



Ensuring generic drug safety and efficacy via a combined effort of FDA, Academia, and the industry in a data-driven era: part 2



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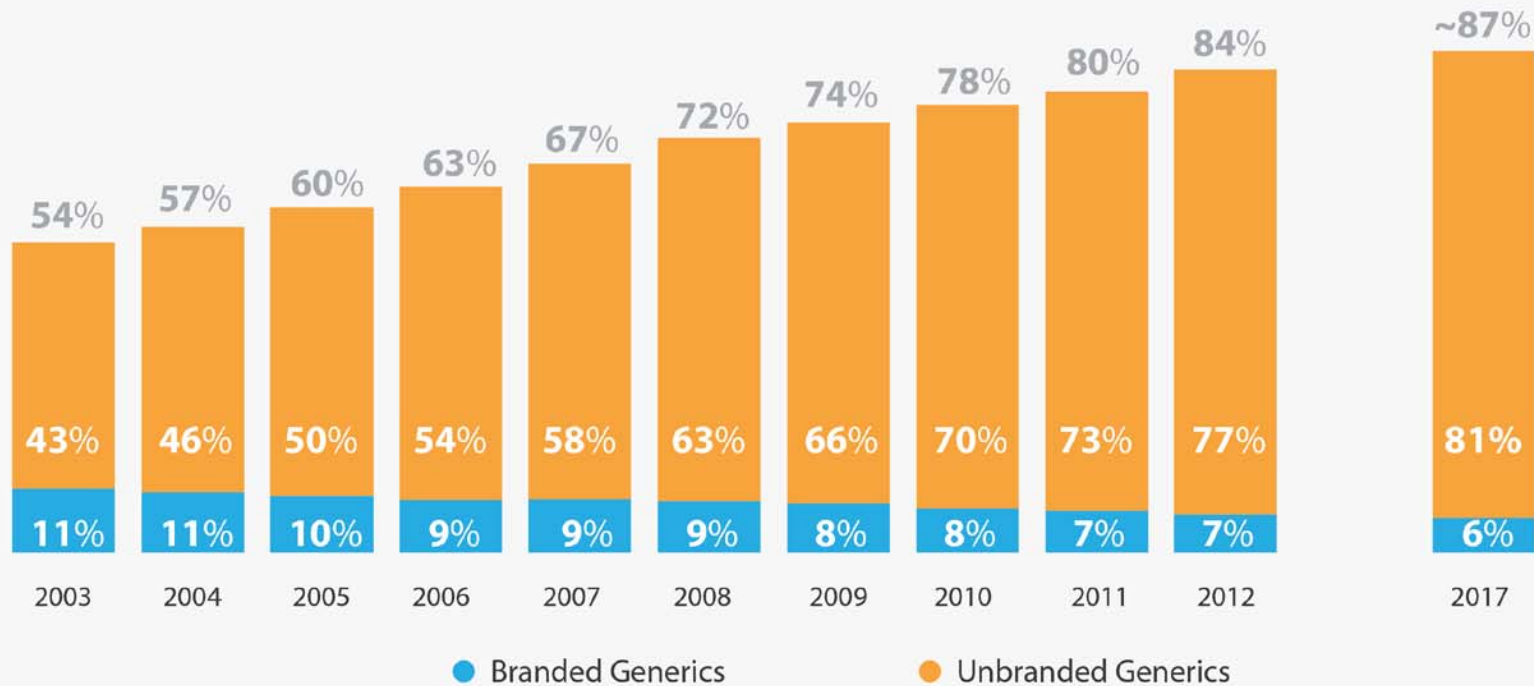
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Market share of generics



- In 2017, 88% of all prescriptions in the US will be for generic drugs
 - 28% of US drug costs

Why the need for post-marketing surveillance of generics?

- Monitor drug use, clinical effectiveness, and safety issues after a drug is marketed in the real-world
- Address negative public perceptions and concerns regarding generics, promote confidence in generic drugs
- Supplement bioequivalence (BE) testing through substitutability studies
- Help to identify any product quality issues that may arise during the manufacturing process
- Identify clinical or regulatory issues that might need to be addressed
- Provide additional evidence for the interchangeability of brand-name and generic drugs

OGD post-marketing research areas

- 1) Public perception and education about generic drugs
- 2) Brand/generic substitution studies
 - In patients
 - In healthy subjects
- 3) Methods development for generic drug surveillance
- 4) *Investigation of in-equivalence issues*
 - *Internal FDA projects*

