

FY2018 GDUFA Science and Research Report: Patient Substitution of Generic Drugs

This section contains only new information from FY2018. For background scientific information and outcomes from previous years on this research topic, please refer to:

- FY2015 GDUFA Science and Research Reports:
Postmarket: Evaluation of Generic Drug Product Substitution
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm500576.htm>)
Postmarket: Data Analysis for Generic Drugs
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm508098.htm>)
Postmarket: Patient Substitution Studies
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm500578.htm>)
- FY2016 GDUFA Science and Research Reports:
Postmarket: Data Analysis for Generic Drugs
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549181.htm>)
Postmarket: Patient Substitution Studies
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549182.htm>)
- FYs 2013-2017 GDUFA Science and Research Reports:
Analysis of Generic Drug Utilization and Substitution
(<https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm596051.htm>)
Patient Substitution Studies
Perceptions of Generic Drugs
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm>)

Introduction

The ultimate goal of the generic drug program is the successful substitution of a generic product for the brand name product. Our research program looks at generic substitution in various ways. We conduct clinical studies of substitution in patients, we analyze medical informatics data to evaluate generic utilization and substitution, and we study how patient and provider perceptions impact generic substitution.

Research

As an example of patient substitution, Grant #1U01FD004899 was awarded to Washington University (PI: Dr. Evan Kharasch) on September 10, 2013, to investigate bioequivalence between generic and brand name bupropion HCl modified-release (MR) products with different release patterns at a steady state in patients. The study evaluated whether patients could perceive the difference in release patterns and experienced lack of efficacy or increased adverse events after they were switched between each treatment. This project was completed in FY18 and the main result is that the three studied bupropion HCl MR products were both bioequivalent and therapeutically equivalent to the brand name drug and to each other in patients with major depressive disorder in stable remission.

Grant #1U01FD005240 was awarded to Massachusetts General Hospital (PI: Dr. Thomas Spencer) in September 2014 for the conduction of a pharmacokinetics/pharmacodynamics (PK/PD) classroom study in pediatric

