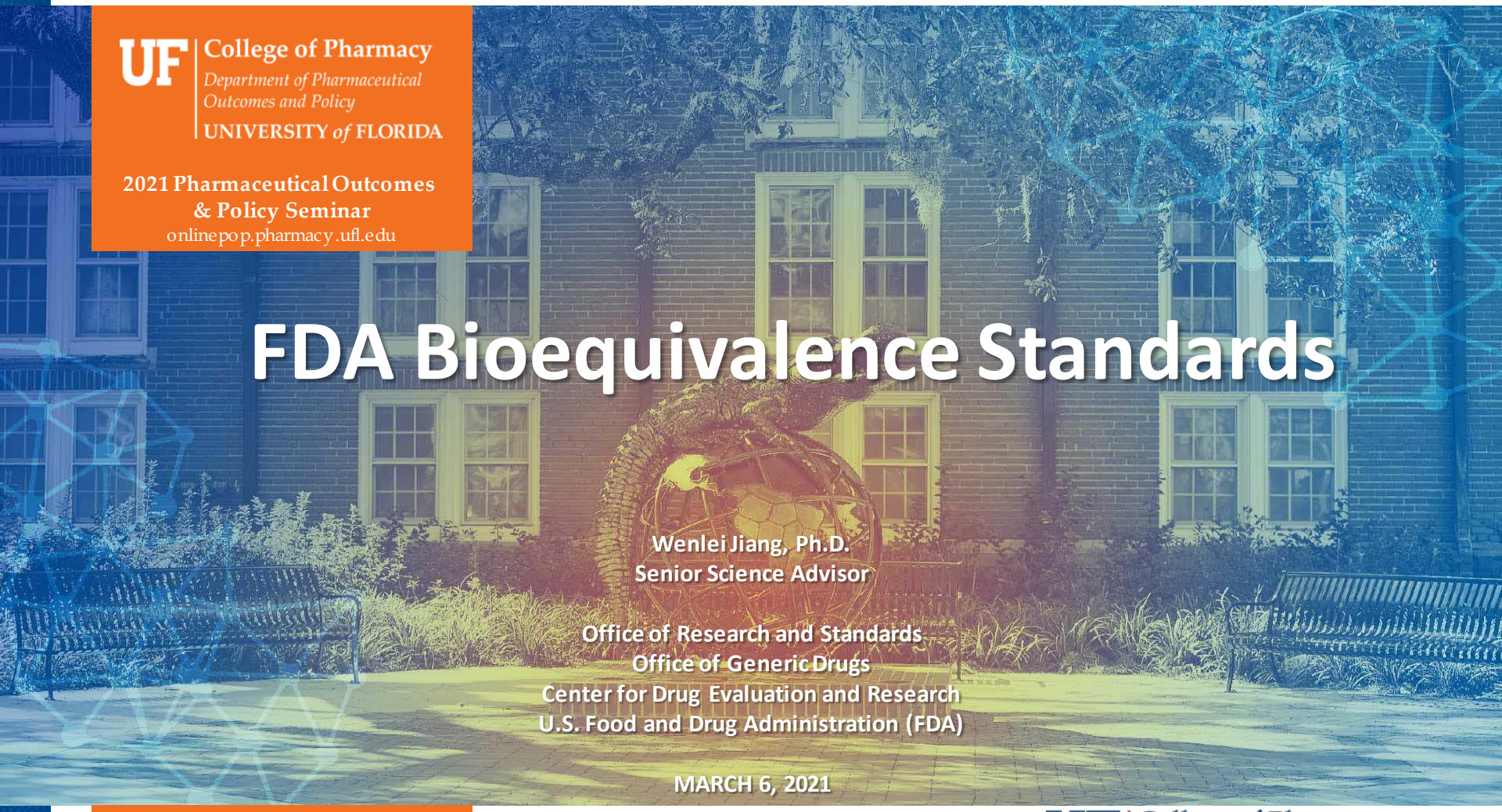

UF College of Pharmacy
Department of Pharmaceutical Outcomes and Policy
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2021 Pharmaceutical Outcomes & Policy Seminar
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FDA Bioequivalence Standards

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Office of Research and Standards
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U.S. Food and Drug Administration (FDA)

MARCH 6, 2021

UF College of Pharmacy
Department of Pharmaceutical Outcomes and Policy
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Disclosure Statement

Wenlei Jiang, Ph.D has disclosed that she has no relevant financial disclosures.

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

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2021 Pharmaceutical Outcomes and Policy Seminar Objectives

Upon completion of this course, the student will:

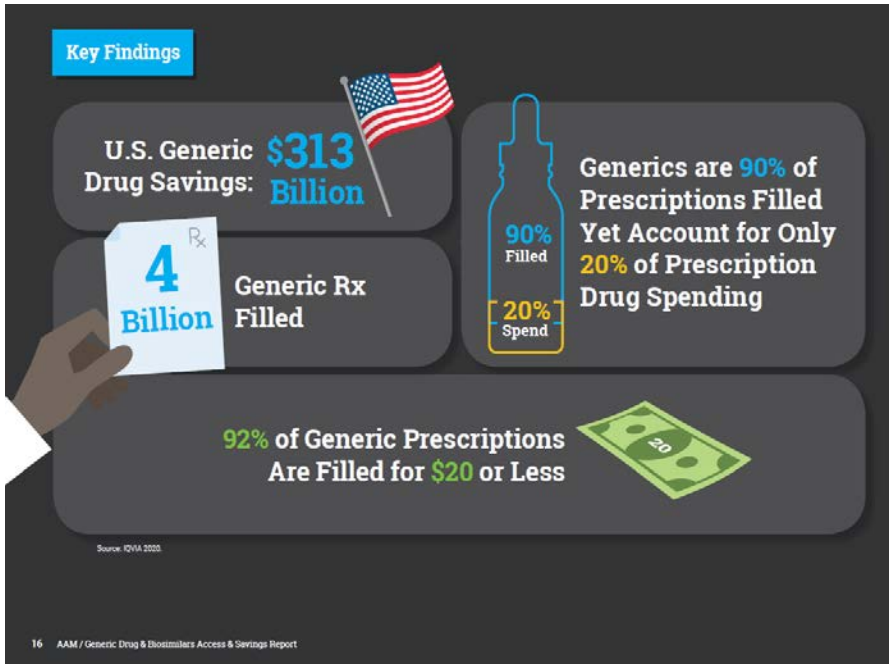
1. State examples of quality control issues for generic and brand-name pharmaceutical drugs.
2. Describe the relationship between pharmaceutical quality issues and drug shortages.
3. List methods and policies that can be used to improve the quality of pharmaceuticals.
4. Explain the role of generic drugs and provide methods to assure the quality of the generic supply chain.
5. Discuss the root causes of quality control issues of pharmaceuticals and propose solutions that address these root causes.

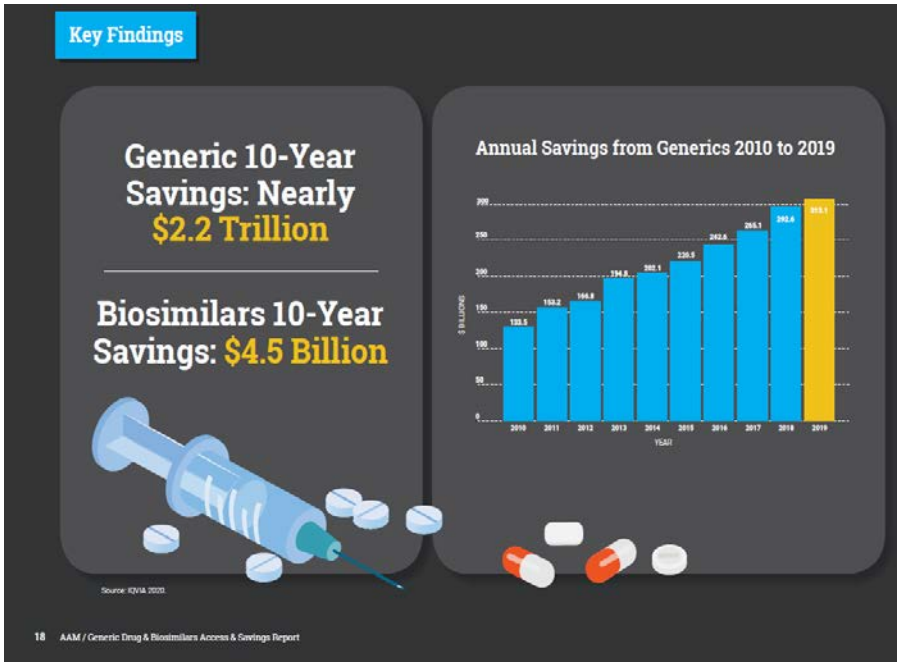
Outline

- Generic drugs and bioequivalence
- Bioequivalence approaches for different drug products
- Misconceptions about bioequivalence and controversies about generic drugs
- FDA's efforts to ensure therapeutic equivalence of generic drugs
- Conclusions

Generic Drugs

- Generic drugs are duplicates of reference listed drugs (RLDs)
- Same active ingredient, conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and bioequivalent to RLD





https://accessiblemeds.org/sites/default/files/2020-09/AAM-2020-Generics-Biosimilars-Access-Savings-Report-US-Web.pdf

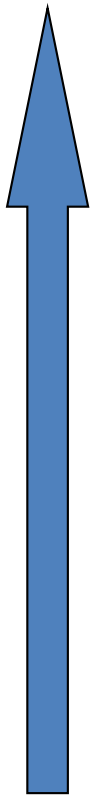
New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)

NDA	ANDA
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Testing	3. Testing
4. Labeling	4. Labeling
5. Inspection	5. Inspection
6. Animal Studies	6. Bioequivalence
7. Clinical Studies	
8. Bioavailability	

Bioequivalence

- "[T]he absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administrated at the same molar dose under similar conditions in an appropriately designed study." (21 CFR § 314.3(b))

Approaches to Determining Bioequivalence (21 CFR 320.24)



- *In vivo* measurement of active moiety or moieties in biologic fluid
  - "Pharmacokinetics (PK) study"
- *In vivo* pharmacodynamic (PD) comparison
  - "PD study"
- *In vivo* limited clinical comparison
  - "Bioequivalence study with comparative clinical endpoints (CE)"
- *In vitro* comparison
- Any other approach deemed appropriate by FDA