Perception and education about generic drugs

- How do patients and healthcare providers perceive generic drugs?
 - What is the public's understanding of how generic drugs are approved?
- Funded studies:
 - “Assessing clinical equivalence for generic drugs approved by innovative methods” (U01FD004856)
 - “Postmarketing surveillance of generic drug usage and substitution patterns” (U01FD004855)
 - “Does Variation in the Physical Characteristics of Generic Drugs Affect Patients' Experiences? A Survey of Pharmacists and Patients” (HHSF223201310232C)

Physician perceptions of generic drugs

- A majority of physicians report positive perceptions of generic drugs
 - 70% would rather prescribe generic over brand-name drugs
 - 85% agreed that Americans should use more generic drugs
 - 78% preferred taking generic drugs themselves
 - 79% recommended generic drugs for their family members

In general, do you think generic drugs...

Are as <u>effective</u> as their corresponding brand-name versions	89%
Are as <u>safe</u> as their brand-name versions	91%
Do not cause more <u>side effects</u> than their brand-name versions	73%

32% defined as generic skeptics

Patient perceptions of generic drugs

- Patients report somewhat positive perceptions about generic drugs
 - 97% comfortable taking a generic drug prescribed by physician
 - 37% preferred taking a brand-name drug

Do you think generic drugs...

Are as <u>effective</u> as their brand-name versions?	87%	} 32% defined as generic skeptics
Are as <u>safe</u> as their brand-name versions?	88%	
Have the same <u>side effects</u> than their brand-name versions?	80%	
Are made of the same <u>active ingredients</u> of their brand-name versions?	84%	

Knowledge of FDA approval processes

- Physicians are more familiar with FDA’s brand drug approval process than the generic drug approval process

	Brand-name drug approval process	Generic drug approval process
Very Familiar	9%	3%
Familiar	40%	24%
A little familiar	39%	46%
Not familiar at all	12%	26%

- Patients have minimal familiarity with FDA’s drug approval processes
 - Brand-name drugs (no/little familiarity): 69%
 - Generic drugs (no/little familiarity): 74%

Perception and education about generic drugs

- How can we educate patients and healthcare providers about generic drugs?
 - What information do we need to disseminate?
 - How should we communicate this information?
- Ongoing studies:
 - “Identifying Messages to PROmote Value and Education (IMPROVE) of generic prescribing” (U01FD005485)
 - “Educating groups influencing generic drug use” (U01FD005486)

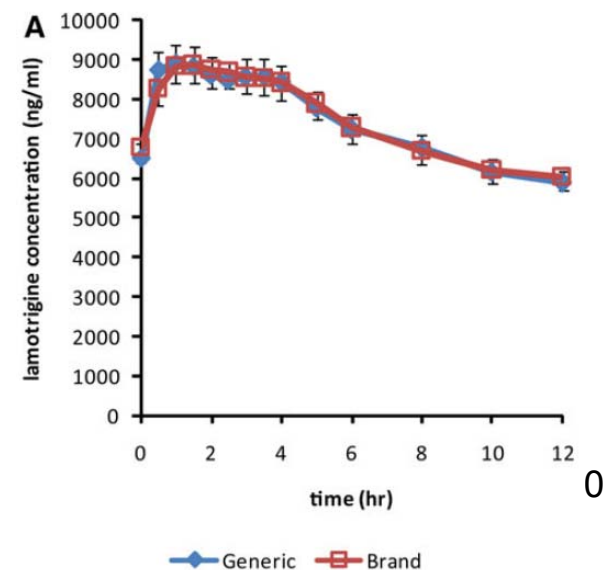
Brand/generic substitution studies in patients

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

“Generic demonstrated bioequivalence to brand...Bioequivalence results in “generic-brittle” patients with epilepsy under clinical conditions support the soundness of the FDA bioequivalence standards.”





Brand/generic substitution studies in patients

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.

