generic drug products. She has been mainly responsible for developing bioequivalence standards of generic complex drug products such as liposomes and nano drug products, revising ANDA review policy of narrow therapeutic index drugs, and initiating post-market generic drug research including generic product bioequivalence in patient populations, generic drug surveillance methods, and patient perception about generic drug usage.

Dr. Jiang has indicated she has no financial relationships with commercial interests to disclose.

Xiaohui "Jeff" Jiang, Ph.D.
Xiaohui (Jeff) Jiang received his Ph.D. in chemistry from the University of California, San Diego. Currently he is a Project Lead in the Office of Research and Standards, under the Office of Generic Drugs in the Cen Dr. Jiang has been working on post-marketing research of generic drugs including anti-epileptic drugs (AEDs) in epilepsy patients. In addition, his research includes developing novel approaches in the evaluation of active ingredient sameness and in vitro bioequivalence for complex generic drugs. Prior joining FDA, Dr. Jiang was working at the Anticonvulsant Screening Program at the National Institute of neurological Disorders and Stroke, NIH

Dr. Jiang has indicated he has no financial relationships with commercial interests to disclose.

James Polli
Dr. James E. Polli is Professor and Ralph F. Shangraw/Noxell Endowed Professor in Industrial Pharmacy and Pharmaceutics at the University of Maryland School of Pharmacy. He is also

co-Director of the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), and Director of the online MS in Regulatory Science program (www.pharmacy.umaryland.edu/regulatoryscience). He is a fellow and past Member-at-Large of American Association of Pharmaceutical Scientists (AAPS), an Associate Editor of Pharmaceutical Research, and a member of the FDA Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology. He has served as advisor to 17 Ph.D. graduates.

Dr. Polli has indicated he has no financial relationships with commercial interests to disclose.

Tricia Ting, M.D.
Dr. Tricia Ting is Associate Professor of Neurology at the University of Maryland School of Medicine and is the Director of Investigational Drug Trials in Epilepsy. In addition to antiepileptic drug trials, she has enjoyed collaborative work with the School of Pharmacy and FDA on generic bioequivalence and understanding the issues that underly generic-brittleness.

Dr. Ting, M.D. discloses receiving support for Contract Research from Acorda sponsor for a PK BE trial of nasal/rectal diazepam Pfizer phase IV safety study of lyrica.

CME Reviewer
Lauren Frey, M.D.
Dr. Frey specializes in the care of adults living with epilepsy. She has an outpatient clinic at the University of Colorado Hospital and is the Director of the Epilepsy Monitoring Unit and an active participant in the Epilepsy Surgery program there. Dr. Frey is also the Director of the Quantitative EEG (QEEG) Laboratory and the Neurofeedback Clinic at the University of Colorado Hospital. Dr. Frey's research interests include how mind-body and lifestyle interventions can affect seizure control and quality of life in people whose seizures are not completely controlled by seizure medications.

Dr Frey discloses receiving support for Ownership (i.e. stocks, stock options or other ownership) from stock in two health care companies (GlaxoSmithKline and Johnson and Johnson). I do not perform any work for these entities or have any contractual arrangement with them.; for Other Service (with or without compensation) from Professional Advisory Board member for the Epilepsy Foundation of Colorado.

Diego Morita, M.D.
Diego Morita is an Assistant Professor of Pediatrics and Neurology at Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine. He is the Medical Director of the Cincinnati Children's New Onset Seizure Program and a Co-Medical Director of the Cincinnati Children's Neuroscience Unit. His clinical and research interests are a) quality improvement in healthcare, b) anti-seizure medications side effects, c) health related quality of life.

Dr. Morita discloses receiving support for Contracted Research from UCB (indirect) Eisai (indirect); as Other Service from Epilepsy Foundation of Greater Cincinnati and Columbus: Board of Directors, Professional Advisory Board.

Paul Levisohn, M.D. (Medical Content Specialist, AES)
Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national

Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Dr. Levisohn has indicated he has no financial relationships with commercial interests to disclose.

AKH STAFF / REVIEWERS
Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

Bernadette Marie Makar, MSN, NP-C, APRN-C (Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

John P. Duffy, RPh, B.S. Pharmacy (Pharmacy Reviewer) has indicated he has no financial relationships with commercial interests to disclose.

AKH staff and planners have nothing to disclose.

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NURSING & PHARMACY

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Nursing and Pharmacy credit (per session) is based on attendance as well as completion of an online evaluation form available at:

WWW.AKHCME.COM/2015AES

THIS MUST BE DONE BY JANUARY 15, 2016 TO RECEIVE YOUR CE CREDIT.
We cannot submit credit to NABP after this date.
If you have any questions, please contact AKH at service@akhcme.com.

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FDA Town Hall Update

Generic Antiepileptic Drug Bioequivalence in Epilepsy Patients: from Anecdotes to Evidence

Michael Prvitera, M.D.
Professor Neurology
Director Epilepsy Center
University of Cincinnati Neuroscience Institute

December 7, 2015

Disclosure

Research Support / Grants

UCB, Eisai, Neuren Pharma;

EQUIGEN: FDA, American Epilepsy Society, Epilepsy Foundation

Other

DSMB: Astellas, Upsher Smith

Learning Objectives

- Describe results and conclusions from current single- and multiple-dose AED bioequivalence trials in epilepsy patients
- List factors which may impact AED clinical outcomes
- Understand NTI drug classification process

Agenda

- BEEP study findingsSub-point 1
  - Tricia Ting, M.D.
- EQUIGEN Single Dose Study Update Sub-Point 1
  - Michael Privitera, M.D.
- Authorized Generics, Pill Appearance, and Patient Adherence
  - Joshua Gagne, PharmD, ScD.
- FDA OGD Updates on Generic AEDs and NTI Designation
  - Wenlei Jiang, M.D.
- Panel Discussion

  Moderators: Michel Berg, M.D. and Xiaohui Jiang, Ph.D.
  Panel members: Tricia Ting, M.D. James Polli, Ph.D., Michael Privitera, M.D., Joshua Gagne, PharmD, ScD Wenlei Jiang, Ph.D.