Pharmacokinetic Bioequivalence Study Design and Criteria

Study design:
Single dose 2-way crossover

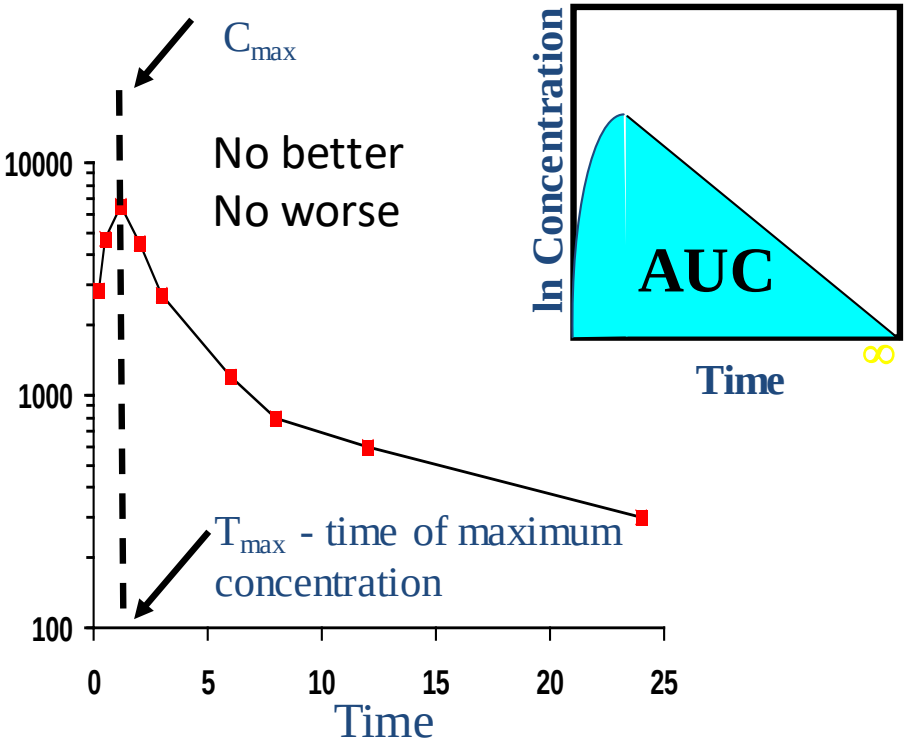
Sequence 1

T – washout period – R

Sequence 2

R – washout period – T

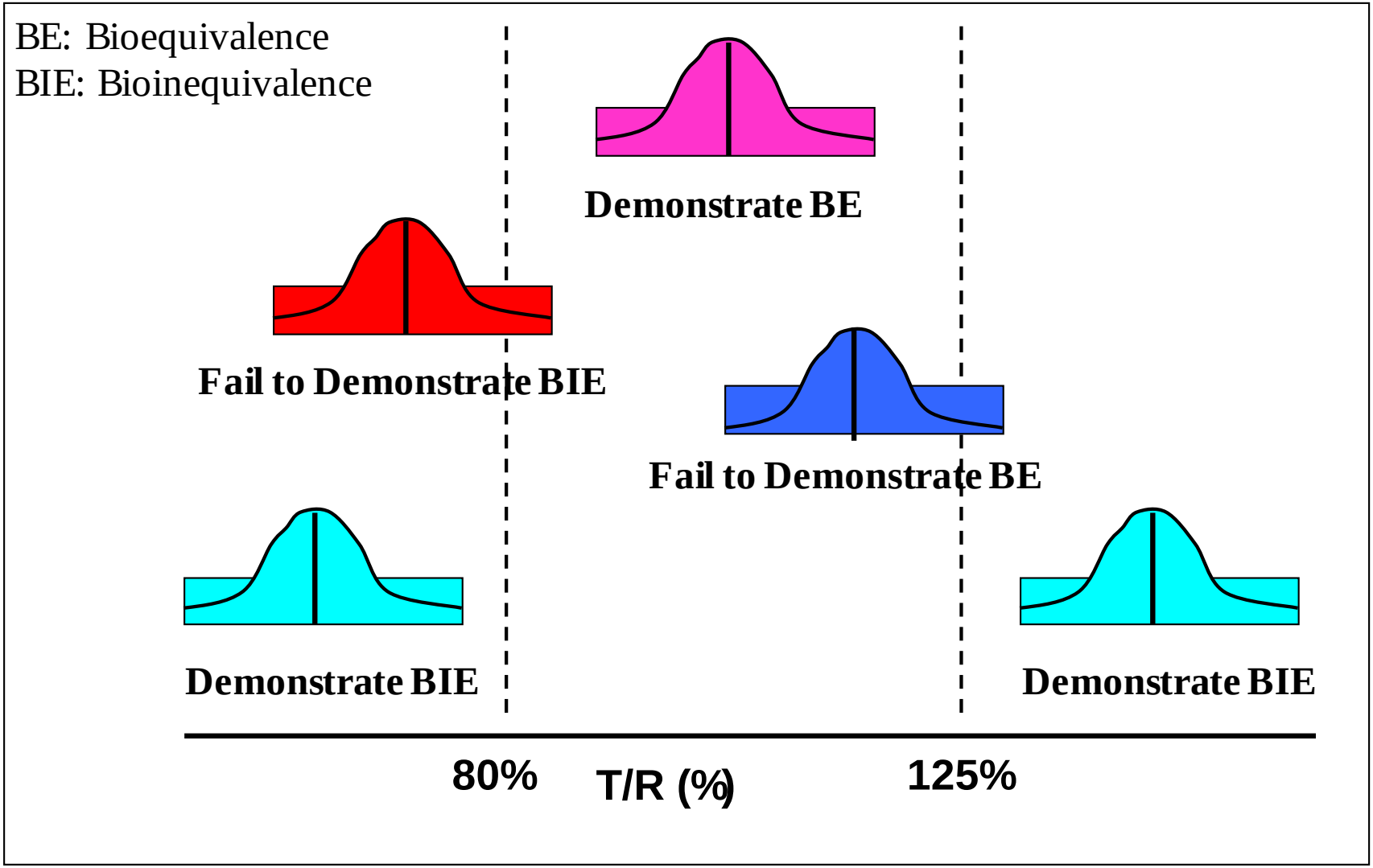
- T= Test Drug
- R= RLD



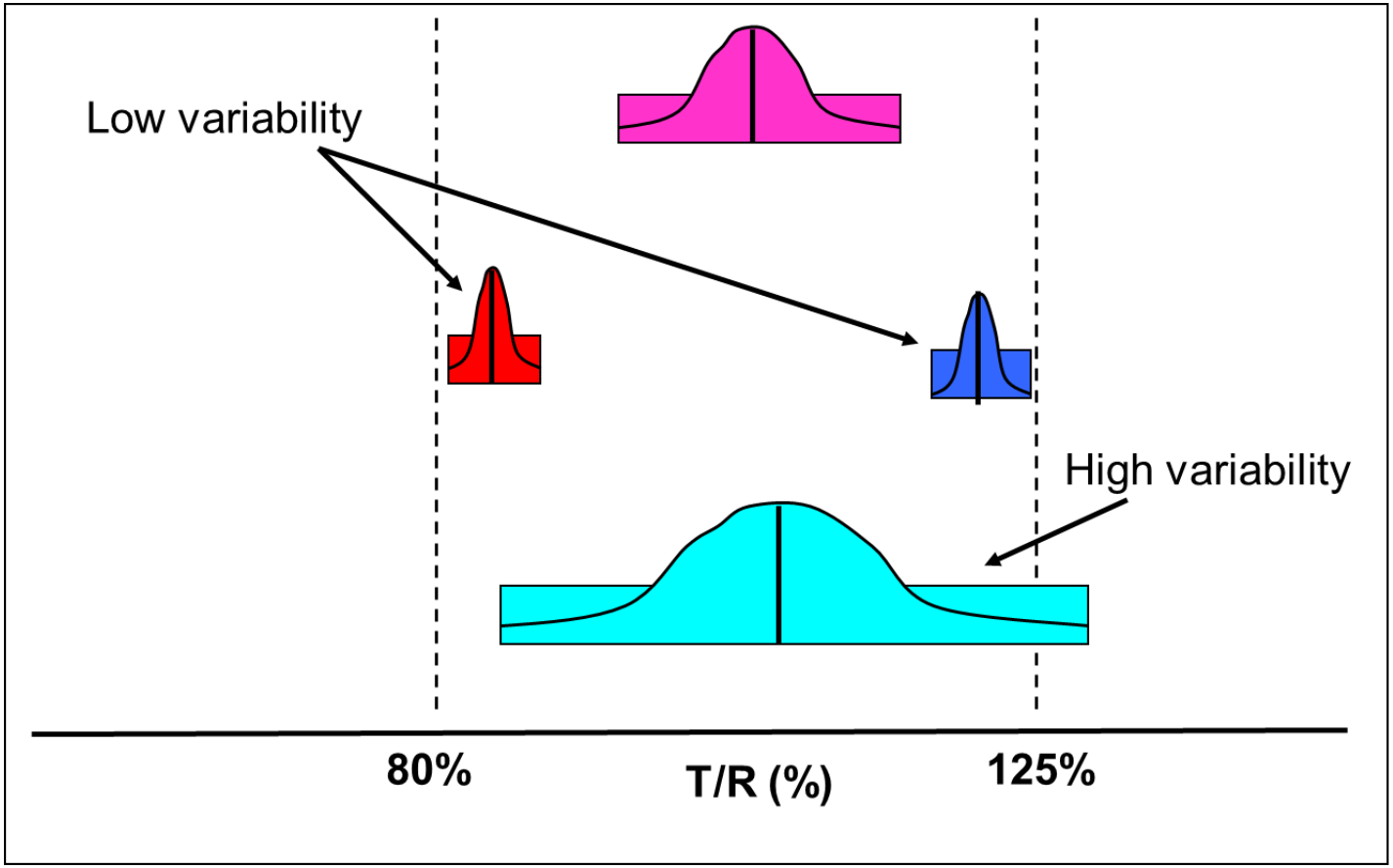
90% confidence interval for the ratio of test/reference within 80.00-125.00%

AUC: Area under the curve

Pharmacokinetic Bioequivalence Standards and Possible Outcomes



One Size Doesn't Fit All



4

Narrow Therapeutic Index (NTI) Drugs

General characteristics

- 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%)

Examples

- Warfarin
- Tacrolimus
- Carbamazepine
- Phenytoin
- Valproic acid

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 2015. 97: 286-291

Bioequivalence Approach for NTI Drugs

Study design: Fully replicated

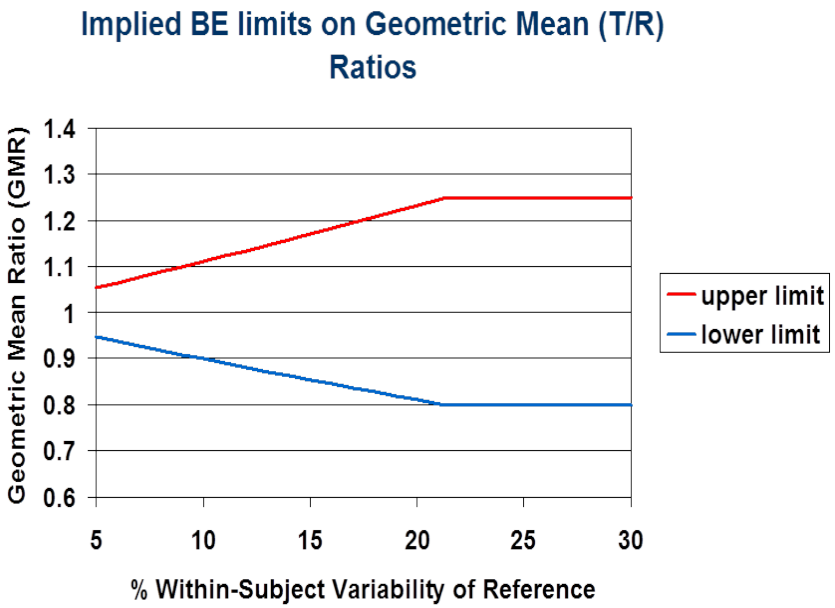
TRTR

RTRT

Acceptance criteria:

- Bioequivalence limits scaled down when the within-subject variability of the reference listed drug (RLD) is less than 0.214
- Variability comparison

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.