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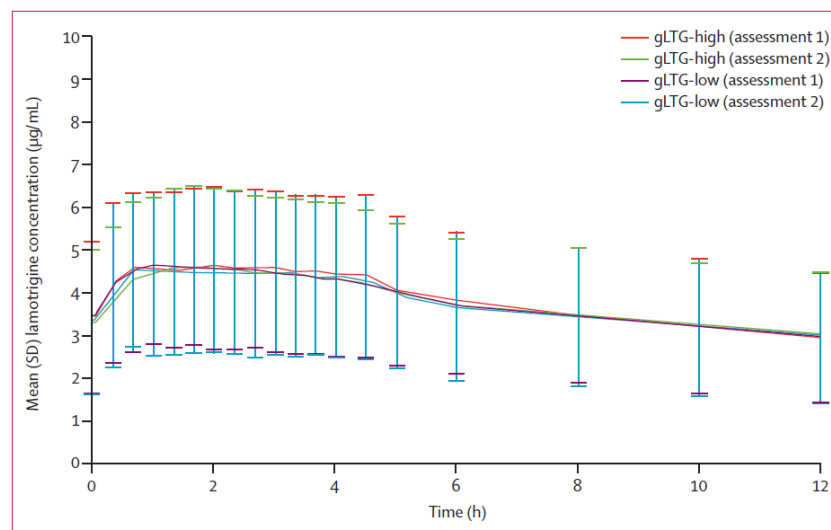
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S1474-4422(16)00014-4

“Disparate generic lamotrigine products in patients with epilepsy showed bioequivalence with no detectable difference in clinical effects, confirming that the US FDA bioequivalence standards are appropriate.”



Brand/generic substitution studies in patients

- Concern whether findings from BE studies in healthy volunteers extend to patients
- Focus on “higher risk” drugs:
 - Antiepileptics: 3
 - Immunosuppressants: 3
 - Previous BE issues: 3
 - Cardiovascular: 1



Brand/generic substitution studies in patients: projects in progress

Project Title	Site Name	Grant/ Contract	Fiscal Year
Pharmacokinetic studies of tacrolimus in transplant patients	University of Cincinnati	Grant	2012
Bioequivalence of Generic Bupropion	Washington University, St. Louis	Grant	2013
Evaluation of clinical and safety outcomes associated with conversion from brand-name to generic tacrolimus products in high risk transplant recipients	University of Cincinnati	Contract	2013
Investigation of inequivalence of bupropion hydrochloride extended release tablets	University of Michigan	Contract	2013
Prospective study on the impact of generic immunosuppressants on acute rejection and long term graft survivals	UCLA	Grant	2014
Characterization of Epilepsy Patients At-risk for Adverse Outcomes Related to Switching Antiepileptic Drug Products [BEEP II]	University of Maryland Baltimore	Contract	2014
Pharmacokinetic pharmacodynamic (PKPD) studies of cardiovascular drugs	University of Florida	Grant	2014
Pharmacokinetic pharmacodynamic studies of methylphenidate extended release products in pediatric attention deficit hyperactivity disorder	Massachusetts General Hospital	Grant	2014

Brand/generic substitution studies in healthy subjects

- Address complex questions:
 - Alternative study designs (parallel vs. crossover)
 - Alternative BE PK parameters
 - Alternative dosage strength
 - Are fresh vs. aged products bioequivalent?

Brand/generic substitution studies in healthy subjects

- Funded studies:
 - “Evaluation of iron species in healthy subjects treated with generic and reference sodium ferric gluconate”
 - “Bioequivalence and characterization of generic drugs”
 - Warfarin
 - Methylphenidate extended release
 - “Formulation, processing, and performance interrelationships for amorphous solid dispersions”
 - “Bioequivalence study of lamotrigine extended release tablets in healthy subjects”