FDA Town Hall: Generic Antiepileptic Drug Bioequivalence in Epilepsy Patients: from Anecdotal to Evidence

Tricia Y. Ting, MD
James E. Polli, PhD

12.07.15

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE

UNIVERSITY of MARYLAND SCHOOL OF PHARMACY

Disclosures: Tricia Ting, MD

FDA

HHSF223201010244A Co-PI

HHSF223201400188C PI

GRANT11682164 Sub-I

Other

GW Pharmaceuticals, Epilepsy Study Consortium (Human Epilepsy Project), Acorda, Pfizer

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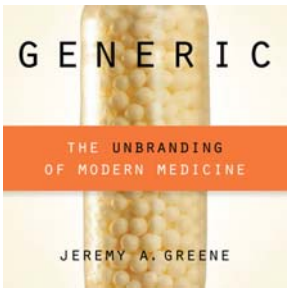
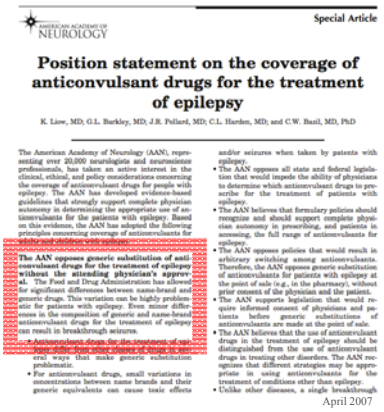
Learning Objectives:

- 1. Understand the process for approval and quality assurance of generic drug products in the US.
- 2. Describe results and conclusions from a current multiple-dose AED bioequivalence trial in epilepsy patients (BEEP1)
- 3. List factors which may impact AED clinical outcomes



…from suspect substances to American healthcare mainstay.



Special Article

Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy

K. Liow, MD; G.L. Barkley, MD; J.R. Pollard, MD; C.L. Harden, MD; and C.W. Bazil, MD, PhD

April 2007

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Nov 2007

AES Position on the Substitution of Different Formulations of Antiepileptic Drugs for the Treatment of Epilepsy

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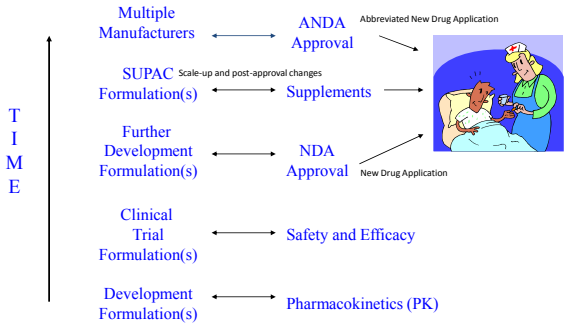
Drug Product Quality



ANDA: U.S. generic drug approval

Abbreviated New Drug Application

- Pharmaceutical equivalence -- requires medicines to have the same exact drug, dose strength, dosage form, and route of administration
- Bioequivalence -- requires that medicines have no significant difference in the rate and extent of drug absorption
  - Usually by PK testing in healthy volunteers receiving a single dose

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Bioequivalence Standard

To pass, must fall within the goalposts of 80-125%

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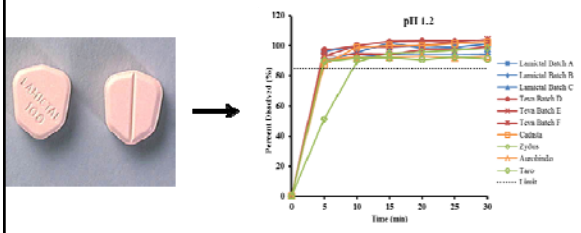
Pharmaceutical Quality Tests



Vaithianathan S, Raman, S, Jiang W, Ting TY, Kane MA, and Polli JE. (2015): Biopharmaceutic Risk Assessment of Brand and Generic Lamotrigine Tablets. DOI: 10.1021/acs.molpharmaceut.5b00154. Mol Pharmaceutics 12: 2436−2443.

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- **BIOPHARMACEUTIC RISK ASSESSMENT OF BRAND AND GENERIC LAMOTRIGINE TABLETS**
  Vaithianathan, Soundarya; Raman, Siddarth; Jiang, W; Ting, Tricia; Kane, Maureen; Polli, James
- All brand name and generic lamotrigine 100mg tablets passed all tests and showed acceptable pharmaceutical quality and low biopharmaceutic risk
- AES, December 2015 Poster Session

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Excipients

Lamictal	Teva lamotrigine
lamotrigine	lamotrigine
lactose	lactose monohydrate
magnesium stearate	magnesium stearate
microcrystalline cellulose	microcrystalline cellulose
povidone	povidone
sodium starch glycolate	sodium starch glycolate
FD&C yellow #6 (100mg), ferric oxide yellow (150mg), and FD&C blue #2 aluminum lake (200mg)	FD&C yellow #6 (100mg), ferric oxide yellow (150mg), and FD&C blue #2 aluminum lake (200mg)
-	colloidal silicon dioxide; pregelatinized starch

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Bioequivalence in Epilepsy Patients 1 (BEEP1) Study

BEEP Study
at University of Maryland

Generic vs BRAND lamotrigine bioequivalence in epilepsy patients:
a field test of the public bioequivalence standard

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BEEP study objectives

Bioequivalence in Epilepsy Patients 1 (BEEP1) Study

- ***Is bioequivalence the same in patients?***
- Primary objective: To assess whether generic Teva lamotrigine tablets are **bioequivalent** to Lamictal
- Secondary objective: To assess incidence of **seizure and (non-seizure) adverse effects** on each formulation

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Innovative Bioequivalence Study Design

- **"Generic brittle"** epilepsy patients and not healthy volunteers
  - Already taking **lamotrigine BID** for epilepsy
  - Evidence of (potential) sensitivity to switching
- Double-blind, multiple-dose, fully replicated design
  - **Outpatient** (e.g. self-dosing)
- Average bioequivalence
  (**brand versus generic** at steady-state)
- Single site at University of Maryland
- Initiated 2010 - completed 2013

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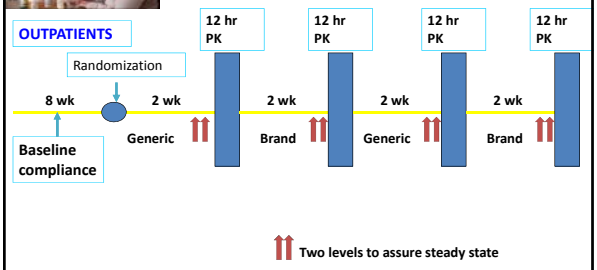
BEEP Study: Brand-Generic AED

Bioequivalence in Epilepsy Patients 1 (BEEP1) Study



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Patient Demographics

Sex	Male N=20	Female N=15	N=35
Age Range (Mean years)	19-66 (44)	20-63 (39)	19-66 (42)
Epilepsy			
Focal	17	10	27
Generalized	3	5	8
AED concomitant			
Valproic acid (inhibitor)	3	0	3
Inducer	3	3	6
Smoking (inducer)	1	2	3
Comorbid conditions			
None	9	4	13
One or more	11	11	22

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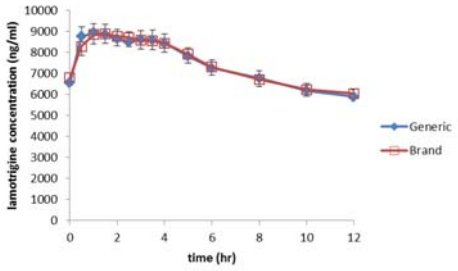
Average profiles



