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

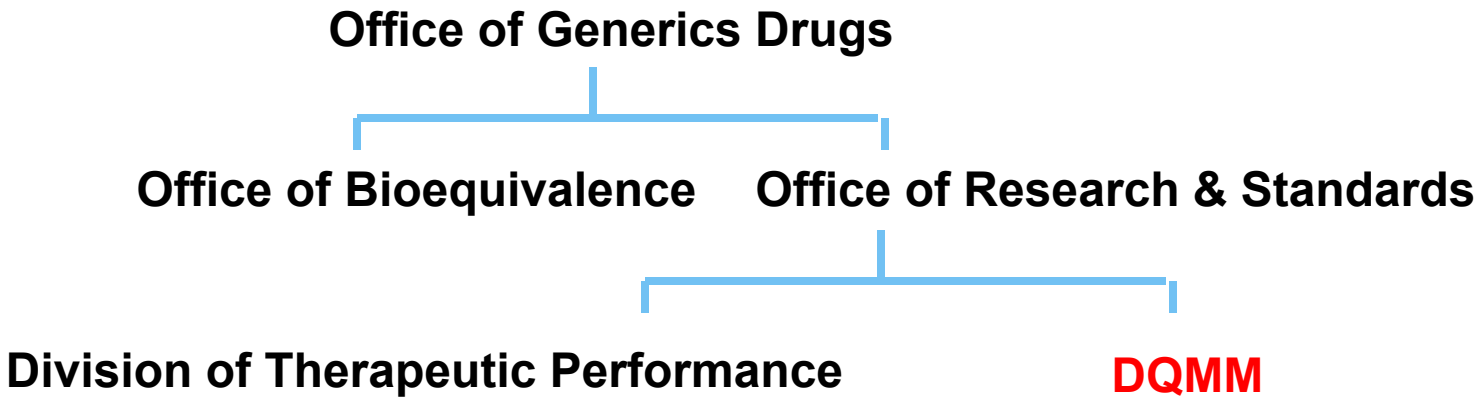
UCSF-Stanford CERSI Visit

August 2nd, 2016

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)



- Regulatory activities
  - Pre ANDA interactions
  - Review consults
- Policy/guidance development
- GDUFA fund managements

DQMM Regulatory Activities (4/1/15 - 4/1/16)

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

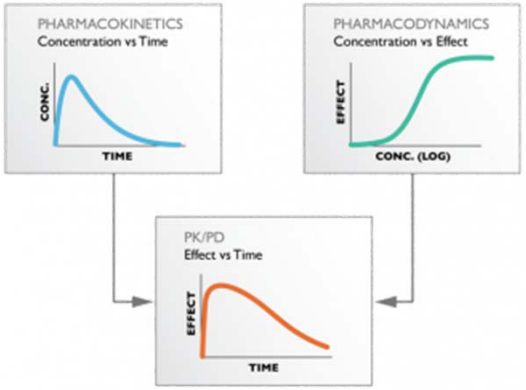
Core DQMM Tool Set

Non-Oral Drug

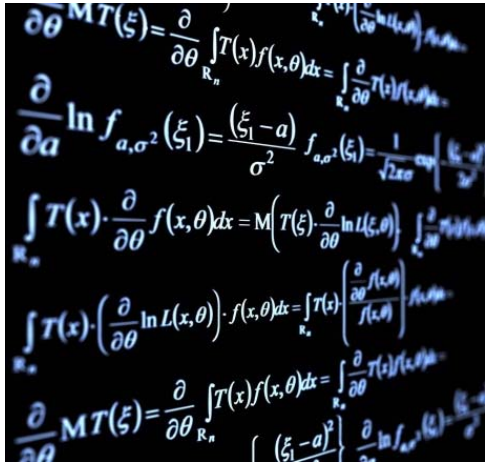
Oral Drug

Our Goal is to support

- Generic drug research
- Policy development
- Regulatory decisions



PK-PD model

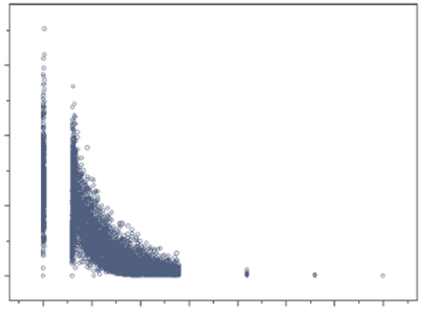


Analytics for complex mixtures
Systems pharmacology
Risk models
Business process models