S_{WR}	BE limits
0.05	94.87 - 105.41
0.1	90.02 - 111.08
0.15	85.35 - 117.02
0.2	81.17 - 123.20
0.214	80.00 - 125.00

W Jiang. F Makhlouf, DJ Schuirmanm, et al. A bioequivalence approach for generic narrow therapeutic index drugs: evaluation of the reference-scaled approach and variability comparison. The AAPS J. 17:891-901. (2015)

Bioequivalence Approach for Highly Variable Drugs

Highly variable drugs (HVDs)

Within-subject variability (CV_{WR}) in bioequivalence parameters AUC and/or $C_{max} \geq 30\%$

The majority of HVDs are BCS II and IV drugs

Extensive presystemic metabolism, low bioavailability, high acid lability

Highly variable PK do not appear to impact safety and efficacy

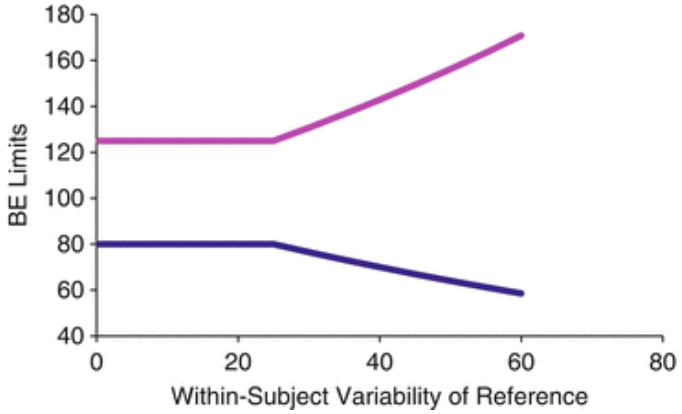
SH Haidar, B Davit, ML Chen, et al. Bioequivalence approaches for highly variable drugs and drug products. Pharm Res. 2008. 25:237-41

Study design:

Fully replicated: TRTR, RTRT

Partially replicated: RRT, TRR, RTR

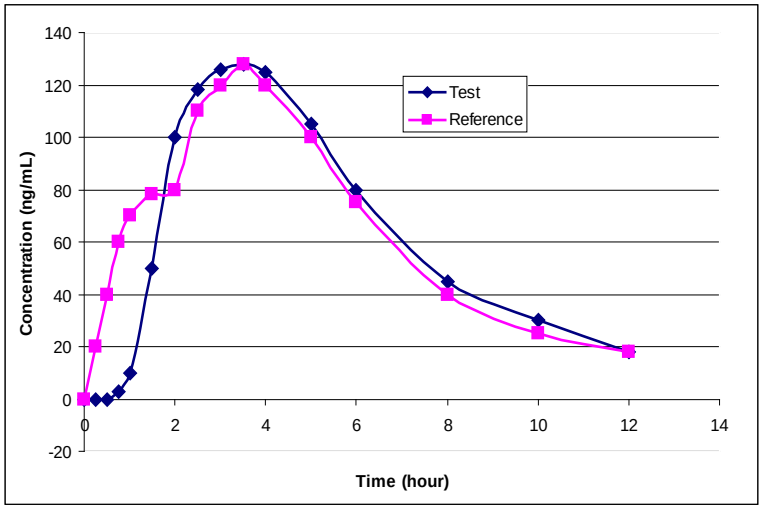
Acceptance criteria:



- Scaling up the BE limits when $S_{WR} \geq 0.294$
- Point estimate constraint of 0.8–1.25 on the GMR

σ_{WR}: population within-subject variability of the reference formulation

Partial AUC (pAUC) for Bioequivalence Demonstration



Pharm Res (2012) 29:1110–1120
DOI 10.1007/s11095-011-0662-8

RESEARCH PAPER

Use of Partial AUC to Demonstrate Bioequivalence of Zolpidem Tartrate Extended Release Formulations

Robert A. Lionberger • Andre S. Raw • Stephanie H. Kim • Xinyuan Zhang • Lawrence X. Yu

Received: 18 October 2011 / Accepted: 19 December 2011 / Published online: 26 January 2012

ABSTRACT

Purpose FDA's bioequivalence recommendation for Zolpidem Tartrate Extended Release Tablets is the first to use partial AUC (pAUC) metrics for determining bioequivalence of modified-release dosage forms. Modeling and simulation studies were performed to aid in understanding the need for pAUC measures and also the proper pAUC truncation times.

Methods Deconvolution techniques, *In Vitro/In Vivo* Correlations,

INTRODUCTION

In August 2009, the FDA published the Draft Guidance on Zolpidem Tartrate Extended Release (ER) Tablets with bioequivalence (BE) recommendations that included partial area-under-the-curve (pAUC) metrics (1). The use of the pAUC as a measure for assessment of early exposure is described in the 2003 General BA/BE guidance (2), but is

C_{max} and AUC may be insufficient for assessing relative bioavailability (BA) or bioequivalence (BE) among two products in cases where rapid onset of action or controlled duration of effect is needed to ensure similar drug efficacy

Partial AUC is defined as the area under the plasma concentration (Ct) versus time profile over two specified time points (t_0 and t_p)

L Fang, R Uppoor, M Xu, et al. Use of partial area under the curve (pAUC) in bioavailability or bioequivalence assessments: a regulatory perspective. Clinical Pharmacology & Therapeutics 2021 https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.2174 epub

Complex Products

According to the **GDUFA II commitment letter**, complex products generally include products with:

1) complex active pharmaceutical ingredients (APIs);
2) complex formulations;
3) complex routes of delivery;
4) complex dosage forms;
5) complex drug-device combination;
6) other products where there is complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

GDUFA: Generic Drug User Fee Amendments

Available at:
https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf

Bioequivalence Approaches for Topical Drug Products

Multiple dosage forms

Creams, emulsions, foams, gels, lotions, ointments, aerosols….

Bioequivalence challenges

Locally acting on skins and their skin site action may not correlate well with systemic drug concentration

Bioequivalence approaches

- bioequivalence study with comparative clinical endpoint
- bioequivalence study with pharmacodynamics endpoint
- *in vivo* dermatopharmacokinetic study
- bioequivalence study with *in vitro* endpoint
- waiver from bioequivalence study

Bioequivalence Approaches for Orally Inhaled and Nasal Drug Products (OINDP)

Nasal Spray

Metered Dose Inhaler (MDI)

Bioequivalence challenges

Locally acting on lungs and their lung site action may not correlate well with systemic drug concentration

Bioequivalence approaches

- bioequivalence study with in vitro characterization, pharmacokinetics, and comparative clinical endpoint study
- bioequivalence study with in vitro characterization
- waiver from bioequivalence study

Product-Specific Guidances (PSGs) for Generic Drug Development

Disclaimer: Due to April 2019 systemwide upgrades to www.fda.gov, the filenames for product-specific guidances on this web page may not match the corresponding guidance titles. In such cases, the name on the document correctly identifies the title of the guidance. These discrepancies will be corrected as soon as possible.

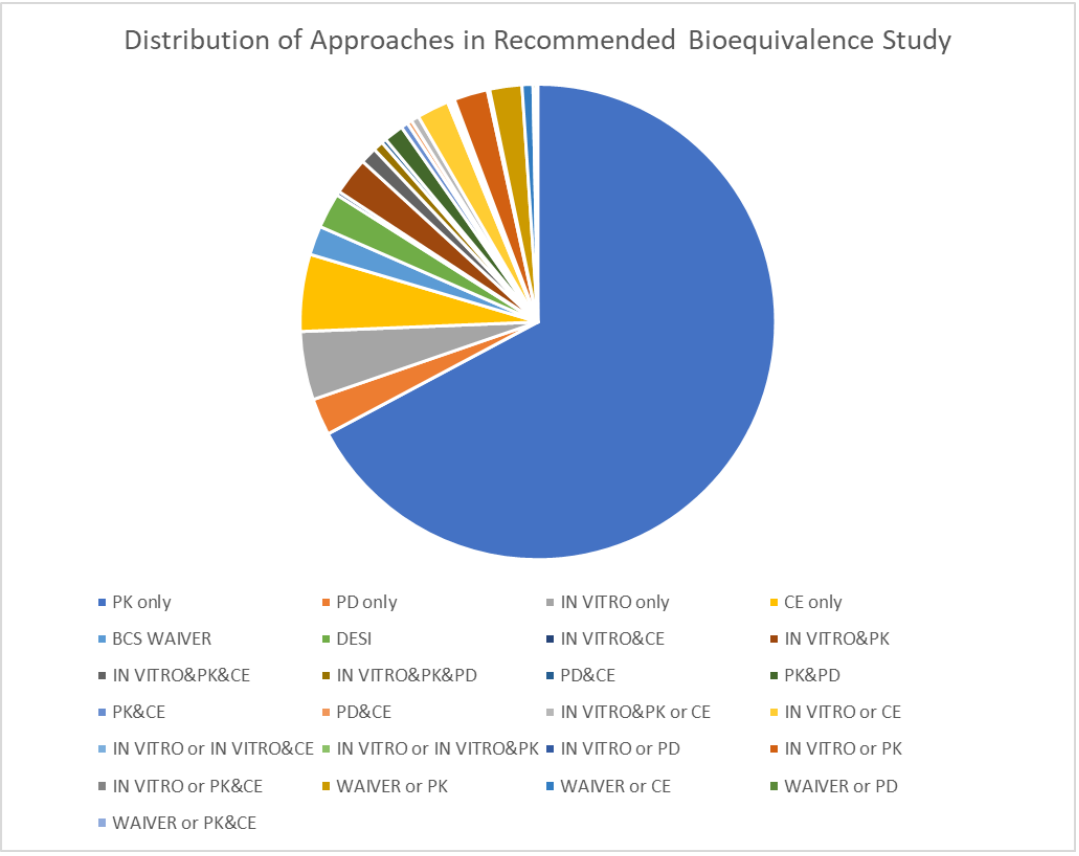
To successfully develop and manufacture a generic drug product, an applicant should consider that their product is expected to be: pharmaceutically equivalent to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use; bioequivalent to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient; and, consequently, therapeutically equivalent, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug.

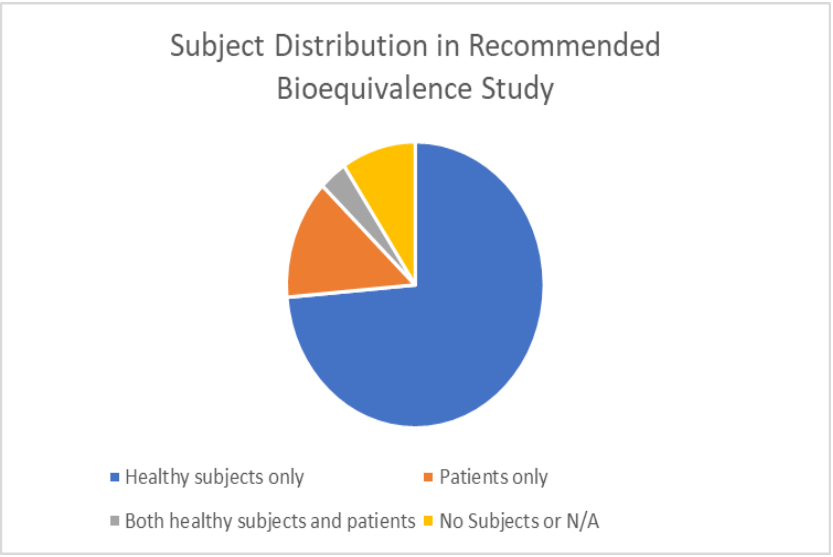
According to 21 CFR 320.24, different types of evidence may be used to establish bioequivalence for pharmaceutically equivalent drug products, including in vivo or in vitro testing, or both. The selection of the method used to demonstrate bioequivalence depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Under this regulation, applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24. As the initial step for selecting methodology for generic drug product development, applicants are referred to the following draft guidance: *Draft Guidance for Industry on Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)* (Dec. 2013).