Cmax 90% CI: (98.8%, 104.5%) with ratio = 101.6%
AUC 90% CI: (97.2%, 101.6%) with ratio = 99.4%

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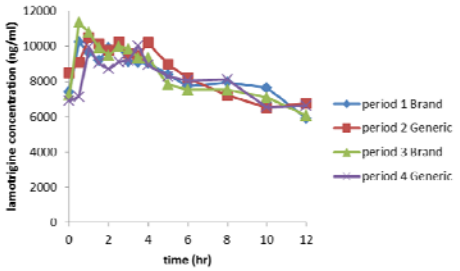
Subject 026



Brand and generic was essentially identical in subject 026, although subject experienced 19, 93, 40, and 115 focal motor seizures during period 1 brand, period 2 generic, period 3 brand, and period 4 generic, respectively

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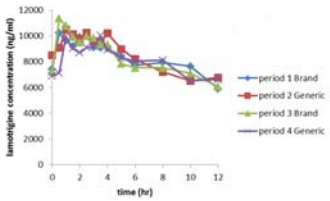
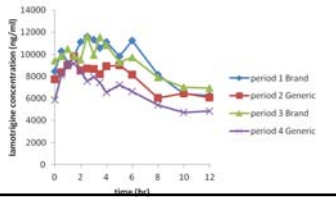
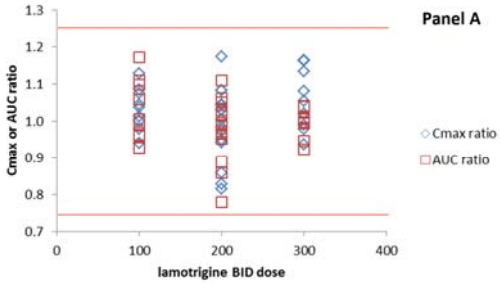
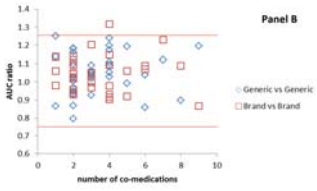


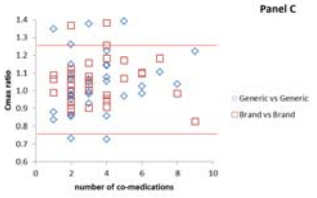
Subject 026



Subject 024







Conclusions

- **Passed conventional BE (Bioequivalence)**
  - validating testing in healthy volunteers
  - passed scaled BE for NTI drugs
- **BEEP: Unique design**
  - Randomized, double-blind, multiple-dose, steady-state, fully replicated BE study in "generic-brittle" **epilepsy patients**
  - First to demonstrate **feasibility** of performing BE evaluations in epilepsy patients
  - First to **a**ssess **BE in "generic brittle"** patients

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What about Mrs. Jones? The outliers?

http://thecanberran.com/2012/11/16/me-mrs-jones/

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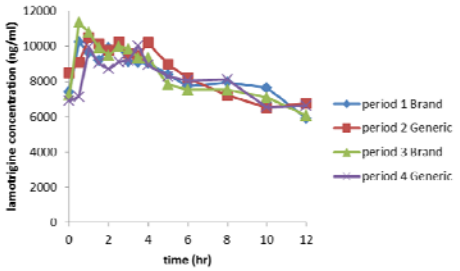
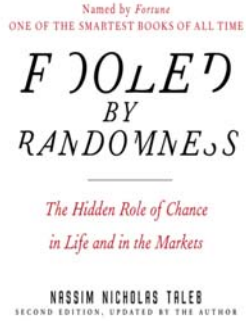
Subject 026



Brand and generic was essentially identical in subject 026, although subject experienced 19, 93, 40, and 115 focal motor seizures during period 1 brand, period 2 generic, period 3 brand, and period 4 generic, respectively

26



BEEP Follow-up

Bioequivalence in Epilepsy Patients Follow-Up (BEEP FU) Study

- Re-challenge for reproducibility
- Attention to clinical outcomes with switching generic and brand formulations
  - Baseline seizure frequency pre- and post-

28

Do Looks Matter?

29

The power of suggestion, or expectation

44% vs 15% Had Erectile Dysfunction

smithsonianmag.com

What Is the Nocebo Effect?

For some patients, the mere suggestion of side effects is enough to bring on negative symptoms

…Hypotension requiring IVF rescuscitation from overdose of PLACEBO

Worsened seizures with generic substitution?...

30

Other clinical factors

- Physiologic states or genetic propensity
- Subject-by-formulation interaction – when a subgroup in a population responds differently to either **T**est or **R**eference formulations than the rest.

31

BEEP 2

Bioequivalence in Epilepsy Patients 2 (BEEP2) Study

- Characterization of Generic Brittle Epilepsy Patients – Are there factors that predict GB?
- Supported by FDA HHSF223201400188C

Thanks to Wenlei Jiang and Xiaohui Jiang

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Generic Antiepileptic Drug Equivalence: The EQUIGEN Trials

Michael Privitera, MD
Professor Neurology
Director Epilepsy Center
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Disclosure: Michael Privitera, M.D.

Research Support / Grants

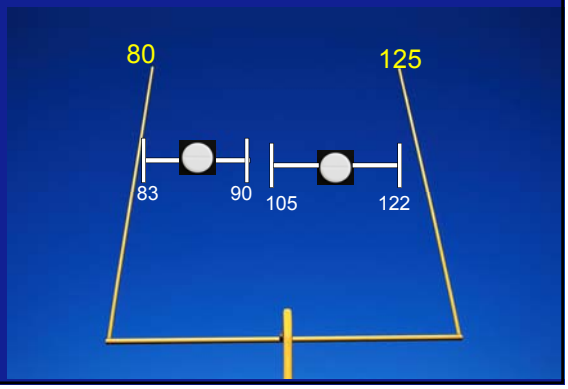
UCB, Eisai, Neuren Pharma;

EQUIGEN: FDA, American Epilepsy Society, Epilepsy Foundation

Other

DSMB: Astellas, Upsher Smith

Compare the Two Most Disparate Generics



Generic Products for Testing Are Close to Reference

	AUC CI
Theoretical Low	83-90
Low Generic 1	95.5-101.4
Theoretical High	105-122
High Generic 1	102.0-113.8

