Ensure Generic Drug Safety and Efficacy via a Combined Effort of FDA, Academia, and the Entrepreneurial Industry in a Data-driven Era

Liang Zhao, Ph.D.
Director, Division of Quantitative Methods and Modeling
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA

UCSF-Stanford CERSI Visit
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Agenda

• Introduction of Division
• Role of Generics in the US health care system
• Pre market assessment of generic drug equivalence
• Post market assessment of therapeutic equivalence
  - Current post market monitoring
  - The advancement of new technologies
• Vision/Strategies for next generation post market monitoring of generic products
Division of Quantitative Methods and Modeling (DQMM)

Office of Generics Drugs

- Office of Bioequivalence
- Office of Research & Standards

Division of Therapeutic Performance

- Regulatory activities
  - Pre ANDA interactions
  - Review consults
- Policy/guidance development
- GDUFA fund managements
## DQMM Regulatory Activities (4/1/15 - 4/1/16)

<table>
<thead>
<tr>
<th>Type</th>
<th>No.</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA Reviews</td>
<td>20</td>
<td>- PD modeling and simulation for Methylphenidate ER product and asthma controllers</td>
</tr>
<tr>
<td>CP, CC, Pre-ANDA</td>
<td>54</td>
<td>- Development of BE criteria for pain killers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Assessment of BE standards for GI locally acting products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Simulation of in vivo alcohol dose dumping studies</td>
</tr>
<tr>
<td>BE Guidance</td>
<td>33</td>
<td>- Simulations for the development of BE criteria for HVDs and NTI drugs</td>
</tr>
<tr>
<td>Regulatory Research Study</td>
<td>37</td>
<td>- PK/PD modeling and simulation to determine the appropriate study design and evaluate BE between generic anti-epilepsy drugs and immunosuppressant drugs in patients</td>
</tr>
</tbody>
</table>
Core DQMM Tool Set

Our Goal is to support
- Generic drug research
- Policy development
- Regulatory decisions

Oral Drug

Non-Oral Drug

Release/ Absorption/ PBPK Models

Big Data

Pharmacometrics

PK-PD model

Population model

Analytics for complex mixtures
Systems pharmacology
Risk models
Business process models
## M&S Matrix

<table>
<thead>
<tr>
<th></th>
<th>PBPK</th>
<th>PK/PD</th>
<th>Big Data (Liang)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complex</strong></td>
<td>Non-oral delivery models</td>
<td>Sensitivity of clinical BE</td>
<td>Advanced Analytical Methods (Meng)</td>
</tr>
<tr>
<td><strong>Solid Oral</strong></td>
<td>Oral absorption</td>
<td>NTI, pAUC</td>
<td>PK Data Warehouse (Andrew)</td>
</tr>
<tr>
<td><strong>Post-Market</strong></td>
<td>Failure mode</td>
<td>Clinical Impact</td>
<td>Signal detect,risk</td>
</tr>
</tbody>
</table>
Increasing Impacts of Generics on US Healthcare System

<table>
<thead>
<tr>
<th>Non-Discounted Spending and Dispensing by Product Type</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spending US$Bn</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total U.S. Market</td>
<td>328.3</td>
<td>317.8</td>
<td>331.5</td>
<td>378.6</td>
<td>424.8</td>
</tr>
<tr>
<td>Brands</td>
<td>74.5%</td>
<td>71.7%</td>
<td>71.0%</td>
<td>72.1%</td>
<td>73.3%</td>
</tr>
<tr>
<td>Unbranded Generics</td>
<td>13.6%</td>
<td>16.1%</td>
<td>16.9%</td>
<td>16.9%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Branded Generics</td>
<td>11.9%</td>
<td>12.2%</td>
<td>12.1%</td>
<td>11.0%</td>
<td>10.7%</td>
</tr>
<tr>
<td><strong>Dispensed prescriptions Mn</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total U.S. Market</td>
<td>4,014</td>
<td>4,155</td>
<td>4,236</td>
<td>4,325</td>
<td>4,368</td>
</tr>
<tr>
<td>Brands</td>
<td>20.2%</td>
<td>15.9%</td>
<td>13.6%</td>
<td>12.3%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Unbranded Generics</td>
<td>72.7%</td>
<td>77.7%</td>
<td>80.5%</td>
<td>82.1%</td>
<td>83.4%</td>
</tr>
<tr>
<td>Branded Generics</td>
<td>7.1%</td>
<td>6.4%</td>
<td>5.9%</td>
<td>5.6%</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

IMS, Medicines Use and Spending in the U.S. April 2016
Savings and Challenges with Generic Drugs
### NDA vs. ANDA Review Process

<table>
<thead>
<tr>
<th>Brand Name Drug NDA Requirements</th>
<th>Generic Drug ANDA Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chemistry</td>
<td>1. Chemistry</td>
</tr>
<tr>
<td>3. Controls</td>
<td>3. Controls</td>
</tr>
<tr>
<td>4. Labeling</td>
<td>4. Labeling</td>
</tr>
<tr>
<td>5. Animal Studies</td>
<td>5. Bioequivalence</td>
</tr>
<tr>
<td>6. Clin/Pharm St.</td>
<td></td>
</tr>
<tr>
<td>7. Clinical Studies</td>
<td></td>
</tr>
</tbody>
</table>