Methods development for generic drug surveillance

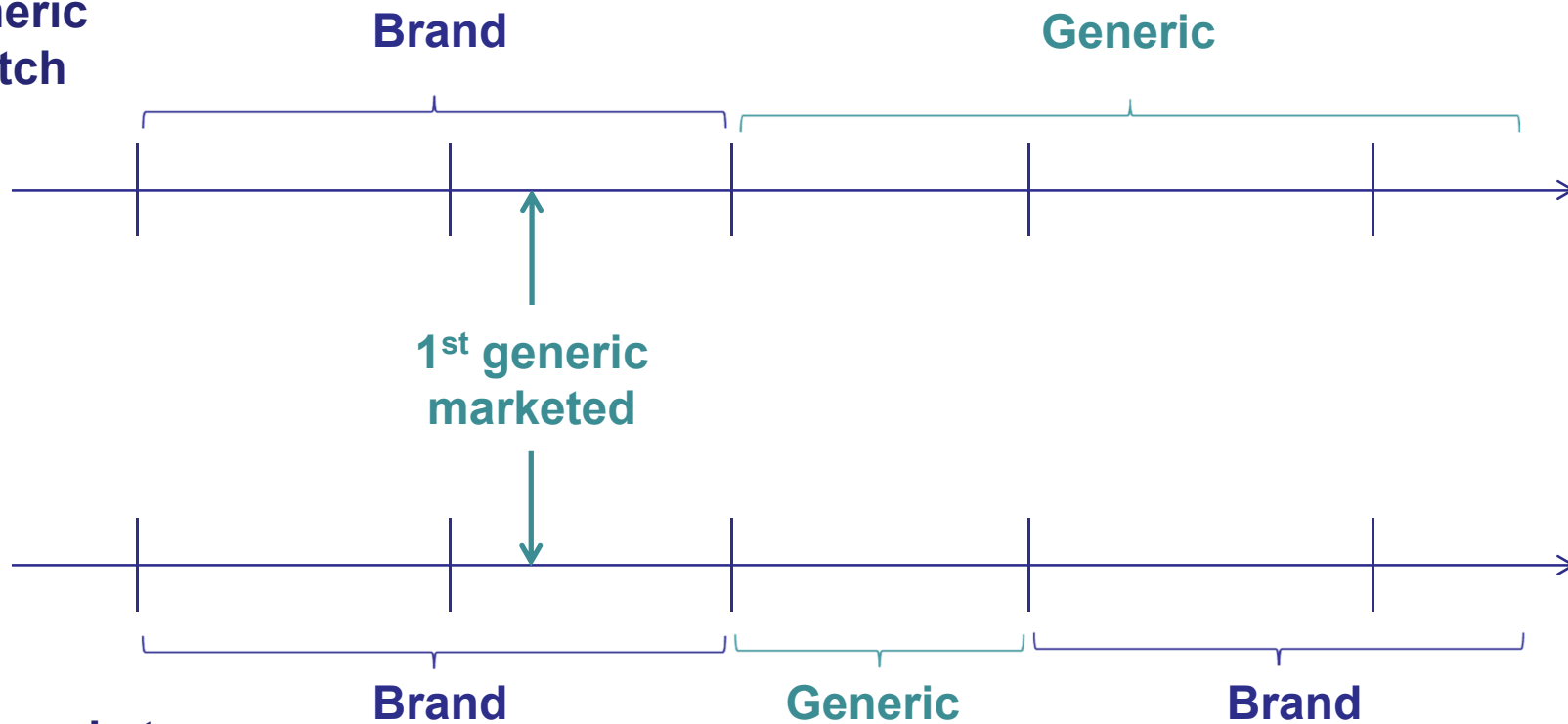
- Study designs:
 - Systematic reviews and meta analysis
 - Surveys, focus groups, interviews
 - Retrospective studies using secondary data
 - Prospective observational studies
- Value of different data secondary data sources
- Development of innovative data analysis methods

Methods development for generic drug surveillance

- 1) What evidence can utilization and switching patterns provide on generic substitution in the real-world?
 - “Switchbacks” to brand
 - “Switch away” to therapeutic alternatives
 - Funded studies
 - “Assessing clinical equivalence for generic drugs approved by innovative methods” (U01FD004856)
 - “Postmarketing surveillance of generic drug usage and substitution patterns” (U01FD004855)
 - “Transplant outcomes using generic and brand name immunosuppressants: studying medications used by people who have received kidney and liver transplants” (U01FD005274)