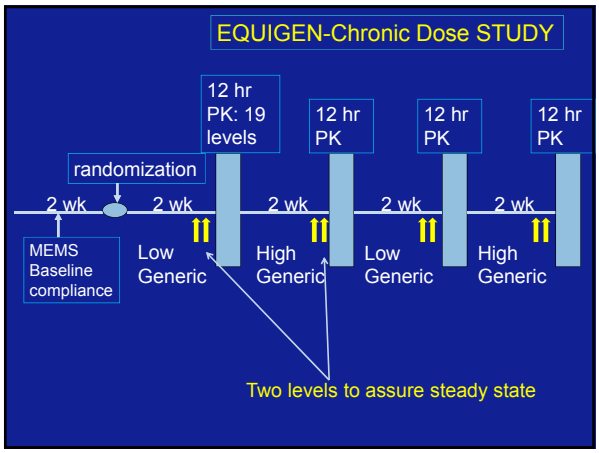
EQUIGEN *Chronic* Dose Study: Methods

- **In contrast to prior research EQUIGEN subjects:**

1. **Had epilepsy**
2. **Were often receiving concomitant medications with potential drug–drug interactions**
3. **Were receiving daily dosing (not single doses)**
4. **Underwent rigorous adherence monitoring through diaries and electronic methods**
5. **Underwent monitoring of adverse effects and seizure control.**

EQUIGEN *Chronic* Study: Methods

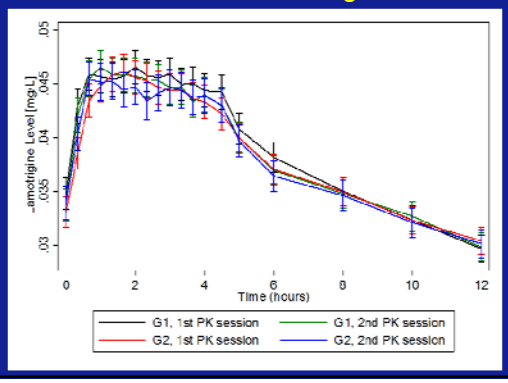
- **Must be on "balanced" dosing of lamotrigine (100 bid, 200 bid, 300 bid, or 400 bid)**
- **Many compliance measures**
  - Tablet counts
  - Medication diaries
  - MEMS caps: microchip measures each time medicine bottle is opened
- **For the 3 days before PK, all doses taken within an hour of scheduled time; no missed doses for the week before**



EQUIGEN *Chronic* Dose Study: Results

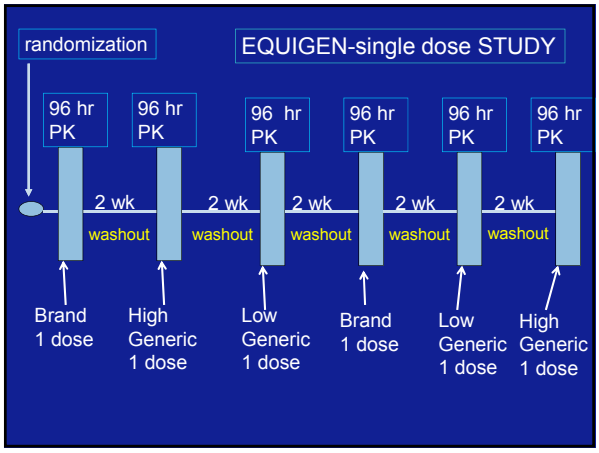
- **No outlier subjects for Cmax or AUC**
- ***Cmax:***
  - ***"high" generic 5.03***
  - ***"low" generic 4.96***
  - ***90%CI: 99-105%***
- ***AUC:***
  - ***"high" generic 2722***
  - ***"low" generic 2710***
  - ***90%CI: 98-103%***

Chronic Dose Study: All Generics Within Range



EQUIGEN *Chronic* Dose Study: Results

- **33 subjects**
- **58% were on polytherapy with other antiepileptic drugs, 18% had enzyme inducing drug-drug interactions with lamotrigine**
- **Remarkable compliance:**
  - 132 completed treatment periods with 3696 doses
  - Only 11 instances of minor compliance violations (single late or missed doses) leading to a makeup period.
- **No loss of seizure control**
- **No unexpected adverse effects and standardized side effect measure scores were not different between generics**



EQUIGEN *Single* Dose Study: Results

- **50 subjects randomized; 46 completed all 6 periods**
- **Bioequivalence**
  - Brand-High Generic
  - Brand-Low Generic
  - High-Low Generic
- **No outliers**
- **No serious adverse effects**

EQUIGEN Studies: Conclusions

- We found no deviation from FDA bioequivalence standards in Cmax and AUC comparing the two most disparate generics in a chronic dosing study, in a single dose study and our findings were replicated by another group Teva vs brand in chronic dosing study
- No difference inducers vs no inducers
- Chronic dosing generic equivalence trials are feasible and compliance is excellent
- *Then why so many problems reported?*
  - Nocebo effect
  - Attributing spontaneous seizures to generics
  - Pill color confusion

It's Easy to Confuse Generic Tablets…

Generic Antiepileptic Drug Equivalence: The EQUIGEN Trial

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Timothy Welty, Pharm D
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Authorized Generics, Pill Appearance, and Patient Adherence

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December 7, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

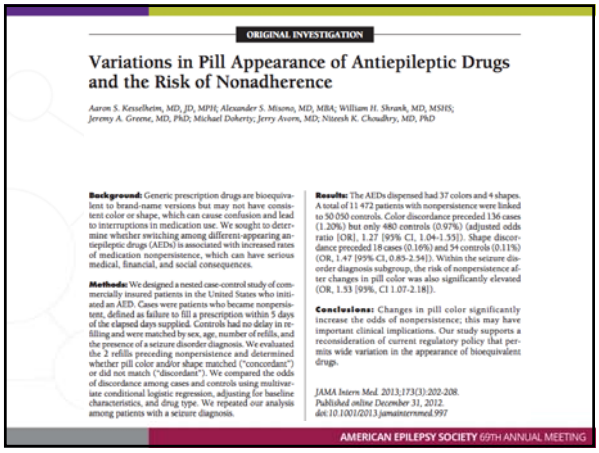
- Work presented today funded by Teva and by the FDA Office of Generic Drugs (opinions expressed here are my own and not necessarily of FDA)
- I am an Investigator in FDA's Sentinel program and Co-Lead of the methods core
- I am PI of other grants from:
  - Agency for Healthcare Research & Quality
  - Patient-Centered Outcomes Research Institute
  - Reagan-Udall Foundation's IMEDS
- I was previously PI of grants from Novartis to the Brigham and Women's Hospital for work unrelated to this presentation
- I am a consultant to Aetion, Inc,m a software company

Learning Objectives

- To understand the frequency of AED pill appearance changes and their impact on non-adherence
- To understand the impact of generic vs. brand-name AEDs on adherence and subsequent clinical outcomes
- To recognize authorized generics and appreciate their role in evaluating the safety and effectiveness of generic AEDs

AED pill appearance and adherence

- As compared to brand-name counterparts, generic drugs:
  - Have the same active ingredient, dosage form, strength, route of administration, intended use
  - Do not have the same color or shape
- Changes in color and/or shape may cause patient confusion and reduced adherence



ORIGINAL INVESTIGATION

Variations in Pill Appearance of Antiepileptic Drugs and the Risk of Nonadherence

Aaron S. Kesselheim, MD, JD, MPH; Alexander S. Misono, MD, MBA; William H. Shrank, MD, MSHS; Jeremy A. Greene, MD, PhD; Michael Doherty; Jerry Avorn, MD; Niteesh K. Choudhry, MD, PhD

Background: Generic prescription drugs are bioequivalent to brand-name versions but may not have consistent color or shape, which can cause confusion and lead to interruptions in medication use. We sought to determine whether switching among different-appearing antiepileptic drugs (AEDs) is associated with increased rates of medication nonpersistence, which can have serious medical, financial, and social consequences.