Total number of currently published PSGs: 1865

Active Ingredient (link to Specific Guidance)	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Bacitracin	Draft	Ophthalmic	Ointment	061212	10/2016
Baclofen	Draft	Oral	Tablet	017851	02/2010
Baclofen	Draft	Oral	Tablet, Orally Disintegrating	021589	11/2019
Baloxavir Marboxil	Draft	Oral	Tablet	210854	09/2019
Balsalazide Disodium	Draft	Oral	Tablet	022205	06/2013
Balsalazide Disodium	Draft	Oral	Capsule	020610	01/2008
Baricitinib	Draft	Oral	Tablets	207924	09/2019
Barium Sulfate	Draft	Oral	Paste	208844	10/2017
Barium Sulfate	Draft	Oral	Suspension	208036	02/2018
Barium Sulfate	Draft	Oral	Suspension	208143	02/2018

Bioequivalence Study Recommendations in PSGs



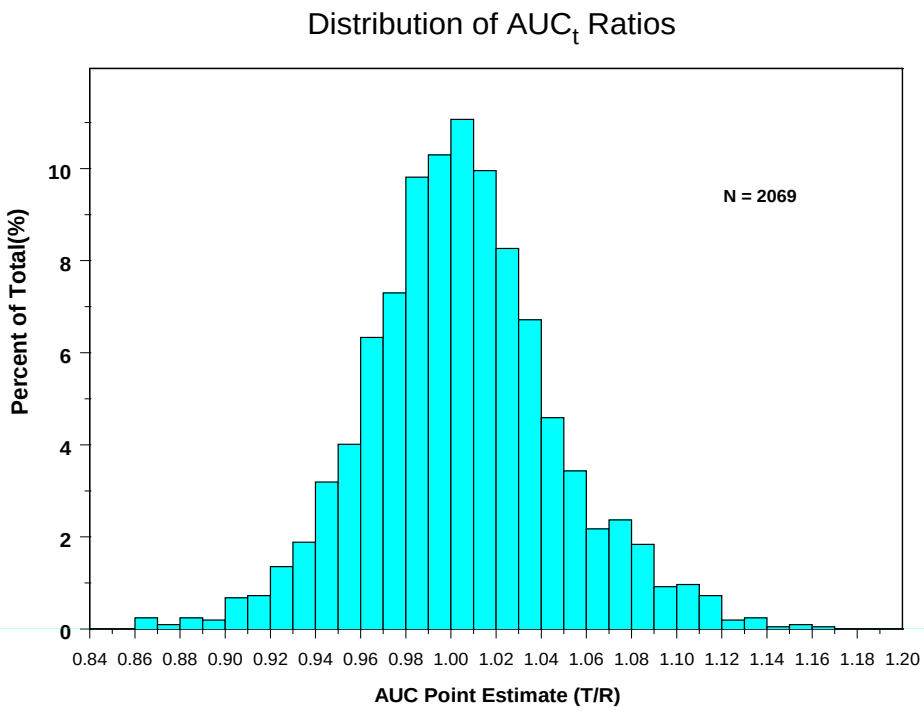


Bioequivalence Misconception vs FDA Bioequivalence Data

Misconceptions about Bioequivalence

- Average values between the reference and test product can vary by –20 to +25% which could lead to large differences up to 45% among generic products. (CSA Rep. X-A-02. Report of the Council on Scientific Affairs)

- Bioequivalence between brand and generic products obtained in healthy subjects may not predict bioequivalence in patients.



BM Davit. Et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. Ann Pharmacother. 43(10):1583-97. 2009

Anecdotes and Controversies about Generic Drugs

"Physician surveys, case reports, and "switchback" rates from large-scale generic conversions imply that all generic formulations may not be equal to the brand drug for all patient groups."

Privitera MD. Generic antiepileptic drugs: current controversies and future directions. *Epilepsy Curr* 2008; 8: 113–17.

"Many physicians and patient groups are insufficiently reassured by current definitions of similarity between generics and innovator brands."

Heaney DC, Sander JW. Antiepileptic drugs: generic versus branded treatments. *Lancet Neurol* 2007; 6: 465–68.

American Academy of Neurology

"The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval"

AMERICAN ACADEMY OF NEUROLOGY

American Academy of Neurology. Position Statement on the Coverage of Anticonvulsant Drugs for the Treatment of Epilepsy. November 2006.

"the society opposes formulation substitution of antiepileptic drugs for the treatment of epilepsy without physician and patient approval"

AMERICAN EPILEPSY SOCIETY

Our Mission: The American Epilepsy Society promotes research and education for professionals dedicated to the prevention, treatment and cure of epilepsy.

American Journal of Transplantation 2011; 11: 1765–1766
Wiley Periodicals Inc.

Editorial

© 2011 The Authors
Journal compilation © 2011 The American Society of Transplantation and the American Society of Transplant Surgeons