Release/ Absorption/ PBPK Models

Big Data

Pharmaco metrics



Population model

M&S Matrix

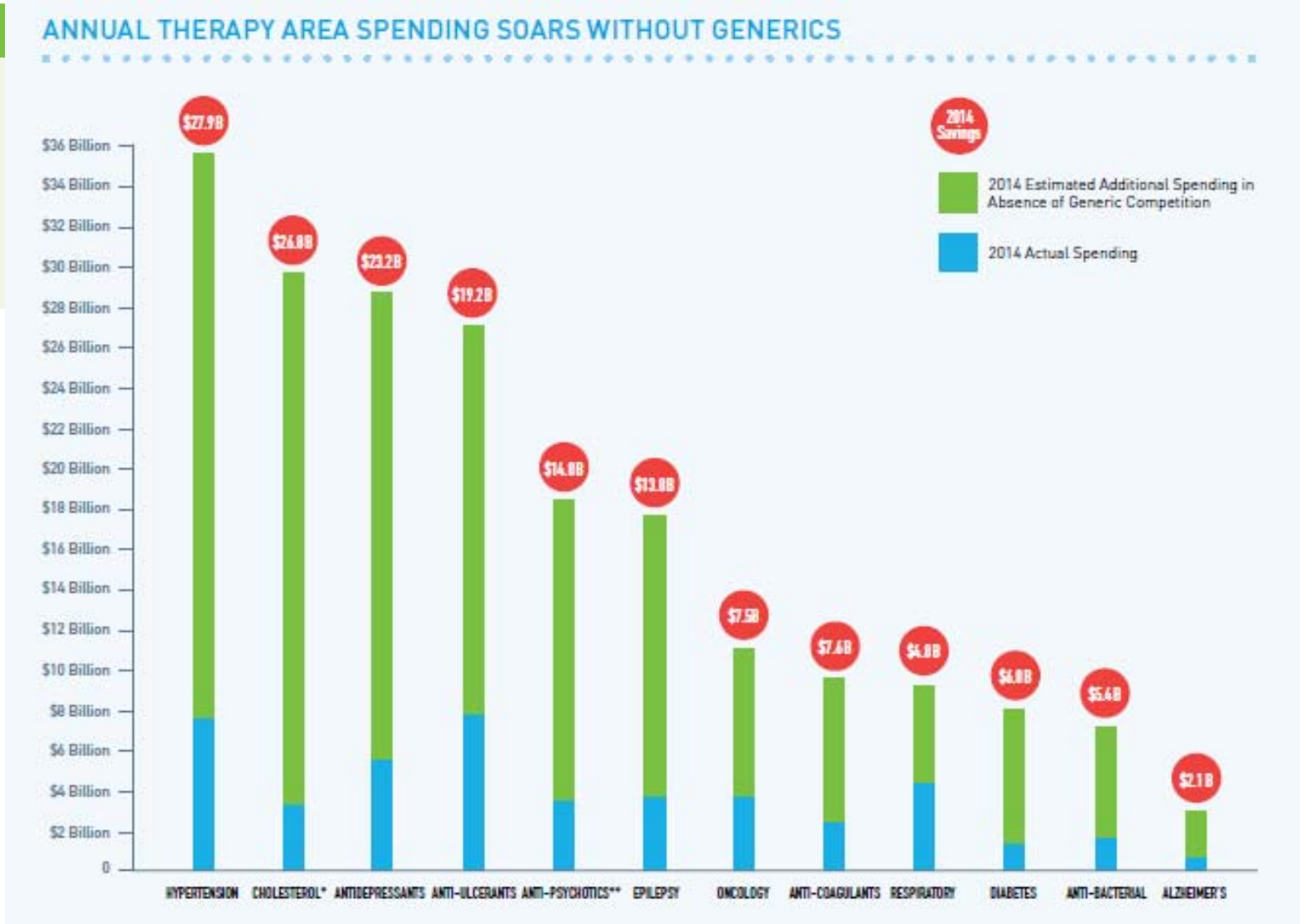
	PBPK	PK/PD	Big Data (Liang)
Complex	Non-oral delivery models	Sensitivity of clinical BE	Advanced Analytical Methods (Meng)
Solid Oral	Oral absorption	NTI, pAUC	PK Data Warehouse (Andrew)
Post-Market	Failure mode	Clinical Impact	Signal detect,risk