Methods: We designed a nested case-control study of commercially insured patients in the United States who initiated an AED. Cases were patients who became nonpersistent, defined as failure to fill a prescription within 5 days of the elapsed days supplied. Controls had no delay in refilling and were matched by sex, age, number of refills, and the presence of a seizure disorder diagnosis. We evaluated the 2 refills preceding nonpersistence and determined whether pill color and/or shape matched ("concordant") or did not match ("discordant"). We compared the odds of discordance among cases and controls using multivariate conditional logistic regression, adjusting for baseline characteristics, and drug type. We repeated our analysis among patients with a seizure diagnosis.

Results: The AEDs dispensed had 37 colors and 4 shapes. A total of 11 472 patients with nonpersistence were linked to 50 050 controls. Color discordance preceded 136 cases (1.20%) but only 480 controls (0.97%) (adjusted odds ratio [OR], 1.27 [95% CI, 1.04-1.55]). Shape discordance preceded 18 cases (0.16%) and 54 controls (0.11%) (OR, 1.47 [95% CI, 0.85-2.54]). Within the seizure disorder diagnosis subgroup, the risk of nonpersistence after changes in pill color was also significantly elevated (OR, 1.53 [95%, CI 1.07-2.18]).

Conclusions: Changes in pill color significantly increase the odds of nonpersistence; this may have important clinical implications. Our study supports a reconsideration of current regulatory policy that permits wide variation in the appearance of bioequivalent drugs.

JAMA Intern Med. 2013;173(3):202-208. *Published online December 31, 2012. doi:10.1001/2013.jamainternmed.997*

AED pill appearance and adherence

- Design: nested case-control study
- Data: HealthCore Integrated Research Database
- Patients: individuals starting treatment with new AED
- Outcome: non-persistence defined as failure to refill an AED within 5 days of the elapsed days supplied
- Analysis:
  - Cases matched to controls based on specific AED used, number of dispensings, sex, age, seizure diagnosis
  - Conditional logistic regression adjusting for clinical conditions and health service utilization
  - Compared odds of change in pill appearance between cases and controls

Ref: Kesselheim AS et al. *JAMA Intern Med* 2013;173:202-8.

AED pill appearance and adherence

Table 1. Shape Variation Among Antiepileptic Prescriptions in Sample

Shape Type	Type of Drug, No. (%)						
	Carbamazepine	Carbamazepine-XR	Lamotrigine	Zonisamide	Ethosuximide	Valproic Acid	Phenytoin Sodium
Round or circular	47 450 (78.3)	31 227 (56.6)	0	0	0	0	0
Oval or elliptical	0	0	0	0	0	365 (32.4)	0
Oblong	12 753 (21.1)	14 736 (26.7)	4 (0)	5438 (97)	38 668 (99.5)	760 (67.6)	12 3814 (100)
Shield	0	0	263 906 (99.9)	0	0	0	0
Unknown	365 (0.6)	9217 (16.7)	134 (0.1)	168 (3)	181 (0.5)	0	2 (0)
Total	**60 568 (100)**	**55 180 (100)**	**264 044 (100)**	**5606 (100)**	**38 849 (100)**	**1125 (100)**	**123 816 (100)**

Ref: Kesselheim AS et al. *JAMA Intern Med* 2013;173:202-8.

Table 2. Color Variation Among Antiepileptic Prescriptions in Sample

Antiepileptic Drug	Color and Prevalence, No. (%)[a]					
	Most Common	Second Most Common	Third Most Common	Fourth Most Common	Fifth Most Common	Others
Carbamazepine	White, 47 477 (78.4)	Pink, 12 753 (21.1)	NA	NA	NA	NA
Carbamazepine-XR	Pink, 15 356 (27.8)	Black and blue-green, 10 747 (19.5)	Brown, 10 141 (18.4)	Gray and blue-green, 6757 (12.3)	Yellow, 5730 (10.4)	Blue-yellow, 1457 (2.6); yellow and blue-green, 159 (0.3); blue-green, 56 (0.1)
Lamotrigine	Peach, 127 824 (48.4)	Blue, 57 118 (21.6)	White, 52 172 (19.8)	Cream, 26 618 (10.1)	Multicolor, 178 (0.1)	NA
Zonisamide	Off-white, 3384 (60.4)	White, 1540 (27.5)	Yellow, 530 (9.5)	Orange, 79 (1.4)	Beige, 42 (0.7)	NA
Valproic acid	Orange, 1125 (100)	NA	NA	NA	NA	NA
Phenytoin sodium	White and violet, 62 935 (50.8)	Clear or colorless, 55 247 (44.6)	Blue, 5482 (4.4)	Natural, 116 (0.1)	White and lavender, 24 (0)	Orange, 10 (0)
Ethosuximide	White and red, 29 053 (74.8)	Blue/violet, 3031 (7.8)	White and gray, 1600 (4.1)	White, 1421 (3.7)	White and green, 669 (1.7)	Red and gray, 602 (1.5); white and orange, 596 (1.5); white and peach, 505 (1.3); violet and lavender, 303 (0.8); white and violet, 289 (0.7); orange, 287 (0.7); gray/gray, 101 (0.3); yellow, 84 (0.2); white and blue, 65 (0.2); white and yellow, 52 (0.1); red-orange, 11 (0); iron gray, 6 (0); pink and peach, 4 (0); gray and red-orange, 1 (0)

Ref: Kesselheim AS et al. *JAMA Intern Med* 2013;173:202-8.

Table 4. Association Between Nonadherence and Color and Shape Discordance in Antiepileptic Drugs

Sample or Subset	No. (%)		OR (95% CI)	
	Discordance Among Cases	Discordance Among Controls	Unadjusted	Adjusted
Main sample				
Color discordance	136 (1.20)	480 (0.97)	1.29 (1.06-1.57)	1.27 (1.04-1.55)
Shape discordance	18 (0.16)	54 (0.11)	1.52 (0.88-2.62)	1.47 (0.85-2.54)
Subset with seizure diagnoses				
Color discordance	45 (1.74)	133 (1.16)	1.54 (1.08-2.20)	1.53 (1.07-2.18)
Shape discordance	4 (0.16)	6 (0.05)	3.22 (0.83-12.4)	3.15 (0.82-12.1)

Abbreviation: OR, odds ratio.