Drug utilization and switching patterns

Brand to generic switch



Generic to brand switchback



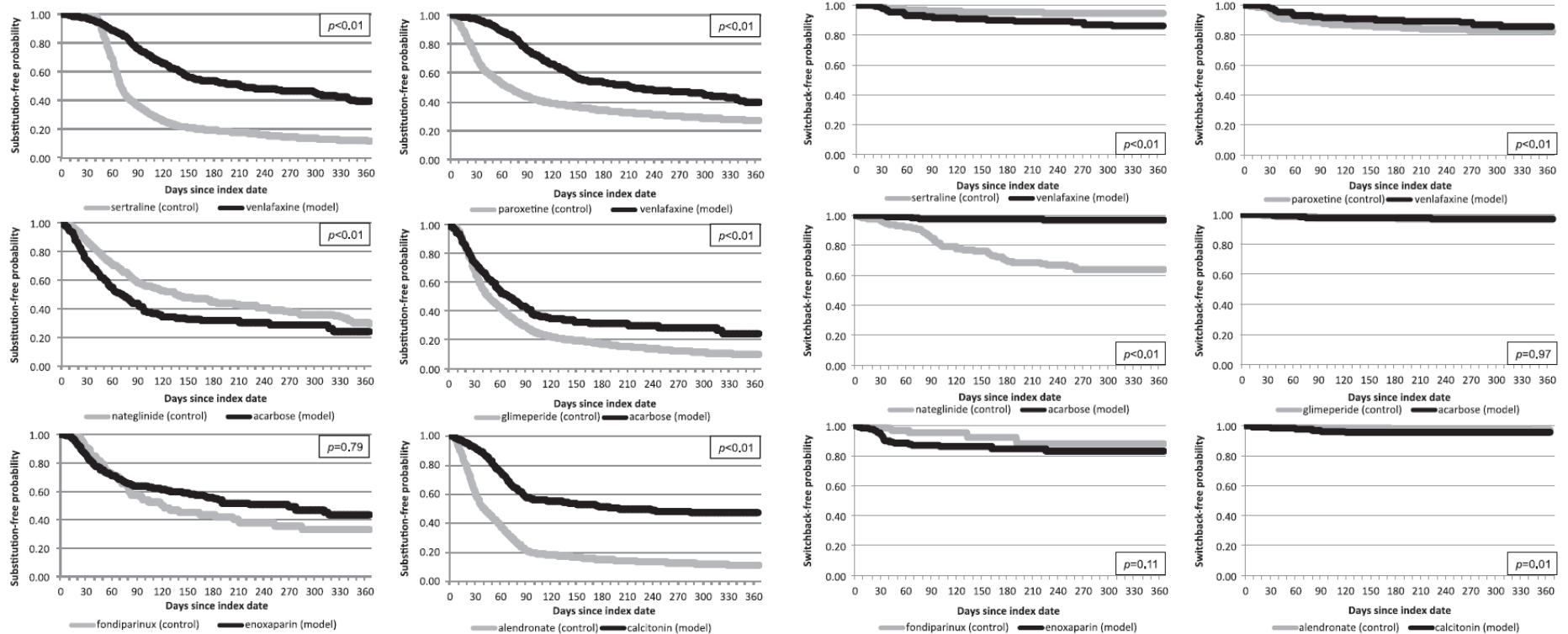
PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2016)

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ORIGINAL REPORT

Switch-backs associated with generic drugs approved using product-specific determinations of therapeutic equivalence

Joshua J. Gagne^{1*}, Jennifer M. Polinski¹, Wenlei Jiang², Sarah K. Dutcher², Jing Xie¹, Joyce Lii¹, Lisa A. Fulchino¹ and Aaron S. Kesselheim¹



Methods development for generic drug surveillance

- 2) How can secondary data be analyzed to assess safety and effectiveness outcomes of generic vs. brand name drugs?
- Funded studies:
 - “Assessing clinical equivalence for generic drugs approved by innovative methods” (U01FD004856)
 - “Postmarketing surveillance of generic drug usage and substitution patterns” (U01FD004855)
 - “Transplant outcomes using generic and brand name immunosuppressants: studying medications used by people who have received kidney and liver transplants” (U01FD005274)