doi: 10.1111/j.1600-6143.2011.03616.x

Immunosuppression, Generic Drugs and the FDA

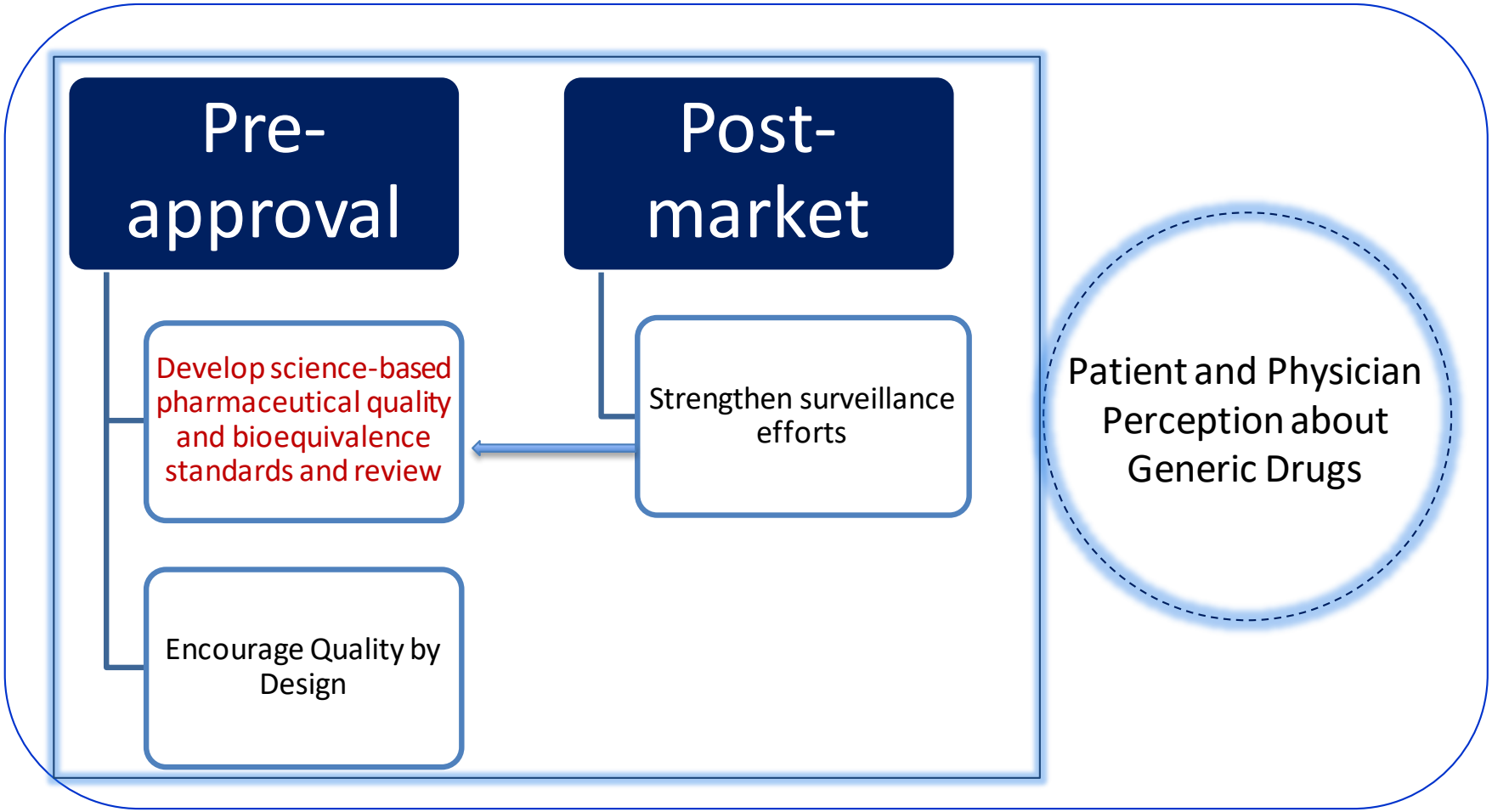
G. B. Klintmalm*

even more concerning. In this study, the follow-up period

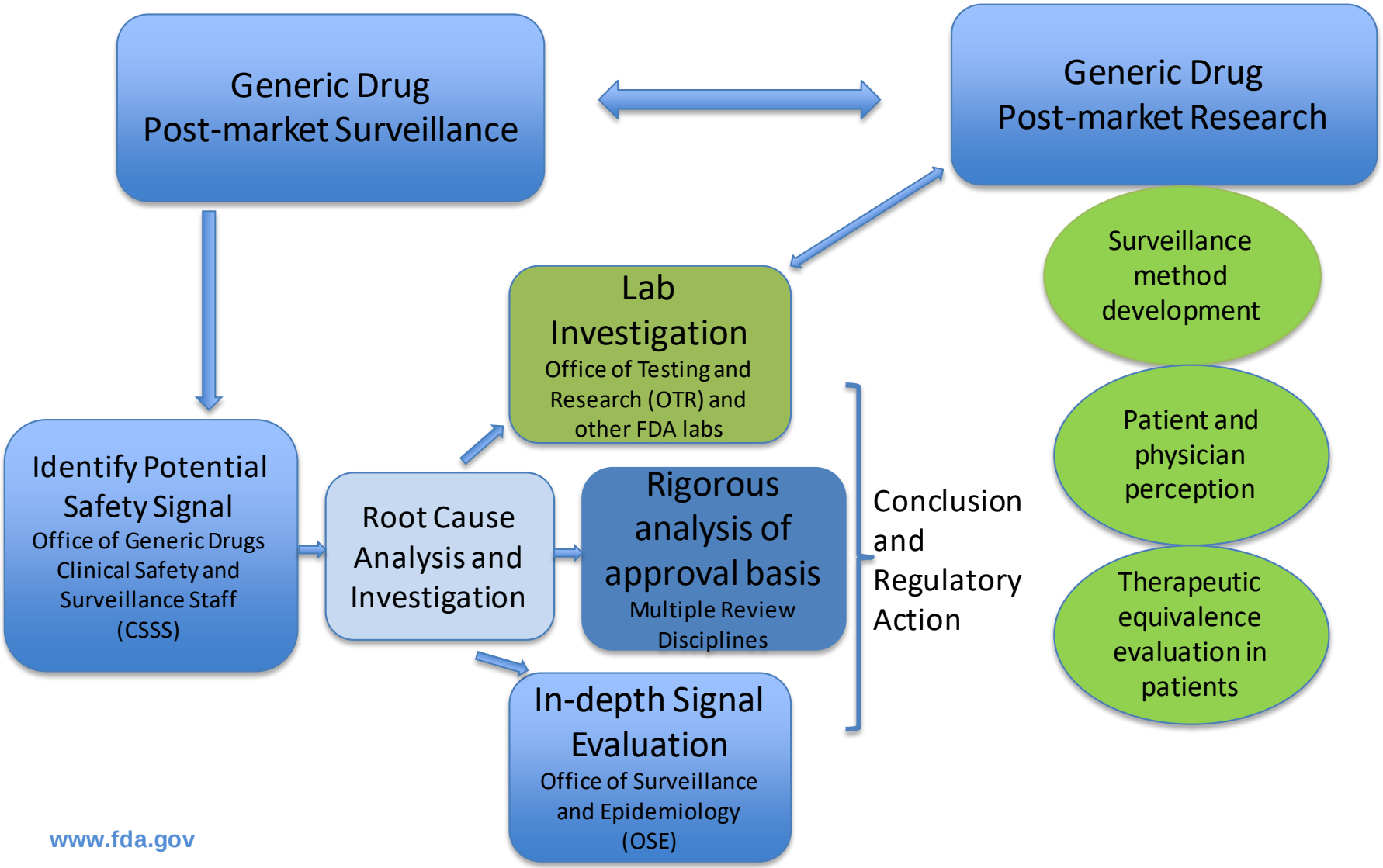
Where are the savings?

Reduced drug cost but Increased monitoring cost

FDA Efforts to Ensure Therapeutic Equivalence of Generic Drugs



Post-market Surveillance and Post-market Research of Generic Drugs



FDA U.S. FOOD & DRUG ADMINISTRATION

Therapeutic Equivalence Evaluation in Patients

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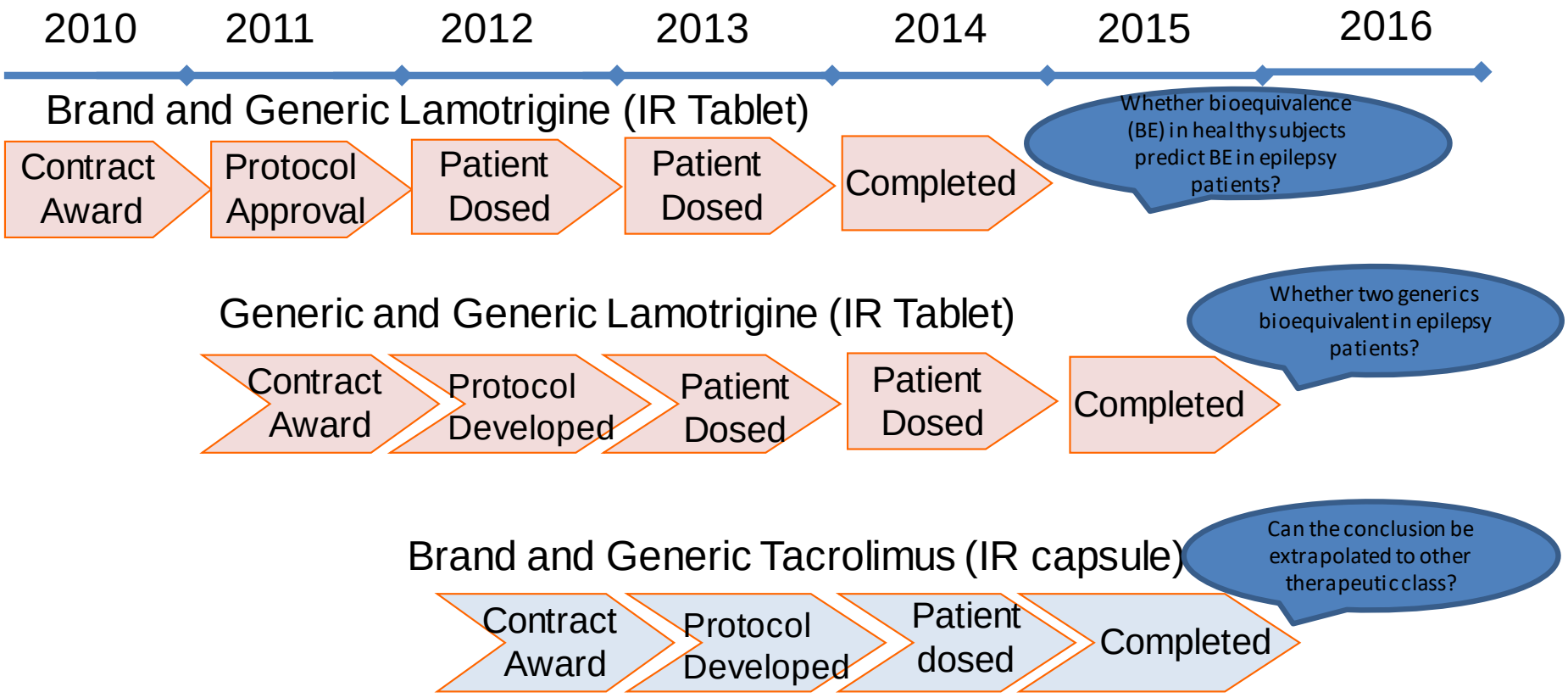
Online Graduate Program
onlinepop.pharmacy.ufl.edu

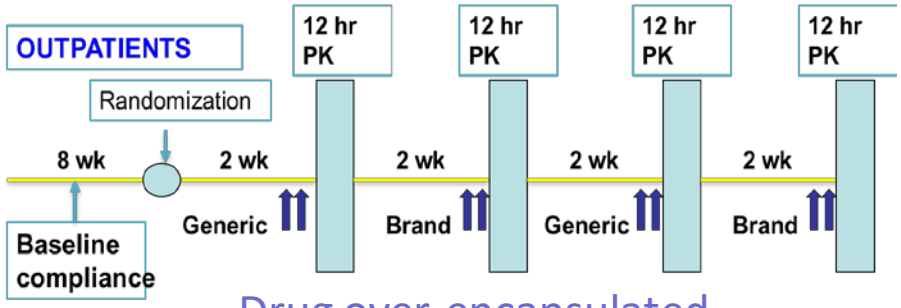
Brand to Generic and Generic to Generic Switching Studies in Patients



Brand vs Generic Lamotrigine Bioequivalence in Epilepsy Patients (BEEP Study)

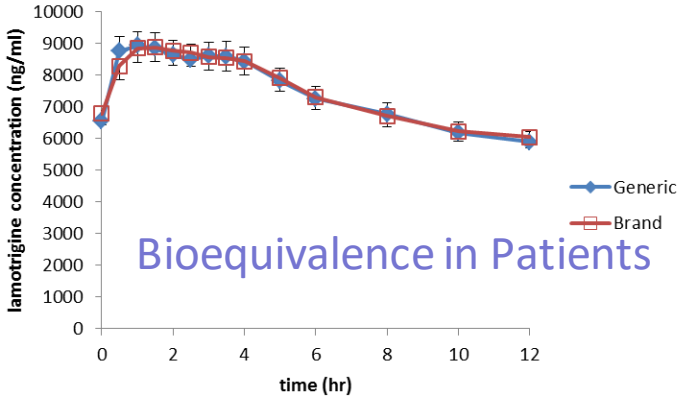
TY Ting, W Jiang, R Lionberger et al. Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: A field test of the FDA bioequivalence standard. Epilepsia. 56:1415-1424. 2015

Study Design



Drug over-encapsulated

Primary Outcome



Bioequivalence in Patients

	Generic to Brand GMR(CI)
AUC	99.4% (97.23-101.61%)
Cmax	101.6% (98.79-104.51%)

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

Generic Brittle Patients

Secondary Outcome

Secondary analysis of seizure control and dose-related adverse events support BE

Epilepsia
Official Journal of the International League Against Epilepsy

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

Dr. Tricia Y. Ting is an epileptologist and associate professor of neurology at University of Maryland.

SUMMARY

Objective: To test the current U.S. Food and Drug Administration (FDA) bioequivalence standard in a comparison of generic and brand-name drug pharmacokinetic (PK) performance in "generic-brittle" patients with epilepsy under clinical use conditions.

Methods: This randomized, double-blind, multiple-dose, steady-state, fully replicated bioequivalence study compared generic lamotrigine to brand-name Lamictal in "generic-brittle" patients with epilepsy (n = 34) who were already taking lamotrigine. Patients were repeatedly switched between masked Lamictal and generic lamotrigine. Intensive PK blood sampling at the end of each 2-week treatment period yielded two 12-h PK profiles for brand-name and generic forms for each patient. Steady-state area under the curve (AUC), peak plasma concentration (C_{max}), and minimum plasma concentration (C_{min}) data were subjected to conventional average bioequivalence (ABE) analysis, reference-scaled ABE analysis, and within-subject variability (WSV) comparisons. In addition, generic-versus-brand comparisons in individual patients were performed. Secondary clinical outcomes included seizure frequency and adverse events.

Results: Generic demonstrated bioequivalence to brand. The 90% confidence intervals of the mean for steady-state AUC, C_{max}, and C_{min} for generic-versus-brand were 97.2–101.6%, 98.8–104.5%, and 93.4–101.0%, respectively. The WSV of generic and brand were also similar. Individual patient PK ratios for generic-versus-brand were similar but not identical, in part because brand-versus-brand profiles were not identical, even though subjects were rechallenged with the same product. Few subjects had seizure exacerbations or tolerability issues with product switching. One subject, however, reported 267 focal motor seizures, primarily on generic, although his brand and generic PK profiles were practically identical.

Significance: Some neurologists question whether bioequivalence in healthy volunteers ensures therapeutic equivalence of brand and generic antiepileptic drugs in patients with epilepsy, who may be at increased risk for problems with brand-to-generic switching. Bioequivalence results in "generic-brittle" patients with epilepsy under clinical conditions support the soundness of the FDA bioequivalence standards. Adverse events on generic were not related to the small, allowable PK differences between generic and brand.

KEY WORDS: Bioequivalence, Switchability, Lamotrigine, Generic-brittle, Narrow therapeutic index.