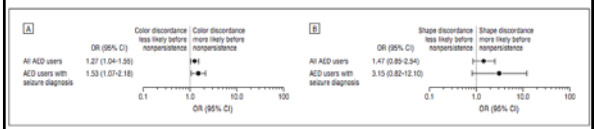


Figure. Comparison of odds ratios (ORs) or color (A) and shape (B) discordance related to antiepileptic drug (AED) nonadherence.

Ref: Kesselheim AS et al. *JAMA Intern Med* 2013;173:202-8.

Generic vs. brand-name AEDs

- Switching between brand-name and generic AEDs is controversial
  - Even more so for switching between generics from different manufactures
- Patients who use generic drugs generally display greater medication adherence
- An observational study that captures "real-world" switch patterns and adherence behavior can compare the impacts of these factors

Generic vs. brand-name AEDs

Contents lists available at ScienceDirect
Epilepsy & Behavior
journal homepage: www.elsevier.com/locate/yebeh

Comparative effectiveness of generic versus brand-name antiepileptic medications

Joshua J. Gagne [a,*], Aaron S. Kesselheim [a], Niteesh K. Choudhry [a], Jennifer M. Polinski [b], David Hutchins [b], Olga S. Matlin [b], Troyen A. Brennan [b], Jerry Avorn [a], William H. Shrank [b]
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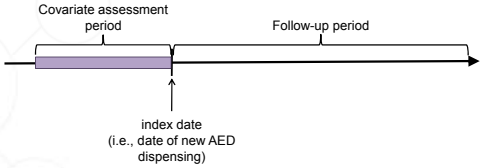
[b] CVS Health, Woonsocket, RI, USA

Generic vs. brand-name AEDs

- Design: observational cohort study



Ref: Gagne JJ et al. *Epilepsy & Behavior* 2015;52(Pt A):14-8.

Generic vs. brand-name AEDs

- Data:
  - CVS Health (formerly CVS Caremark) pharmacy claims
  - Medicare Parts A and B claims
  - US census data
- Patients: individuals starting starting treatment with new AED
- Analysis: propensity score matching adjusting for:
  - Demographics (e.g., age, sex)
  - Clinical variables (e.g., prior fracture, anxiety, dementia)
  - Proxies of socioeconomic status (median household income)
  - Health service utilization (# hospitalization, # ER visits)

Ref: Gagne JJ et al. *Epilepsy & Behavior* 2015;52(Pt A):14-8.

Generic vs. brand-name AEDs

- Outcomes:
  - Persistence:
    - Time to first treatment gap of >14 days
  - Clinical outcomes:
    - Seizure-related ER visit of hospitalization (ICD-9 codes 345.xx [excluding 345.6x] or 780.39)
    - ER visit of hospitalization for bone fracture or head injury
    - Composite comprising both clinical outcomes

Ref: Gagne JJ et al. *Epilepsy & Behavior* 2015;52(Pt A):14-8.

Table 1
Characteristics of generic and brand-name AED initiators in full and propensity score-matched cohorts.

	Full cohort	
	Generic (n = 18,306)	Brand-name (n = 1454)
Demographic characteristics		
Age, mean (sd)	75.3 (7.6)	74.9 (7.6)
Female, n (%)	7266 (39.7)	595 (40.9)
Median household income in census block	58,210.2 (29,807.6)	64,601.8 (36,538.5)
Health service utilization measures, mean (sd)		
No. unique drugs dispensed	11.0 (5.7)	10.1 (5.7)
Physician visits	5.3 (4.9)	5.3 (4.9)
Hospitalizations	0.4 (0.8)	0.4 (0.8)
Emergency room visits	0.5 (1.1)	0.5 (1.3)
Nursing home admissions	0.2 (0.8)	0.1 (0.7)
Clinical characteristics		
Combined comorbidity score, mean (sd)	1.5 (2.5)	1.3 (2.3)
Epilepsy diagnosis, n (%)	203 (1.1)	219 (15.1)
Hospitalization for fracture, n (%)	181 (1.0)	11 (0.8)
Emergency room visit for fall, n (%)	21 (0.1)	1 (0.1)
Depression diagnosis, n (%)	1329 (7.3)	126 (8.7)
Anxiety diagnosis, n (%)	2217 (12.1)	184 (12.7)
Mania diagnosis, n (%)	123 (0.7)	32 (2.2)
ADHD diagnosis, n (%)	38 (0.2)	18 (1.2)
Alcohol abuse diagnosis, n (%)	73 (0.4)	15 (1.0)
Drug abuse diagnosis, n (%)	119 (0.7)	14 (1.0)
Psychosis diagnosis, n (%)	452 (2.5)	68 (4.7)
Dementia diagnosis, n (%)	488 (2.7)	71 (4.9)

Ref: Gagne JJ et al. *Epilepsy & Behavior* 2015;52(Pt A):14-8.

Generic vs. brand-name AEDs

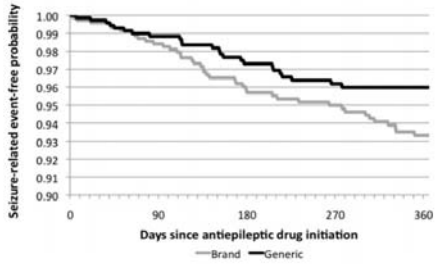


Fig. 1. Cumulative seizure-related event-free probability following initiation of a generic versus brand-name antiepileptic drug.

Ref: Gagne JJ et al. *Epilepsy & Behavior* 2015;52(Pt A):14-8.

Generic vs. brand-name AEDs

Table 2
Hazard ratios for outcomes in patients starting generic versus brand-name AEDs: primary analyses.

Outcome	Hazard ratio (95% CI)
Seizure-related hospitalization or emergency room visit	0.53 (0.30, 0.96)
Hospitalization or emergency room visit for bone fracture or head injury	0.67 (0.19, 2.36)
Composite hospitalization or emergency room visit for seizure, bone fracture, or head injury	0.51 (0.30, 0.89)

AED, antiepileptic drug; CI, confidence interval.

- Mean time to first treatment gap >14 days:
  - Generic AED initiators: 124 days
  - Brand AED initiators: 128 days

} $p = 0.01$

Ref: Gagne JJ et al. *Epilepsy & Behavior* 2015;52(Pt A):14-8.