By Dr. Dale Conner
**FDA Snapshot**

- 7 Pending Filing Review
- 498 Filed - No Review Comm.
- 2,138 At Least One Review Communication Issued
- 2,643 with FDA

**Monthly Average**
(June - Sept)

- Complete Response 99
- Amendments 100
- Tentative Approvals 85

**Industry Snapshot**

- 846 Pending Industry Response
- 267 Tentative Approval with Industry
- 1,113 with Industry

**Current ANDA Workload of Original Applications**

- 3,756

**Total Pre-Y3 Application Cohort**
(Since 10/1/2012)

- 1,316 Approvals
- 122 Refuse to Receive
- 422 Withdrawals (from Cohort)
- 3,756

**Total**

= 5,720

*Numbers are based on current data and will be further scrubbed for formal reporting purposes*
Purpose of UCSF-Stanford CERSI Visit

How can we assess therapeutic equivalence in a post marketing stage by taking advantage of new technologies?
Why Post Market Surveillance?

- Assess and quantify known or suspected drug safety issues
- Identify and characterize potential new risks and risk factors following product marketing
- Monitor medication use patterns
- Improve the understanding of "real world" use of a product
- Identifying off-label use and potential medication errors
- Detect new safety information
- Evaluate risk mitigation and interventions

How can it be applied to assess generic therapeutic equivalence?
Post Marketing Database, Tools and Methods

Challenge: Not ideally set up to directly assess generic:brand therapeutic equivalence
Passive Surveillance

• Definition and objectives
  - A system by which a health jurisdiction receives reports submitted from hospitals, clinics, public health units, or other sources
    - Assembling a series of cases to examine specific types of events, such as overdose and product re-challenge

• Methods and Resources
  - Spontaneous adverse event reports (MedWatch)
  - Scientific literature publications

• Advantage
  - Relatively inexpensive strategy to cover large areas
  - Easy to develop and implement
  - Provides critical information for monitoring a community’s health

• Limitations
  - Data quality and timeliness are difficult to control
  - Potential underreporting of events
  - Unknown parameters (denominator/numerator) for calculation of incidence
  - Incomplete reporting information for causality
Active Surveillance

• **Definition and objectives**
  - A system employing staff members to regularly contact healthcare providers or the population to seek information about health conditions
  - Detect safety issues such as rare events or latent onset, quantify the effects of misuse or overdose

• **Methods and Resources**
  - Regular, periodic and stimulated collection of case reports or data in other forms from healthcare providers or facilities
  - Sentinel sites, prescription monitoring, patient registries, electronic medical record research

• **Advantage**
  - Efficient
  - Provide accurate and timely information
  - Allow for a focus on patient subgroups that would not be available in a passive reporting system

• **Limitations**
  - Expensive to conduct
  - May have small sample size and selection bias
Data Collection &
Way We Live our L...
Some Quotes on Problem Solving in the Modern Era

“In God we trust. All others must bring data.” – W. Edwards Deming

“Data beats emotions.” – Sean Rad
“Numbers have an important story to tell. They rely on you to give them a voice.” – Stephen Few
“Torture the data, and it will confess to anything.” – Ronald Coase

“With too little data, you won’t be able to make any conclusions that you trust. With loads of data you will find relationships that aren’t real… Big data isn’t about bits, it’s about talent.” – Douglas Merrill
Limits of Using Post-market Studies to Assess Generic:Brand Equivalence

• **Forms for comparative observational studies**
  - Retrospective analyses of secondary data
  - Surveys and prospective cohorts
  - Other descriptive studies

• **Data quality**
  - Not collected with specific aims to compare
  - Active analysis on retrospectively collected data

• **Cost**
  - Cost for randomization can be an issue
  - Potentially large sample size

• **Operational difficulty**
  - Interactions/coordination: pharmacy, physician, and healthcare professionals
Component of a Good Report/Documentation in AE Report

- Description of event
- Suspected and concomitant product therapy details (e.g., dose, dates of therapy)

- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition, family history, other risk factors

- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information
- Any other relevant information
Realization of Information Collection in a Modern Data Era

Can this provide an opportunity?
Vision/Strategies for Next Generation Post Market Assessment of Generic Products

• Conduct active monitoring study based on proactively collected data using smart phones or relevant technologies


• Use information/model to confirm study finding

http://stanfordmedicine.org/communitynews/2015summer/app.htm
An Integrated Model Approach to Confirm Post Market Finding

DDI: Drug-drug interaction
PBPK: Physiologically based PK model
PKPD: Pharmacokinetics-Pharmacodynamics
E-R: Exposure-response model
QSP: Quantitative systems pharmacology
PM: Post market
Thoughts Developed during this Visit

• Who are the stakeholders? What are the incentives?

• How to run post market studies in the most cost effective manner?

• How to integrate HMO, physicians, pharmacy chain, and health data server interactions?
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