Use of Regulatory Science Research to Support Post-marketing Surveillance of Generic Drug Products

Sarah Dutcher, PhD
Office of Generic Drugs
Office of Research and Standards
Division of Quantitative Methods & Modeling

October 3, 2017
Why Generic Drug Surveillance?

<table>
<thead>
<tr>
<th>New Drug Surveillance</th>
<th>Generic Drug Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown safety risks in real-world patient population</td>
<td>Unexpected safety outcomes due to allowed differences</td>
</tr>
<tr>
<td>Surveillance of the active ingredient</td>
<td>Surveillance of the generic product</td>
</tr>
<tr>
<td>Patient and physician unfamiliarity</td>
<td>Perceptions about product quality inferiority</td>
</tr>
<tr>
<td>Focus: safety</td>
<td>Focus: substitutability</td>
</tr>
</tbody>
</table>
Postmarketing Surveillance in OGD

- Support OGD Clinical Safety and Surveillance Staff
- Follow up on reports and findings from published literature
- Respond to letters and public comments submitted to FDA
Today’s Objective

• Describe the current extramural research activities sponsored by OGD to evaluate post-marketing generic drug substitutability

Methods development for generic drug surveillance

Substitution studies in:
- Patients
- Healthy subjects

Perception and education about generic drugs

Investigation of in-equivalence issues
Secondary Data Sources Used for Generic Drug Surveillance

- FDA adverse event reporting system (FAERS)
- Administrative claims data
  - Collected by health insurers for billing purposes
  - Includes information on health care visits, diagnoses, medical procedures, medications dispensed, costs
- Electronic health records
  - Maintained by health care organizations and institutions
  - Includes information on medical history, clinical diagnoses, laboratory and test results, medication orders
- Registries
  - Disease and drug registries
Methods Development Areas

1. Utilization and switching patterns
2. Equivalence in safety and effectiveness
3. Reduction of bias and error
4. Role of authorized generics
5. Analysis of FAERS data
6. Therapeutic class substitution
1. Utilization and Switching Patterns

What evidence can utilization and switching patterns provide on generic substitution in the real-world?

- Can these patterns help identify substitutability issues?
- Do these patterns vary across populations?
2. Equivalence in Safety and Effectiveness

How can secondary data be used to assess safety and effectiveness of generic vs. brand name drugs?

- Clinical outcomes
- Health services outcomes
- Medication outcomes

Diagram:
- Generic initiators
- Generic switchers
- 1st generic marketed
- Follow up for safety or effectiveness outcomes
- Brand
- Generic
3. Reduction of Bias and Error

Hypothetical Drug A

% prescriptions

Month

1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35

0% 20% 40% 60% 80% 100%

Brand

Generic

Temporal Confounding

Brand

Generic

Selection Bias, Sample Size

Brand
3. Reduction of Bias and Error

Can we develop and apply methods to reduce bias and error in observational studies using secondary data?

• Confounding control
  • Cohort sample selection
  • Covariate control

• Analytical approaches
  • Summary score matching techniques (e.g., PS matching)
  • Difference-in-difference analysis
  • Regression discontinuity analysis
  • Machine learning

• Multiple linked data sources
  • Linked at patient-level or region-level
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 that has been approved under subsection 505(c) of the act and is 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.

Figure adapted from Brigham & Women’s Hospital meeting presentation.
4. Role of Authorized Generics

Risk of adverse clinical outcomes was not statistically different between AGs and generic switchers

4. Role of Authorized Generics

Generic switchers did not have worse outcomes than AG switchers

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimate</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of all-cause outpatient visits per year</td>
<td>1.05</td>
<td>0.071</td>
</tr>
<tr>
<td>Number of all-cause urgent care visits per year</td>
<td>1.08</td>
<td>0.395</td>
</tr>
<tr>
<td>All-cause emergency department visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any visit</td>
<td>1.33</td>
<td>0.003</td>
</tr>
<tr>
<td>Number per year</td>
<td>1.23</td>
<td>0.026</td>
</tr>
<tr>
<td>All-cause hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any visit</td>
<td>1.14</td>
<td>0.257</td>
</tr>
<tr>
<td>Number per year</td>
<td>1.09</td>
<td>0.582</td>
</tr>
<tr>
<td>Medication discontinuation</td>
<td>0.95</td>
<td>0.508</td>
</tr>
</tbody>
</table>

5. Analysis of FAERS Data

How can we use FAERS data to identify potential signals of generic drug inequivalence?