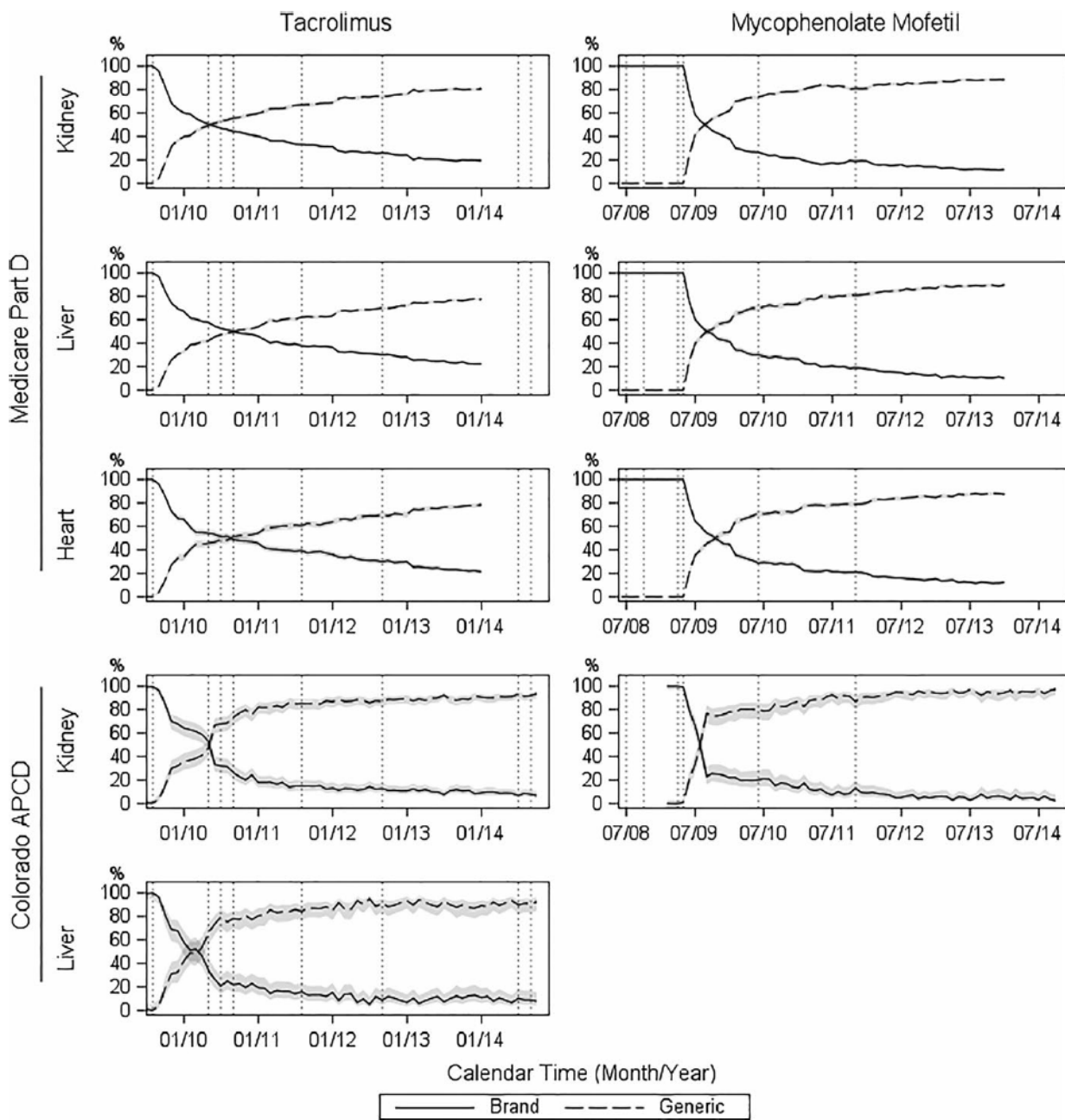
Attention Deficit Hyperactivity Disorder (ADHD) patients (6-12 years of age) to link the PK profiles to the time-course of PD activity of methylphenidate extended-release (ER) products. A unique feature of this study is that PK sampling was performed through dried blood spots rather than traditional phlebotomy due to the subject population and to reduce interference between PK and PD measures (i.e., intravenous blood draws could impact subject behavior in the classroom). In June 2018, the last subject visit for the study occurred with 74 completers. For the remainder of FY18 and into FY19, the study data will be finalized and data analysis will begin.

In collaboration with the Office of Surveillance and Epidemiology (OSE) at the FDA and Brigham and Women's Hospital, we developed and evaluated a modular tool for analyzing manufacturer-level drug utilization and switching patterns within the FDA's Sentinel system. The new Sentinel tool provides another option for FDA's Office of Generic Drugs (OGD) to support its post-marketing surveillance of generic drugs.

A retrospective Arbor Research study investigated the uptake, use, and savings from the introduction of generic immunosuppressant medications (mycophenolate mofetil (MMF) and tacrolimus (TAC)) among U.S. kidney, liver, and heart transplant recipients between 2008 and 2013 using Medicare Part D prescription drug event (PDE) data, Colorado All-Payer Claims Database (APCD), and the Scientific Registry of Transplant Recipients (SRTR). Initial results demonstrated that overall generic substitution increased rapidly following first availability and that utilization of generic immunosuppressants exceeded that of brand products within a year of market entry (see **Figure 1**). Results also showed that Medicare Part D patient out-of-pocket and Low Income Subsidy payments for MMF and TAC decreased between 2008 and 2013, with out-of-pocket payments for transplant recipients not receiving a low-income subsidy showing the largest percentage decrease. These results suggest that introduction of generic immunosuppressant medications resulted in cost savings for both patients and Medicare.