Generic vs. brand-name AEDs

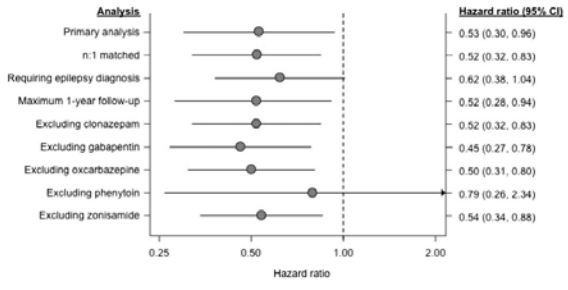


Fig. 2. Forest plot of hazard ratios from sensitivity analyses.

Ref: Gagne JJ et al. *Epilepsy & Behavior* 2015;52(Pt A):14-8.

Authorized generics

- Authorized generic:
  - Brand-name drug (approved via an NDA) marketed as a generic under a different labeler
  - Typically the same size, shape, and color as a brand-name drug but with different markings, labeling, packaging
- AEDs with authorized generics:
  - Carbamazepine extended release tablets
  - Gabapentin capsules
  - Lamotrigine tablets for oral solution/suspension
  - Oxcarbazepine tablets

Authorized generics

- FDA OGD-funded project (U01FD005279)
- Aims to compare:
  - Outcomes (clinical, adherence) among patients who use:
    - Brand-name drugs
    - Authorized generic drugs
    - Other generic drugs
  - Adverse event reporting before and after generic introduction when an AG is available vs. not

Summary

- Variation in appearance of generic AEDs may be a barrier to adherence
- Patient out-of-pocket cost is an important driver of AED adherence
- Leveraging AGs, we are attempting to tease out the relative impacts on adherence and clinical outcomes of:
  - Differences in bioequivalence
  - Negative perceptions of generics
  - Variations in pill appearance
  - Costs

#AESmtg15

AMERICAN EPILEPSY SOCIETY

69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Bioequivalence Approach for Narrow Therapeutic Index (NTI) Drugs and NTI Designation for Anti-epileptic Drugs (AEDs)

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Deputy Director (Acting)
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December 5, 2015

Disclosure

- Dr. Jiang has no financial interests or COI to disclose.
- The opinions and conclusions expressed in this presentation are those of the presenter and should not be interpreted as those of the FDA.

Learning Objectives

At the completion of this presentation, the participant will be able to:

- Describe FDA bioequivalence approach for NTI drugs
- Identify general characteristics of NTI drugs
- Understand that not all AEDs should be classified as NTI drugs

Epilepsy and Generic Anti-epileptic drugs (AEDs)

http://www.gphaonline.org/

3 million Americans affected by epilepsy

+

Many AEDs with approved generic versions available

II

Significant drug cost reduction with generic AED substitution

What Neurologists Say about Generic Antiepileptic Drugs (AEDs)

- Patients complained about inadequate control of seizure after they switch to generic AEDs
- AEDs are narrow therapeutic index (NTI) drugs
- Generic AEDs should be subject to more stringent bioequivalence criteria
- Generic drug products may not have the same quality as the reference listed drug (RLD)
- Bioequivalence studies in healthy subjects cannot predict equivalence in patients

Global Variations in NTI Definition

Regulatory Agencies	Term Used	Regulatory Definition
Health Canada	Critical dose drugs	Drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death.
Europe Medicines Agency (EMA)	Narrow therapeutic index drugs	No definition
US Food and Drug Administration (FDA)	Narrow therapeutic index drugs	Drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity.
Japan Pharmaceutical and Food Safety Bureau (JPFSB)	Narrow therapeutic range drugs;	No definition

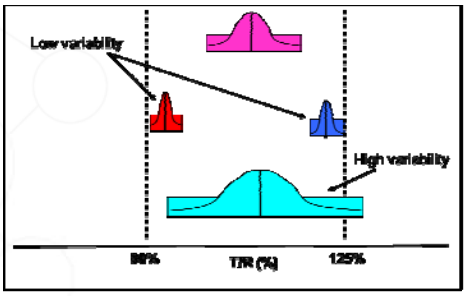
W Jiang and LX Yu. Bioequivalence for narrow therapeutic index drugs. In L.X. Yu and B.V. Li (eds.), FDA Bioequivalence Standards, 2014 AAPS Advances in the Pharmaceutical Sciences Series, Springer Science New York 2014

General Characteristics for NTI Drugs

- Little separation between therapeutic and toxic doses (or associated blood/plasma concentrations)
- Sub-therapeutic concentration may lead to serious therapeutic failure
- Drugs are subject to therapeutic monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures
- Drugs possess low-to-moderate (i.e., no more than 30%) within-subject variability
- In clinical practice, doses are often adjusted in very small increments (less than 20%)

LX Yu, W Jiang, X Zhang, R Lionberger, F Makhlouf, DJ Schuirmann, L Muldowney, M-L Chen, B Davit, D Conner and J Woodcock. Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs. Clinical Pharmacology & Therapeutics 2014

One Size Fits All?



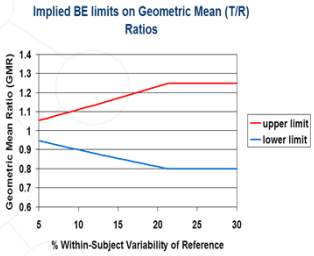
BE Study Design for NTI Drugs

Regulatory Agencies	Bioequivalence Study Design
Health Canada	Single-dose two-way crossover or parallel study in healthy subjects
EMA	Same as above
JPFSB	Same as above
US FDA	Single-dose, fully replicated, four way crossover study in healthy subjects

BE Criteria for NTI Drugs

Regulatory Agencies	Bioequivalence Criteria	
	AUC	Cmax
Health Canada	90.0% -112.0%	80.0-125.0%
EMA	90.00-111.11%.	80.00-125.00% Where Cmax is of particular importance for safety, efficacy or drug level monitoring, the 90.00-111.11% acceptance interval should also be applied to Cmax
JPFSB	80.0-125.0%	80.0-125.0%
US FDA	Must pass both the reference scaled limits and the unscaled average bioequivalence limits of 80.00-125.00%. The upper limit of the 90% confidence interval of ***the ratio of the within-subject standard deviation of the test to reference product*** is less than or equal to 2.5.	