Methods development for generic drug surveillance

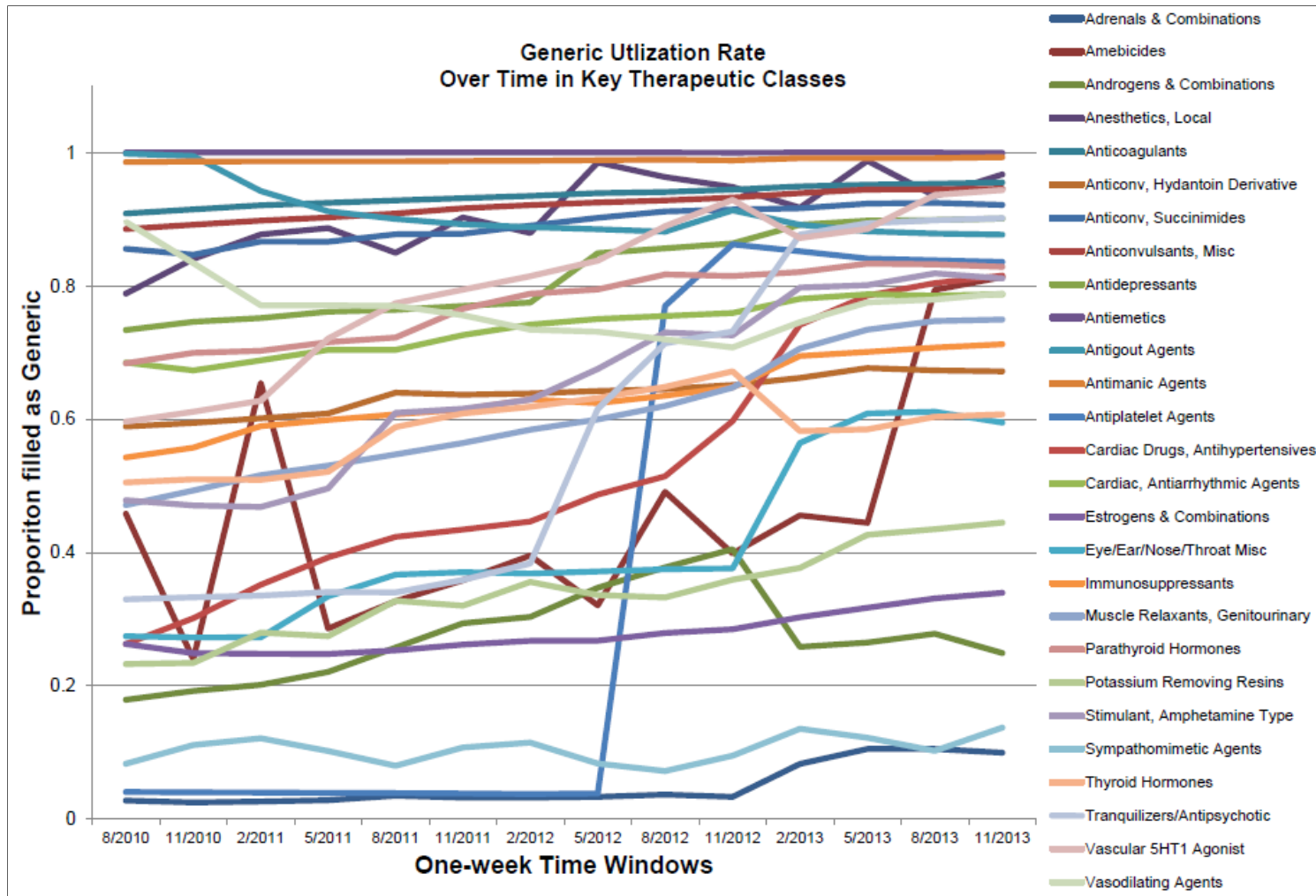
3) Can authorized generics act as a “control” group to reduce bias in observational studies evaluating generic vs. brand name drugs?

- Authorized generic: a listed drug...marketed, sold, or distributed directly or indirectly to retail class of trade with either labeling, packaging, product code, labeler code, trade name, or trade mark that differs from that of the listed drug
- Funded studies
 - “Assessing the post-marketing safety of authorized generic drug products” (U01FD005279)
 - “Post-market authorized generic evaluation (PAGE)” (U01FD005272)

Methods development for generic drug surveillance

- 4) Does generic uptake vary across drug classes?
 - What factors are associated with generic drug substitution?
 - Does this vary by drug or therapeutic class?
- Funded study: “Effect of therapeutic class on generic drug substitution” (U01FD005267)

Generic utilization across classes



Methods development for generic drug surveillance

- 5) Can we develop and apply statistical methods to reduce bias and error in observational studies using secondary data?
- “Novel approaches for confounding control in observational studies of generic drugs” (U01FD005555)
 - “Structural nested models for assessing the safety and effectiveness of generic drugs” (U01005556)

Methods development for generic drug surveillance

- 6) How can we use pharmacometric modeling in post-marketing surveillance of generic drugs?
- Funded studies:
 - “Pharmacometric modeling and simulation for a generic drug substitutability evaluation and post marketing risk assessment” (U01FD005192)
 - “A model- and systems-based approach to efficacy and safety questions related to generic substitution” (U01FD005210)

Summary of OGD's post-marketing research activities

- Monitor drug use, effectiveness, and safety in the real-world
- Evaluate substitutability of generic vs. brand drugs
 - In healthy subjects and patients
 - Supplements BE testing
- Develop new data sources and methodological approaches to evaluate generic drug interchangeability
- Address negative public perceptions and concerns regarding generics
 - Promote confidence in generic drugs via education

Future work

- Incorporate innovative healthcare technology into post-marketing research of generic drugs
 - To expand our research capabilities, enhance efficiency, and maximize cost-effectiveness
 - Example: use of a mobile app in a prospective study to collect data about medication adherence and adverse event
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Thank you