Two ongoing studies – *Educating Groups Influencing Generic Drug Use* (Auburn University) and *Identifying Messages to Promote Value and Education of Generic Prescribing* (University of Chicago) – have demonstrated the behaviors of key groups including patients, physicians, nurse practitioners, pharmacists, formulary managers, and policymakers impact generic drug use. Generic prescribing is also affected by multiple factors related to patients, providers, the health system, formulary management/cost containment, promotional activities, educational initiatives, and technology. The effects exerted on generic prescribing by individual bias, varied health system policies, and efforts to contain costs are at the forefront and are self-evident. Alternatively, the effects of promotional activities (e.g., coupons and vouchers) for increasing the likelihood of prescribing brand name drugs, and of educational initiatives targeted at providers and patients or of technology such as e-prescribing for increasing the likelihood for generic drug prescribing was less apparent. Results from the University of Chicago team demonstrated that nurse practitioners (NPs) were identified as generic skeptics more than primary care physicians (PCPs) (18.4% NP vs. 12.7% PCP, $p=0.023$), and both groups were less willing to prescribe generic oral contraceptives than antidepressants (Odds Ratio 0.69, 95% CI 0.59-0.80, $p<0.001$). Understanding the factors influencing the generic drug use is being used to develop standardized educational interventions as part of both studies.

Figure 1. Percent of Patients Dispensed Generic vs Brand Name Immunosuppressants Over Time.



Each vertical line marks the date of U.S. Food and Drug Administration (FDA) approval of a generic tacrolimus or mycophenolate mofetil product. The 95% confidence intervals (CIs) for the percentages are displayed as gray bands. APCD, All-Payer Claims Databa

Research Projects and Collaborations

New Grants and Contracts

- New Grant (1U01FD005938) *Use of Instrumental Variable Approaches to Assess the Safety and Efficacy of Brand-Name and Generic Drugs Used to Treat Hypothyroidism* with Joseph Ross and Nilay Shah at Yale/Mayo CERSI

Continuing Grants and Contracts

- Active Grant (1U01FD005875) *Characterizing use, safety and efficacy of brand-name and generic drugs used to treat hypothyroidism* with Joseph Ross and Nilay Shah at Yale/Mayo CERSI
- Active Grant (1U01FD004899) *Bioequivalence and Clinical Implications of Generic Bupropion* with Evan D. Kharasch at Washington University
- Active Grant (1U01FD005235) *Pharmacokinetic and Pharmacodynamic (PK-PD) Studies of Cardiovascular Drugs* with Larisa Humma Cavallari at University of Florida
- Active Grant (1U01FD005240) *Pharmacokinetic Pharmacodynamic Studies of Methylphenidate Extended Release Products in Pediatric Attention Deficit Hyperactivity Disorder* with Thomas J Spencer at Massachusetts General Hospital
- Active Grant (1U01FD005191) *Pharmacometric Modeling of Immunosuppressants for Evaluation of Bioequivalence Criteria* with Robert Ward at University of Utah
- Active Grant (1U01FD005192) *Pharmacometric Modeling and Simulation for Generic Drug Substitutability Evaluation and Post Marketing Risk Assessment* with Jogarao Gobburu at University of Maryland
- Active Grant (3U01FD005210-03S1) *A Model and System Based Approach to Efficacy and Safety Questions Related to Generic Substitution* with Lawrence Lesko at University of Florida
- Active Grant (1U01FD005271) *Prospective Study Comparing Brand and Generic Immunosuppression On Transplant Outcomes Adherence and Immune Responses* with Suphamai Bunnapradist at University of California at Los Angeles
- Active Grant (1U01FD005274) *Transplant Outcomes Using Generic and Brand Name Immunosuppressants: Studying Medications Used by People Who Have Received Kidney and Liver Transplants* with Alan B Leichtman at Arbor Research
- Active Contract (HHSF223201400188C) *Characterization of Epilepsy Patients at-Risk for Adverse Outcomes Related to Switching Antiepileptic Drug Products* with James Polli at University of Maryland
- Active Contract (HHSF223201610004I) *Base IDIQ for Postmarket Bioequivalence Study* with Biopharma Services USA
- Active Grant (1U01FD005875) *Generic Drug Substitution in Special Populations* with Jingjing Qian at Auburn University