Revised BE Criteria for NTI Drugs (FDA)



S_{WR}	BE limits
5	94.87 - 105.41
10	90.02 - 111.08
15	85.35 - 117.02
20	81.17 - 123.20
>21.42	80.00 - 125.00

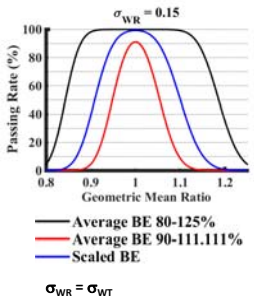
W Jiang, F Makhlouf, DJ Schuirmann, X Zhang, N Zheng, D Conner, LX Yu, and R Lionberger. *A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion*. AAPS Journal 2015

Warfarin Sodium guidance.
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm204955.htm

Reference Scaled Average Bioequivalence (RSABE) vs. Tightened ABE Limits 90-111%

- Tightened ABE limits could be too strict in certain cases
  - RLD compared to itself

  (GMR=1, $\sigma_{WR} = \sigma_{WT}$): passing rate = 91.18%
- RSABE limit will vary based on the within subject variability of reference drug but capped within 80-125%
- Additional variability comparison



NTI or Critical Dose Drug list

- Health Canada: Digoxin, flecainide, lithium, **phenytoin**, sirolimus, tacrolimus, cyclosporine, theophylline, and warfarin
- EMA: Tacrolimus, sirolimus, cyclosporine
- FDA: Warfarin, tacrolimus, **phenytoin, carbamazepine,** more pending for systematic evaluation
- JPFSB: Aprindine, Carbamazepine, Clindamycin, Clonazepam, Clonidine, Cyclosporine, Digitoxin, Digoxin, Disopyramide, Ethinyl Estradiol, Ethosuximide, Guanethidine, Isoprenaline, Lithium, Methotrexate, Phenobarbital, Phenytoin, Prazosin, Primidone, Procainamide, Quinidine, Sulfonylurea antidiabetic drugs compounds, Tacrolimus, Theophylline compounds, Valproic Acid, Warfarin, Zonisamide, Glybuzole

NTI Classification: Serious Therapeutic Failure and Adverse Events?

Serious therapeutic failure

- Epilepsy, immunosuppression, heart failure, anticoagulation…..

Serious adverse events

- Dose-dependent drug substance related adverse events

NTI Classification: Determine Little Separation between Toxic and Therapeutic doses (conc.)

- Calculate based on population level PK/PD data
- Estimate based on therapeutic window

Drugs	Therapeutic range	Plasma concentration associated with serious toxicity	Estimated toxic/effective concentration ratio
Phenytoin (http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=484&n=Phenytoin)*	10–20 mcg/ml	>40 mcg/ml	2.7

- Infer from individual level data

  TDM and small dose adjustment can be a hint of steep exposure-response relationship within individuals, therefore, little separation is anticipated.

NTI Classification: Estimate Within-subject Variability

- Estimated via root mean square error (RMSE) values of the bioequivalence parameters Cmax and AUC0-t from single-dose two-way crossover BE studies

		AUC0-t		C_{max}	
Drug products	# of BE Studies	Mean	Range	Mean	Range
Warfarin	29	5.7	3.3, 11.0	12.7	7.7, 20.1
Lithium carbonate	16	7.8	4.5, 14.0	13.5	6.4, 24.4
Digoxin	5	21.7	13.1, 32.2	21.0	14.3, 26.1
Phenytoin	12	9.2	4.1, 18.6	14.9	7.4, 20.0
Theophylline	3	17.9	12.8, 24.2	18.2	11.8, 25.8
Tacrolimus	6	21.9	16.8, 26.6	19.0	15.0, 24.4

LX Yu, W Jiang, X Zhang, R Lionberger, F Makhlouf, DJ Schuirmann, L Muldowney, M-L Chen, B Davit, D Conner and J Woodcock. Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs. Clinical Pharmacology & Therapeutics 2014

NTI Classification: Subject to Therapeutic Drug Monitoring (TDM)?

- Monitoring purpose
- Routine or occasionally
- In special population
- Health care environment may not favor drugs with TDM

NTI Classification: Evaluate Dose Adjustment

- Multiple dose strength available for the product
- Actual clinical practice data show small increment or decrement with patients
  - Dose adjustment when therapeutic failure or adverse events occurred
  - Drug-drug interaction data
  - Food effect label

NTI Evaluation for AEDs

Drug Product	Estimated toxic/effective concentration ratio *	Sub-therapeutic concentrations may lead to serious therapeutic failure?	Therapeutic monitoring	Within-subject variability (AUC)**	Dose adjustment in small increment***
Phenytoin	2	Yes	Yes	5.9-18.6%	possible (33%)
Carbamazepine	2.5	Yes	Yes	9.9-17%	possible (25%)
Valproic acid	2-2.7	Yes	Yes	4.8-10.4%	possible (33%)
Topiramate	ND	ND	No	3.8-14.4%	possible (13%)
Lamotrigine	10	Yes	Not routinely done	5.5-18.5%	Possible (13%)
Levetiracetam	ND	ND	No	7.5-27.7%	Possible (25%)

- is estimated by the minimal toxic concentration (defined by physicians the minimum concentration that would significantly increase the likelihood of serious adverse reaction) divided by the minimal effective/therapeutic concentration (defined by physicians the minimum concentration that would give the desired pharmacological effect) in plasma/blood

** denotes the mean residual variability from two-way crossover studies; fasted study only; IR or CR formulation; AUC_t or AUC_{0-inf}

***denotes smallest possible strength available for dose adjustment

Revised BE Guidance for NTI drugs

Draft Guidance on Phenytoin Sodium

Active Ingredient: Phenytoin sodium

Dosage Form; Route: Extended release capsule; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
Strength: 300mg (dose: 1 X 300mg)
Subjects: Normal healthy males and females, general population
Additional comments: Washout period of at least 14 days. The strength(s) designated in the Orange Book as the reference listed drug (RLD) should be used in the studies. The applicant should use the reference-scaled average bioequivalence approach for phenytoin sodium.

2. Type of study: Fed
Design: Single-dose, 2-treatment, 2-sequence, 4-period, fully replicated crossover in vivo
Strength: 300mg (dose: 1 X 300mg)
Subjects: Normal healthy males and females, general population
Additional comments: See comments above

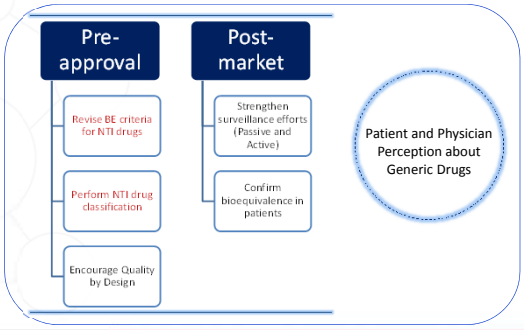
Recommended May 2007; Revised Dec 2014

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081332.htm

Summary

- NTI definition, list of NTI drugs, BE approach/criteria for NTI drugs vary among different regulatory bodies
- FDA developed novel BE approach and criteria for NTI drugs
  - Fully replicated study design
  - Scaled based on within-subject variability of the RLD
  - Variability comparison
- FDA established process to classify NTI drugs
- AEDs classified as NTIs are subject to tighter BE standards

FDA OGD Efforts to Ensure Generic AED Safety and Efficacy



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Thank you

Questions?

FDA Town Hall Update Panel Discussion

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Panel Discussion

#AESmtg15