Accepted June 29, 2015; Early View publication July 23, 2015.
*Department of Neurology, University of Maryland, Baltimore, Maryland, U.S.A.; †Food and Drug Administration, White Oak, Maryland, U.S.A.; and ‡Department of Pharmaceutical Sciences, University of Maryland, Baltimore, Maryland, U.S.A.
Address correspondence to James E. Polli, Department of Pharmaceutical Sciences, University of Maryland, 20 Penn Street, Baltimore, MD 21201, U.S.A. E-mail: jpolli@rx.umaryland.edu

EPILEPSY CURRENTS

Current Literature
In Clinical Science

Generic Substitution of AEDs: Is it Time to Put This Issue to Rest?

by Barry E. Gidal, PharmD

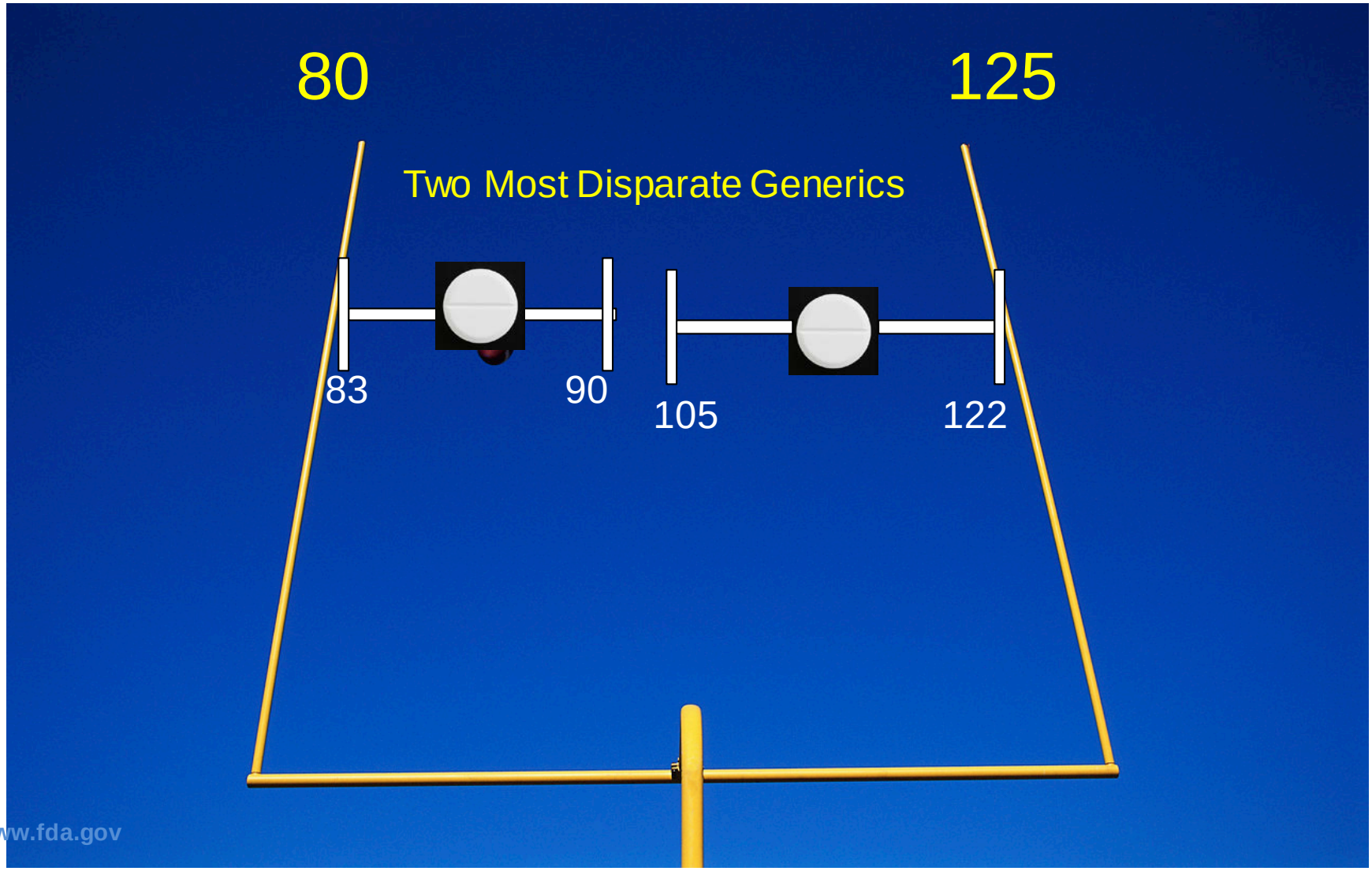
Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 18–20

"Clearly, this well designed study represents a major step forward in addressing the epilepsy community's concerns and provides valuable insight regarding AED PK variability."

"While encouraging, these observations do require confirmation in other patient populations. This issue of individual outliers certainly merits further study."

"Final data analysis from the EQUIGEN study group (EQUIvalence among GENeric AEDs) is near completion and should help further clarify this issue."

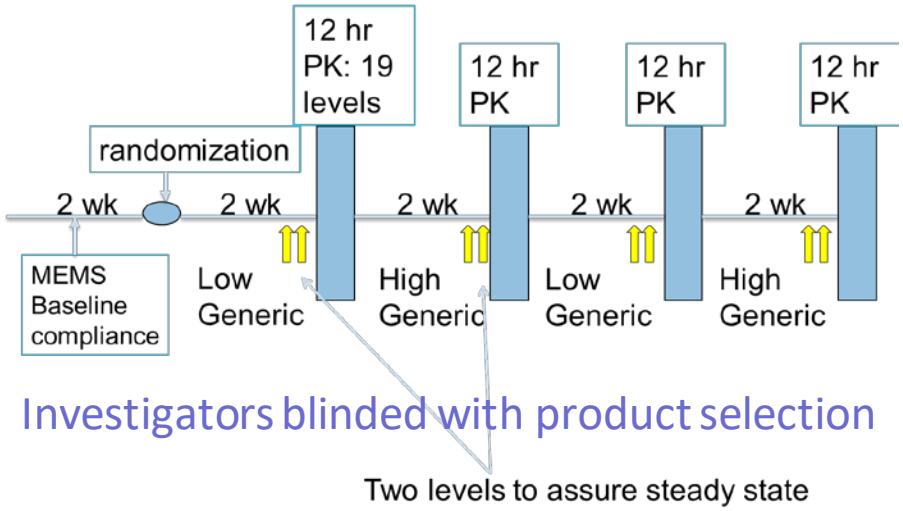
Generic vs Generic Lamotrigine Bioequivalence in Epilepsy Patients (EQUIGEN Study)



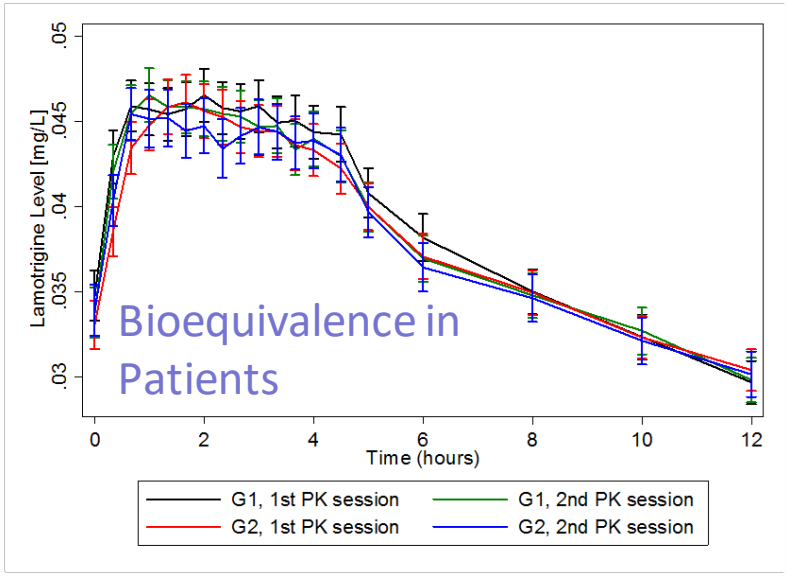
Generic vs Generic: Multiple Dose Study Design

MD Privitera, TE Welty, BE Gidal. et al. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. Lancet Neurol. 15: 365-72. 2016

Study Design



Primary Outcome



Patient Demographics

	Sequence 1 (n=14)	Sequence 2 (n=19)
Age, years	42·7 (31·2–55·9)	49·4 (32·6–52·6)
Previous history of sensitivity to drug product switches	1 (7%)	3 (16%)
Seizure exacerbations	1 (7%)	2 (11%)
Increased adverse events	0	1 (5%)

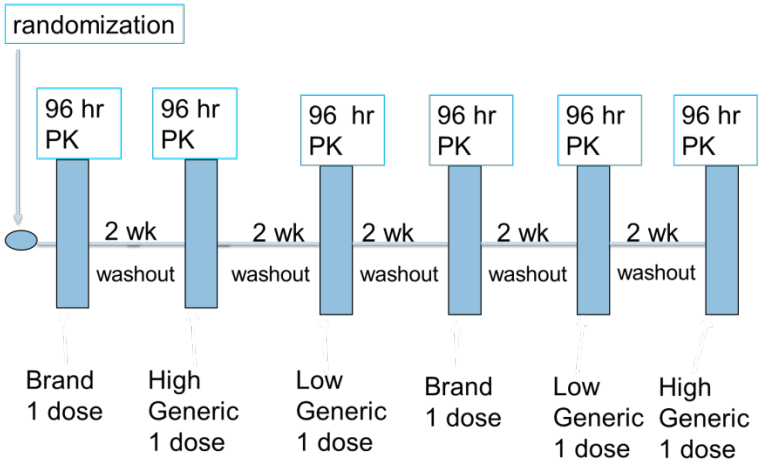
Secondary Outcome

- No loss of seizure control

- No unexpected adverse effects and standardized side effect measure scores were not different between generics

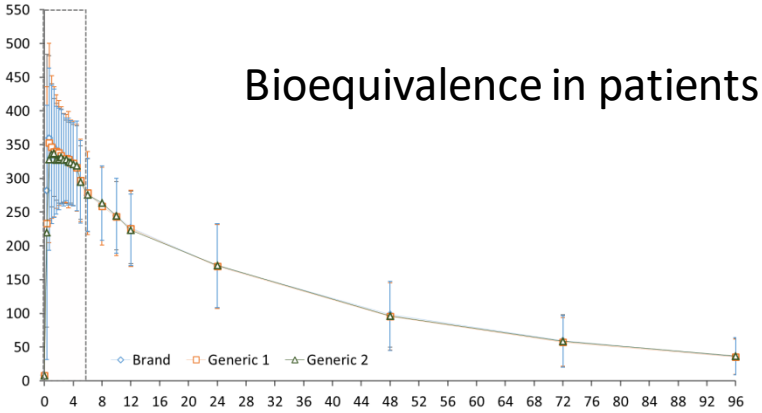
Brand vs Generic vs Generic: Single Dose Study Design

Study Design



Investigators blinded with product selection

Primary Outcome



Bioequivalence in patients

Patient Demographics

Subjects had epilepsy, on at least 1 AED (but not taking lamotrigine)
Other drugs excluded: valproate, estrogens, sertraline

Secondary Outcome

No difference.

3 Serious Adverse Events, judged unrelated to study

M Berg, TE Welty et al. Bioequivalence between generic and branded lamotrigine in people with epilepsy. JAMA Neurol. 2017. 74:919-928

THE LANCET Neurology

Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial

Michael D Privitera, Timothy E Welty, Barry E Gidal, Francisco J Diaz, Ron Krebill, Jerzy P Szaflarski, Barbara A Dworetzky, John R Pollard, Edmund J Elder Jr, Wenlei Jiang, Xiaohui Jiang, Michel Berg

Summary

Background Patients and clinicians share concerns that generic drug substitution might lead to loss of efficacy or emergence of adverse events. In this trial, we assessed US Food and Drug Administration (FDA) bioequivalence standards by studying the effects of switching between two disparate generic immediate-release lamotrigine products in patients with epilepsy.