Outcomes

Publications

- Alloway, R., Vinks, A., Fukuda, T., Mizuno, T., King, E., Zou, Y., Jiang, W., Woodle, E., Tremblay, S., Klawitter, J., Klawitter, J., and Christians, U. *Bioequivalence Between Innovator and Generic Tacrolimus in Liver and Kidney Transplant Recipients: A Randomized, Crossover Clinical Trial*. PLoS Med. (2017) **14**(11):e1002428. doi: [10.1371/journal.pmed.1002428](https://doi.org/10.1371/journal.pmed.1002428). PMID: [29135993](https://pubmed.ncbi.nlm.nih.gov/29135993/).

- Brown, J. D. and Pham, P. N. *The Need for Deliberate and Thorough Design and Critique of Observational Comparative Effectiveness Research*. Research in Social and Administrative Pharmacy. (2018) **14**:1085–1087. doi: [10.1016/j.sapharm.2018.07.012](https://doi.org/10.1016/j.sapharm.2018.07.012). PMID: [30041916](https://pubmed.ncbi.nlm.nih.gov/30041916/).
- Desai, R. J., Sarpatwari, A., Dejene, S., Khan, N. F., Lii, J., Rogers, J. R., Dutcher, S. K., Raofi, S., Bohn, J., Connolly, J., Fischer, M. A., Kesselheim, A. S., and Gagne, J. J. *Differences in Rates of Switchbacks After Switching From Branded to Authorized Generic and Branded to Generic Drug Products: Cohort Study*. BMJ. (2018) **361**:k1180. doi:[10.1136/bmj.k1180](https://doi.org/10.1136/bmj.k1180). PMID: [29615391](https://pubmed.ncbi.nlm.nih.gov/29615391/).
- Gagne, J., Polinski, J., Jiang, W., Dutcher, S., Xie, J., Lii, J., Fulchino, L., and Kesselheim, A. *Correction To: Outcomes Associated with Generic Drugs Approved Using Product-Specific Determinations of Therapeutic Equivalence*. Drugs. (2018) **78**(4):523–4. doi: [10.1007/s40265-0180890-x](https://doi.org/10.1007/s40265-0180890-x). PMID: [29520639](https://pubmed.ncbi.nlm.nih.gov/29520639/).
- Gandhi, A., Beekman, C., Parker, R., Fang, L., Babiskin, A., and Matta, M. K. *Novel and Rapid LC-MS/MS Method for Quantitative Analysis of Methylphenidate in Dried Blood Spots*. Bioanalysis. (2018) **10**(11):839–850. doi: [10.4155/bio-2018-0024](https://doi.org/10.4155/bio-2018-0024). PMID: [29863895](https://pubmed.ncbi.nlm.nih.gov/29863895/).
- Hohmann, N., Hansen, R., Garza, K. B., Harris, I., Kiptanui, Z., and Qian, J. *Association Between Higher Generic Drug Use and Medicare Part D Star Ratings: An Observational Analysis*. Value in Health. (2018) **21**:11861191. doi: [10.1016/j.jval.2018.03.005](https://doi.org/10.1016/j.jval.2018.03.005). PMID: [30314619](https://pubmed.ncbi.nlm.nih.gov/30314619/).
- Liu, Q. et al. *The Adoption of Generic Immunosuppressant Medications in Kidney, Liver, and Heart Transplantation Among Recipients in Colorado or Nationally with Medicare Part D*. Am J Transplant. (2018) **18**(7):1764–1773. doi: [10.1208/s12248-008-9010-2](https://doi.org/10.1208/s12248-008-9010-2). PMID:[29603899](https://pubmed.ncbi.nlm.nih.gov/29603899/).
- Rower, J. E., Stockmann, C., Linakis, M. W., Kumar, S. S., Liu, X., Korgenski, E. K., Sherwin, C. M. T., and Molina, K. M. *Predicting Tacrolimus Concentrations in Children Receiving a Heart Transplant Using a Population Pharmacokinetic Model*. BMJ Paediatr Open. (2017) **1**:e000147. doi: [10.1177/1060028017705393](https://doi.org/10.1177/1060028017705393). PMID: [29177199](https://pubmed.ncbi.nlm.nih.gov/29177199/).