- Disproportionality analysis
- Development of algorithms to identify generic drug reports
- Interrupted time series analysis
5. Analysis of FAERS Data

Interrupted time series analysis

Sarpatwari A et al. Differences in adverse event reporting following the loss of market exclusivity among drugs with and without authorized generics. Manuscript in preparation.
6. Therapeutic Class Substitution

Does generic uptake vary across drug classes?

- What factors are associated with generic drug substitution?
- Do these factors vary across therapeutic classes or across different populations?
6. Therapeutic Class Substitution

6. Therapeutic Class Substitution

Factors associated with lower generic levothyroxine prescribing:

- Younger age
- Fewer co-medications
- Higher income
- Severe disease status
- Initial prescription
- In-person visit
- Prescribed by endocrinologist

Moving Forward

• Proactively monitor drug use, effectiveness, and safety in the real-world
  – Internal: Sentinel Initiative, FAERS
  – External: Grants and contracts
• Assess clinical or regulatory issues that arise
• Develop and refine methodological approaches to evaluate generic drug substitutability
• Continue to provide additional evidence for the interchangeability of brand-name and generic drugs
www.fda.gov/GDUFARegScience
Backup Slides
## Methods Development for Generic Drug Surveillance

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Site Name</th>
<th>Grant/Contract</th>
<th>Year Funded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization, Switching, and Switchback Safety and Effectiveness Outcomes in Secondary Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessing clinical equivalence for generic drugs approved by innovative methods</td>
<td>Brigham &amp; Women’s Hospital</td>
<td>Grant</td>
<td>2013</td>
</tr>
<tr>
<td>Postmarketing surveillance of generic drug usage and substitution patterns</td>
<td>University of Maryland Baltimore</td>
<td>Grant</td>
<td>2013</td>
</tr>
<tr>
<td>Transplant outcomes using generic and brand name immunosuppressants: studying medications used by people who have received kidney and liver transplants</td>
<td>Arbor Research Collaborative for Health</td>
<td>Grant</td>
<td>2014</td>
</tr>
<tr>
<td>Generic Drug Substitution in Special Populations</td>
<td>Auburn University</td>
<td>Grant</td>
<td>2016</td>
</tr>
</tbody>
</table>
## Methods Development for Generic Drug Surveillance

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Site Name</th>
<th>Grant/Contract</th>
<th>Year Funded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authorized Generics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessing the post-marketing safety of authorized generic drug products</td>
<td>Brigham &amp; Women’s Hospital</td>
<td>Grant</td>
<td>2014</td>
</tr>
<tr>
<td>Post-market authorized generic evaluation (PAGE)</td>
<td>Auburn University</td>
<td>Grant</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Generic drug substitution across therapeutic classes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of therapeutic class on generic drug substitution</td>
<td>Johns Hopkins University</td>
<td>Grant</td>
<td>2014</td>
</tr>
</tbody>
</table>
# Methods Development for Generic Drug Surveillance

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Site Name</th>
<th>Grant/Contract</th>
<th>Year Funded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statistical Methods for Observational Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel approaches for confounding control in observational studies of generic drugs</td>
<td>Brigham &amp; Women’s Hospital</td>
<td>Grant</td>
<td>2015</td>
</tr>
<tr>
<td>Structural nested models for assessing the safety and effectiveness of generic drugs</td>
<td>Johns Hopkins University</td>
<td>Grant</td>
<td>2015</td>
</tr>
<tr>
<td>Comparative surveillance of generic drugs by machine learning</td>
<td>Marshfield Clinic Research Foundation</td>
<td>Contract</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Use of Pharmacometric Modeling in Surveillance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacometric modeling and simulation for a generic drug substitutability evaluation and post marketing risk assessment (U01FD005192)</td>
<td>University of Maryland Baltimore</td>
<td>Grant</td>
<td>2014</td>
</tr>
<tr>
<td>A model- and systems-based approach to efficacy and safety questions related to generic substitution (U01FD005210)</td>
<td>University of Florida</td>
<td>Grant</td>
<td>2014</td>
</tr>
</tbody>
</table>
Rates of switchback to the brand-name product were consistently lower among AG users compared to generic users.

- No significant difference in brand switchback rates for generic vs. AG for 9 of 10 study drugs.
- Trend toward higher AG switchback rates for 7 drugs.