Lancet Neurol 2016; 15: 365–72
Published Online
February 11, 2016
http://dx.doi.org/10.1016/S1474-4422(16)00014-4

The safety of generic substitution in epilepsy

Emilio Perucca

Lancet Neurology, Feb 2016

"The EQUIGEN trial by Michael Privitera and colleagues published in *The Lancet Neurology* provides strong evidence that, at least for lamotrigine, concerns about generic substitution are largely misplaced."

"Overall, Privitera and colleagues' findings are quite reassuring, and organisations with a negative attitude to generic antiepileptic drug substitution should consider reviewing their position."

AMERICAN EPILEPSY SOCIETY

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

There is equipoise about the therapeutic equivalence of the various formulations of Antiepileptic Drugs (AEDs) when used to treat people with epilepsy. The U.S. Food and Drug Administration (U.S. FDA) states that the current regulations guarantee that the approved AED formulations of each specific AED can be used interchangeably without concern for safety or efficacy and that no additional testing is needed when formulations of the same AED are interchanged. However, physicians and patients, in several surveys including one performed of AES members in 2007, express a majority opinion that the various formulations of the same AED are not always therapeutically equivalent in every patient. Positions taken by several organizations including the American Academy of Neurology, the Epilepsy Foundation and the International League Against Epilepsy (French Chapter) reflect this equipoise and advocate for physician and patient consent prior to switching formulations. The AES recognizes that controlled, prospective data on therapeutic equivalence of different AED formulations in people with epilepsy is not available because appropriate studies have not been conducted.

The American Epilepsy Society offers its support of the following principles concerning the continuity of Antiepileptic Drugs for adults and children with epilepsy:

- The American Epilepsy Society supports the development and completion of a valid controlled, prospective clinical trial, with protocol approval by the U.S. FDA, studying the impact of differences between the same AED formulations of different manufacturers. Until such data becomes available, the following positions are adopted:
- Physicians who treat people with epilepsy are skilled in choosing appropriate AEDs at appropriate dosages to reduce or eliminate seizures and avoid adverse effects. Physicians are trained to do this by using the best available scientific evidence in combination with clinical expertise. As such, the Society opposes formulation substitution of antiepileptic drugs for the treatment of epilepsy without physician and patient approval.

2007

EPILEPSY CURRENTS

It's Current

Epilepsy Resources and Updates

AES Position Statement on Generic Substitution of Antiepileptic Drugs

David G. Vossler, MD, FAAN,[1*] Gail D. Anderson, PhD,[2] and Jacquelyn Bainbridge, PharmD[3]
[1]Department of Neurology, University of Washington, Seattle, and UW Medicine, Valley Medical Center, Renton, WA
[2]Department of Pharmacy, University of Washington, Seattle
[3]Skaggs School of Pharmacy and Pharmaceutical Sciences and Department of Neurology, University of Colorado Anschutz Medical Campus, Denver
*Address correspondence to David G. Vossler, MD, Neuroscience Institute, UW Medicine | Valley Medical Center, 400 S. 43rd St., Renton, WA 98055. E-mail: david_vossler@valleymed.org

- The AES acknowledges that drug formulation substitution with FDA-approved generic products usually reduces cost, and does not compromise efficacy.
- The AES supports ongoing research by the FDA to study factors (e.g., extended-release products, tablet or capsule color and shape, nocebo effect) related to the generic substitution of AEDs in adults and children.
- When dispensing medications to patients, healthcare professionals should ensure that a bioequivalent FDA-approved generic product is substituted for the brand or another generic AED. For example, an immediate-release generic product should not be dispensed as a substitute for a delayed-release or an extended-release product.

……

2016

U.S. FOOD & DRUG ADMINISTRATION

FDA Lab Investigation

UF College of Pharmacy
Department of Pharmaceutical Outcomes and Policy
UNIVERSITY of FLORIDA

Online Graduate Program
onlinepop.pharmacy.ufl.edu

www.fda.gov

Lansoprazole Delayed-release (DR) Orally Disintegrating Tablet (ODT)

Indication

- Duodenal ulcer, gastric ulcer

Administration option

- Oral, with or without water
- Oral syringe
- Nasogastric tube administration (>= 8 French)

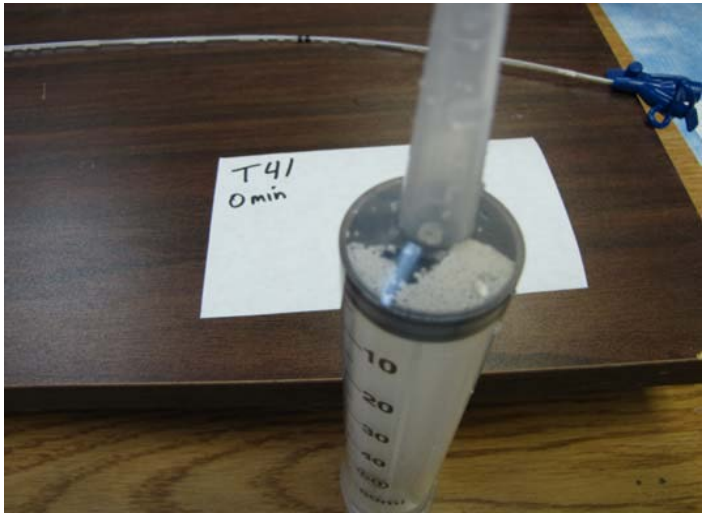
Issue

- A generic lansoprazole DR ODT has clogged and blocked oral syringes and feeding tubes
- In some cases, patients have had to seek emergency medical assistance and their feeding tubes have had to be unclogged or removed and replaced.

Brand and Generic Product Analysis

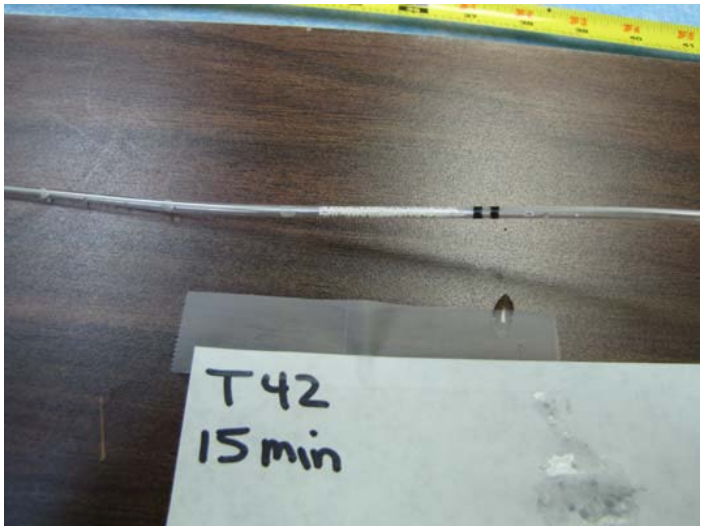
Formulation analysis

- Generic contains 30% more excipients than the RLD, including the insoluble excipients
- RLD and generic have different outermost coating which may affect its interaction with the tubing



Lab investigation

- RLD disintegrates faster than the generic
- RLD microgranule size smaller than that of generic
- Generic beads stick to the inner wall of tubes more



Regulatory Action and Communication

- The generic firm voluntarily withdrew the product from distribution.

- The FDA recommends not dispense or administer the product to patients who take the drug through an oral syringe or feeding tube.

- FDA updated guidances for products with feeding tube administration.

  Lansoprazole, Esomeprazole Magnesium, Rivaroxaban, and others

Levetiracetam Extended-Release (ER) Tablet

Indication

- Treating partial-onset, myoclonic, or generalized tonic-clonic seizures in patients with epilepsy

Drug property

- Highly permeable and highly soluble, BCS class I drug

Issue

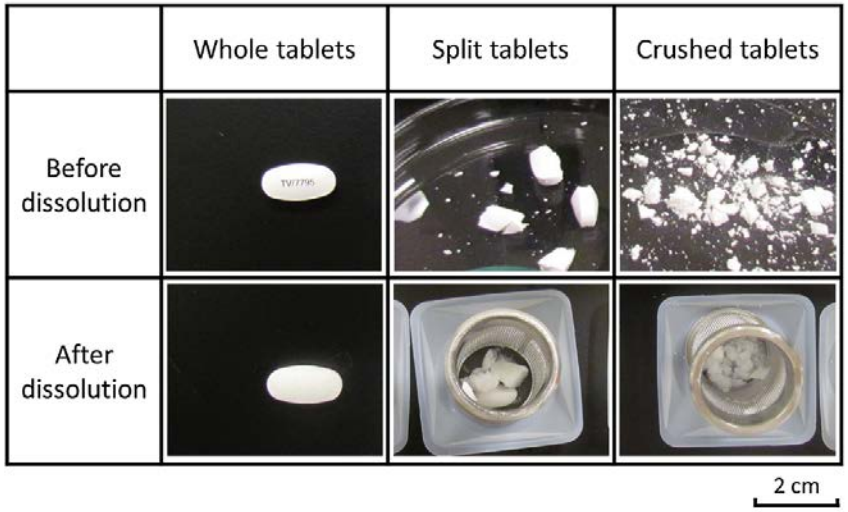
- Patients noticed intact generic levetiracetam ER tablets in the stool
- Patients did not experience any GI disorders that might have accidentally accelerated the gastric emptying rate
- Anxiety has ensued among patients and clinicians

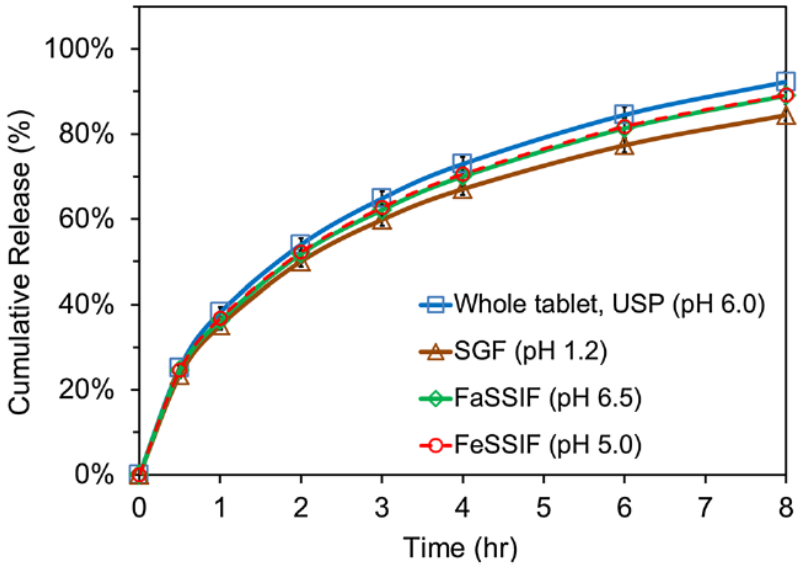
Brand and Generic Product Analysis

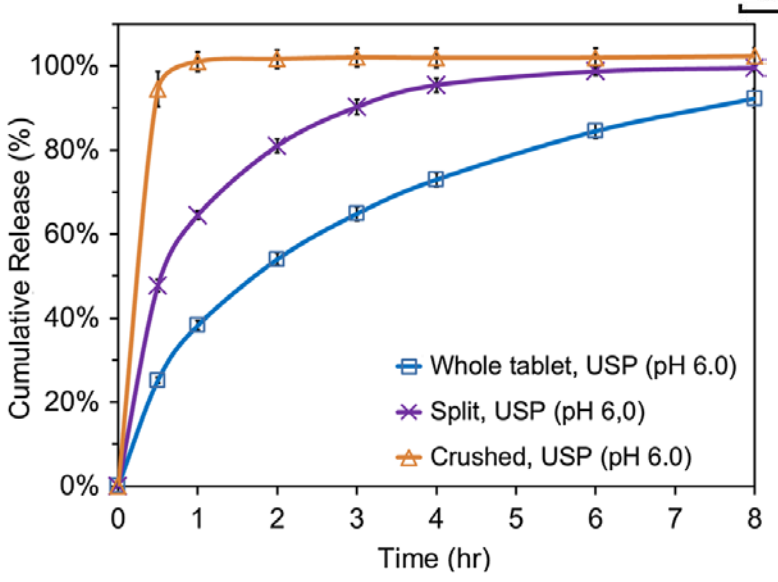
Formulation analysis:

- RLD monolithic tablet based on slowly dissolving hypromellose
- Generic beads coated by ethylcellulose

Lab investigation:







Regulatory Action and Communication

- **Generic product labeling updated**

"Patients receiving levetiracetam extended-release tablets may notice an inert matrix tablet passing in the stool. Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert matrix tablet"

- **Scientific publication in medical journal**

CNS Drugs
DOI 10.1007/s40263-016-0332-9

ORIGINAL RESEARCH ARTICLE

Ghost-Pill-Buster: A Case Study of Intact Levetiracetam Extended-Release Tablets after Dissolution Testing

Dajun Sun[1] · Hong Wen[1] · Anna Externbrink[2] · Zongming Gao[2] · David Keire[2] · Gregory Krauss[3] · Wenlei Jiang[1]

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Surveillance Method Development

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Utilization and Switchback Analysis

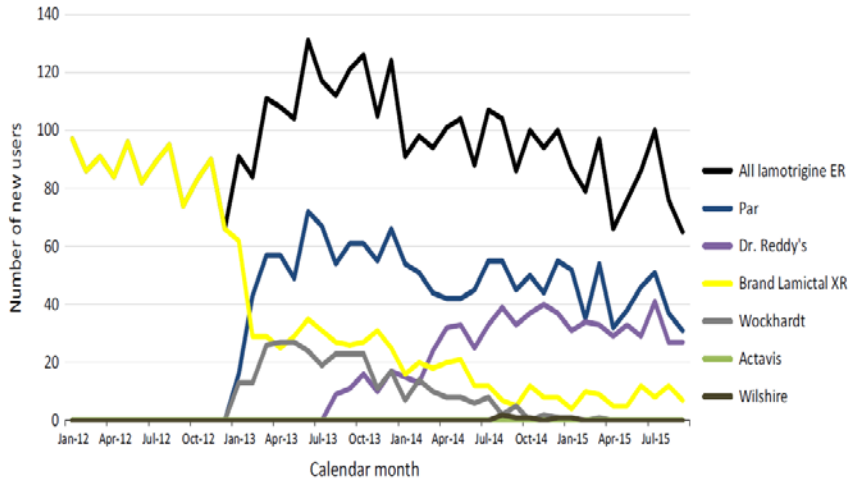

Fig. 5 Monthly number of new users of lamotrigine extended release (ER) by manufacturer across four Sentinel data partners, January 2012 to September 2015

Switchback

- Brand to Generic to Generic
- Generic to Brand

Switchback reflect choices made by patients and/or physicians than the initial brand to generic switch.

Utilization analyses

Sentinel - FDA's national medical product safety monitoring system containing administrative claims and clinical information

Gagne JJ et al. Evaluation of Switching Patterns in FDA's Sentinel System: A New Tool to Assess Generic Drugs. Drug Saf. 41: 1313-1323. 2018

Switchback analyses

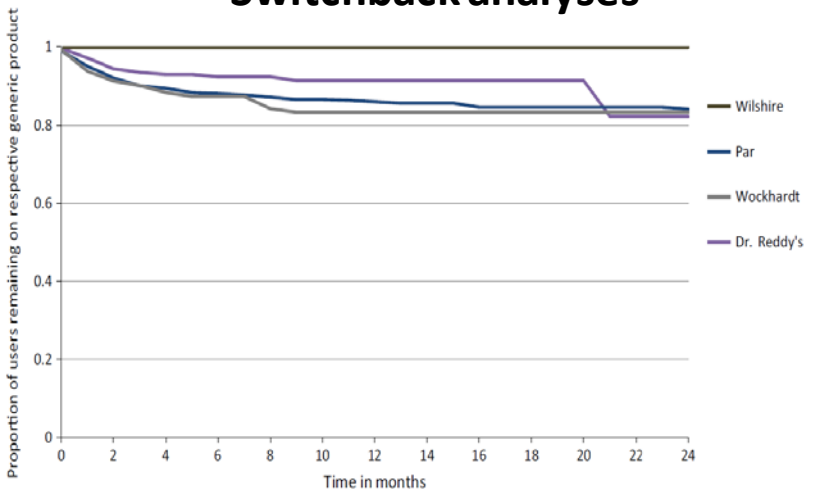

Fig. 6 Time to switchback to brand lamotrigine extended release (ER) following switch from brand to generic

Linking Claims Database and Laboratory Results

JAMA Network Open

Original Investigation | Diabetes and Endocrinology

Comparative Effectiveness of Generic vs Brand-Name Levothyroxine in Achieving Normal Thyrotropin Levels

Juan P. Brito, MD, MSc; Joseph S. Ross, MD, MHS; Lindsey Sangaralingham, MPH; Sarah K. Dutcher, PhD; David J. Graham, MD, MPH; Zhong Wang, PhD; Yute Wu, PhD; Xiaoxi Yao, PhD; Robert C. Smallridge, MD; Victor Bernet, MD; Nilay D. Shah, PhD; Kasia J. Lipska, MD, MHS

Study design: A retrospective, 1:1 propensity score–matched longitudinal cohort study used the OptumLabs Data Warehouse administrative claims database linked to laboratory results from commercially insured and Medicare Advantage enrollees throughout the United States.

Results: Initiation of generic vs brand-name levothyroxine formulations was associated with similar rates of normal and stable thyrotropin levels.

Relevance: These results suggest that generic levothyroxine as initial therapy for mild thyroid dysfunction is as effective as brand-name levothyroxine.

JAMA Network Open. 2020;3(9):e2017645. doi:10.1001/jamanetworkopen.2020.17645

FDA U.S. FOOD & DRUG ADMINISTRATION

Understand Patient, Physician, and Pharmacist's Perception

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UNIVERSITY of FLORIDA

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Substantial Increase about Patient Preference about Generic Drugs

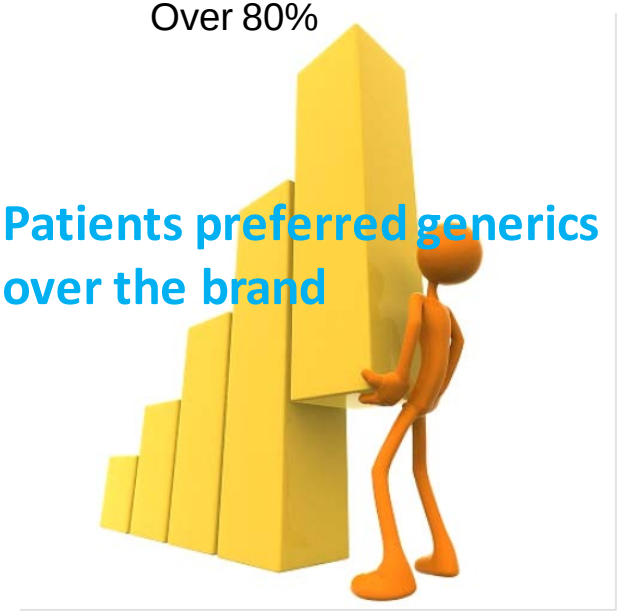
Variations in Patients' Perceptions and Use of Generic Drugs: Results of a National Survey

Aaron S. Kesselheim, M.D., J.D., M.P.H.[1,3], Joshua J. Gagne, Pharm.D., Sc.D.[1,3], Jessica M. Franklin, Ph.D.[1,3], Wesley Eddings, Ph.D.[1,3], Lisa A. Fulchino, B.A.[1,3], Jerry Avorn, M.D.[1,3], and Eric G. Campbell, Ph.D.[2,3]

J Gen Intern Med
DOI: 10.1007/s11606-016-3612-7

Do you think generic drugs	% (95 % Confidence Interval) respondents answering definitely/ probably yes
Are as effective as their brand-name versions	87 (85, 90)
Are as safe as their brand-name versions	88 (86, 91)
Have the same side effects as their brand-name versions	80 (77, 83)
Are made of the same active ingredients as their brand-name versions	84 (82, 87)
How comfortable do you feel:	% (95 % Confidence Interval) responden answering very/somewhat comfortable
Asking your doctor to write a prescription for a generic drug if one is available	94 (92, 96)
Taking a generic drug that was prescribed for you by your doctor	97 (95, 98)
If your pharmacist filled the prescription with an FDA-approved generic version of that drug when your doctor prescribed a brand-name drug	90 (87, 92)
If your health insurance company required use of an available and FDA-approved generic version of a brand-name drug that your doctor prescribed*	60 (56, 63)

2014 Survey (Kesseheim et al.)
Over 80%



2007 Survey (Shrank et al.)
Less than 40%

Non-Caucasians
- prefer brand over generic
- More skeptical of generic drug clinical equivalence

Greater Physician Confidence about Generic Drug Safety and Efficacy

Prevalence and predictors of generic drug skepticism among physicians: Results of a National Survey

Kesselheim et al.
JAMA Internal Medicine, In press

Perceptions	Respondents who strongly or somewhat agree, proportion (%(95% CI))
Generics are as effective as their corresponding brand-name versions	89 (86-91)
Generics are as safe as their corresponding brand-name versions	91 (89-93)
Do not cause more adverse effects than their corresponding brand-name versions	73 (70-76)

2014 Survey (Kesselheim et al.) 89% believe generic is as effective as the RLD

2009 Survey (Shrank et al.) Over 23% expressed negative perceptions

Further work
- Limiting interactions with pharmaceutical marketing
- Directed educational outreach

Conclusions

- Bioequivalence is essential for generic drug safety and efficacy.
- There are different approaches for bioequivalence demonstration.
- FDA publishes product-specific guidances to guide generic drug development.
- FDA is committed to ensure that the best science is available to evaluate and approve safe, effective, and affordable generic drugs.

Acknowledgements

- Office of Generic Drugs
- Office of Pharmaceutical Quality
- Office of Surveillance and Epidemiology

Generic Drug User Fee Amendment (GDUFA)
Regulatory Science Funding

https://www.fda.gov/drugs/generic-drugs/science-research

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Thank you!

Any Questions?

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