Presentations

- Kharasch, E. D. *Bioequivalence and Clinical Implications of Generic and Brand Bupropion*. Presentation at ACCP Annual Meeting. Bethesda, MD, Sept. 23, 2018.
- Lionberger, R. *Can Clinical Pharmacology Break Down Barriers to Generic Substitution?* Presentation at ACCP Annual Meeting. Bethesda, MD, Sept. 24, 2018.
- Schmidt, S. *A Model- and System-Based Approach to Efficacy and Safety Questions Related to Generic Substitution* Presentation at Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review. Oct. 2, 2017.
- Schmidt, S. *A Model- and System-Based Approach to Efficacy and Safety Questions Related to Generic Substitution* Presentation at GDUFA Regulatory Science Public Workshop. May 24, 2018.

Posters

- Emoto, C., Fukuda, T., Hahn, D., Christians, U., Alloway, R., and Vinks, A. *Tacrolimus Pbpk Modeling Using Realistic Physiological Factors In Renal Transplant Patients*. Poster Presentation at ASCPT. Orlando, FL, Mar. 22, 2018.
- Hahn, D., Emoto, C., Christians, U., Alloway, R., Vinks, A., and Fukuda, T. *Genetic Polymorphisms at the Pregnane X Receptor And CYP3A5 Loci Influence the Pharmacokinetics of Tacrolimus in Renal Transplant Patients*. Poster Presentation at ASCPT. Orlando, FL, Mar. 22, 2018.
- Kiptanui et al. *Consistency of Publicly-Accessible Generic Drug Labels with Reference Listed Drug Labels in Dailymed: A Case Analysis for the Special Populations*. Poster Presentation at International Society for Pharmacoepidemiology and outcomes research. Baltimore, MD, May 19, 2018.

- Kiptanui et al. *Consistency of Publicly-Accessible Generic Drug Labels with Reference Listed Drug Labels in Dailymed: A Case Analysis for the Special Populations*. Poster Presentation at 33th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Prague, Cech, Aug. 22, 2018.
- Lichvar, A., Tremblay, S., Naik, D., King, E., Vinks, A., Christians, U., and Alloway, R. *Evaluation of Clinical and Safety Outcomes Following Uncontrolled Tacrolimus Conversion in Adult Renal Transplant Recipients*. Poster Presentation at ACCP Annual Meeting. Phoenix, AZ, Oct. 7, 2017.
- Lichvar, A., Tremblay, S., Naik, D., King, E., Vinks, A., Christians, U., and Alloway, R. *Evaluation of Clinical and Safety Outcomes Following Uncontrolled Tacrolimus Conversion in Adult Renal Transplant Recipients*. Poster Presentation at American Transplant Congress. Seattle, WA, June 2, 2018.
- Qian, J., Li, C., Huo, N., Mishuk, A., Chen, L., Hansen, R., Harris, I., and Kiptanui, Z. *Generic Substitution Patterns of Levothyroxine and Escitalopram in Subgroups of U.S. Medicare Beneficiaries*. Poster Presentation at 33th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Prague, Cech, Aug. 22, 2018.