Increasing Impacts of Generics on US Healthcare System

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

IMS, Medicines Use and Spending in the U.S. April 2016

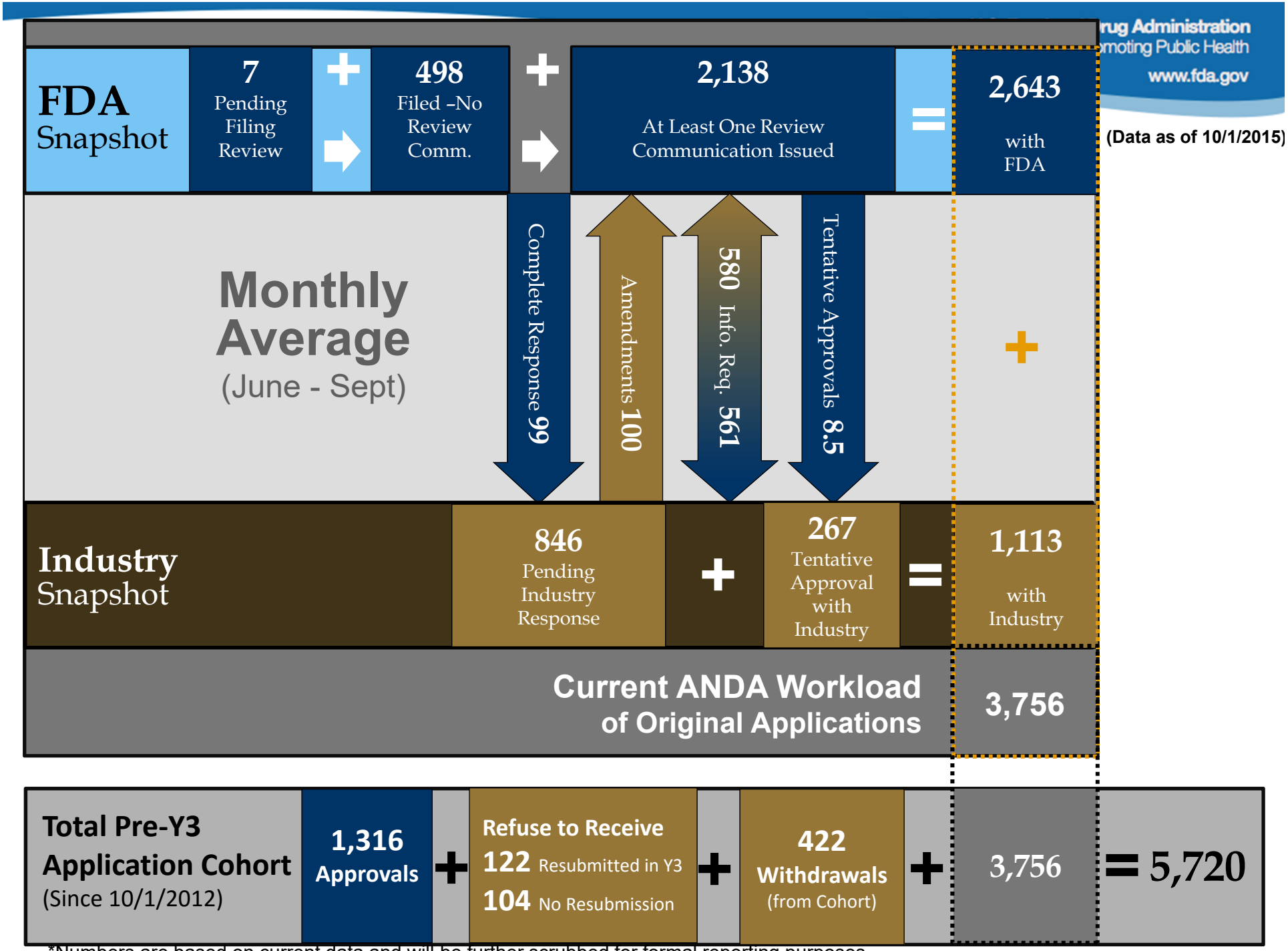
Savings and Challenges with Generic Drugs



NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements		Generic Drug ANDA Requirements
1. Chemistry	O	1. Chemistry
2. Manufacturing	P	2. Manufacturing
3. Controls	Q	3. Controls
4. Labeling		4. Labeling
5. Animal Studies		
6. Clin/Pharm St.		5. Bioequivalence
7. Clinical Studies		

By Dr. Dale Conner



*Numbers are based on current data and will be further scrubbed for formal reporting purposes

Purpose of UCSF-Stanford CERSI Visit

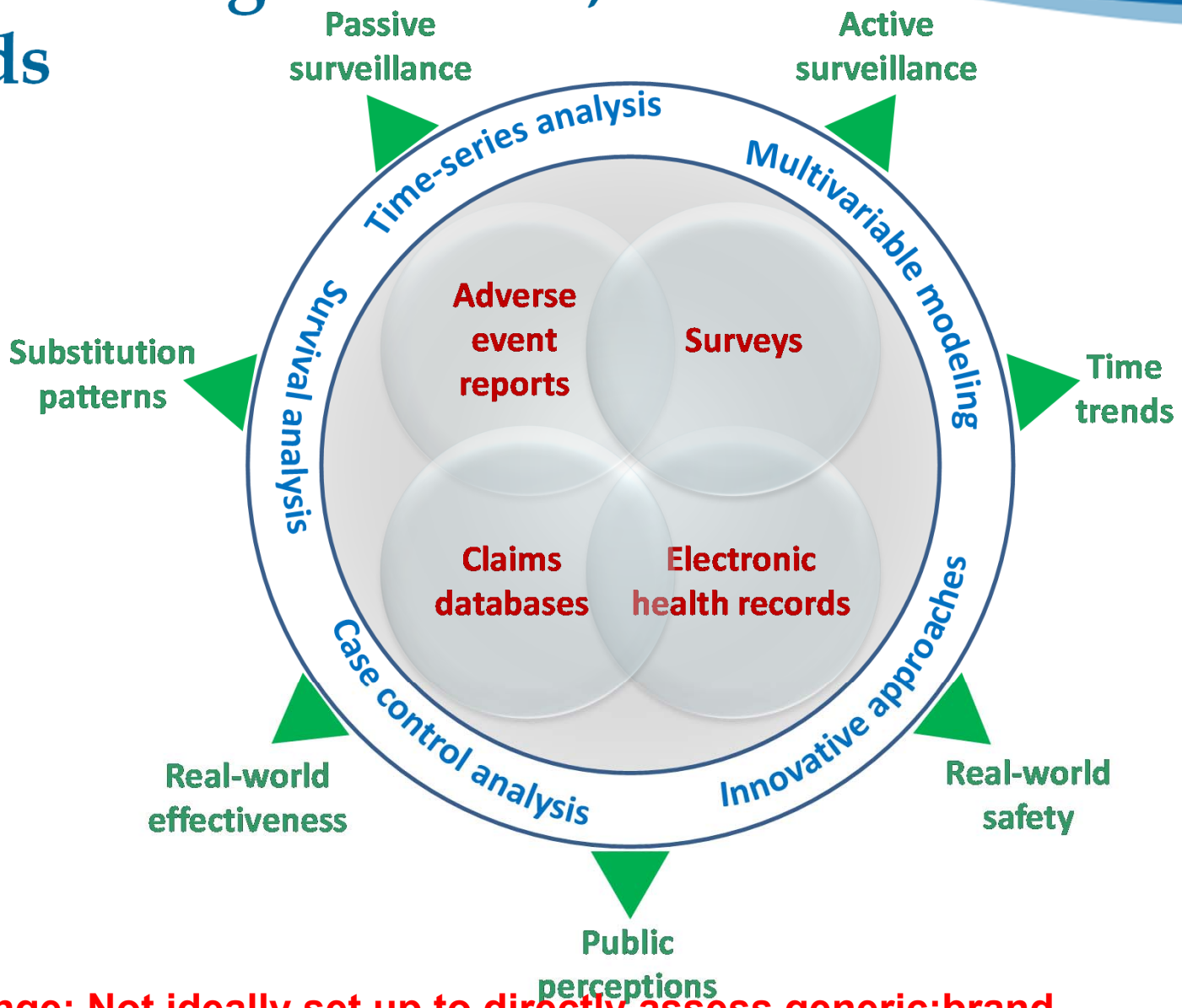
How can we assess therapeutic equivalence in a post marketing stage by taking advantage of new technologies?

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



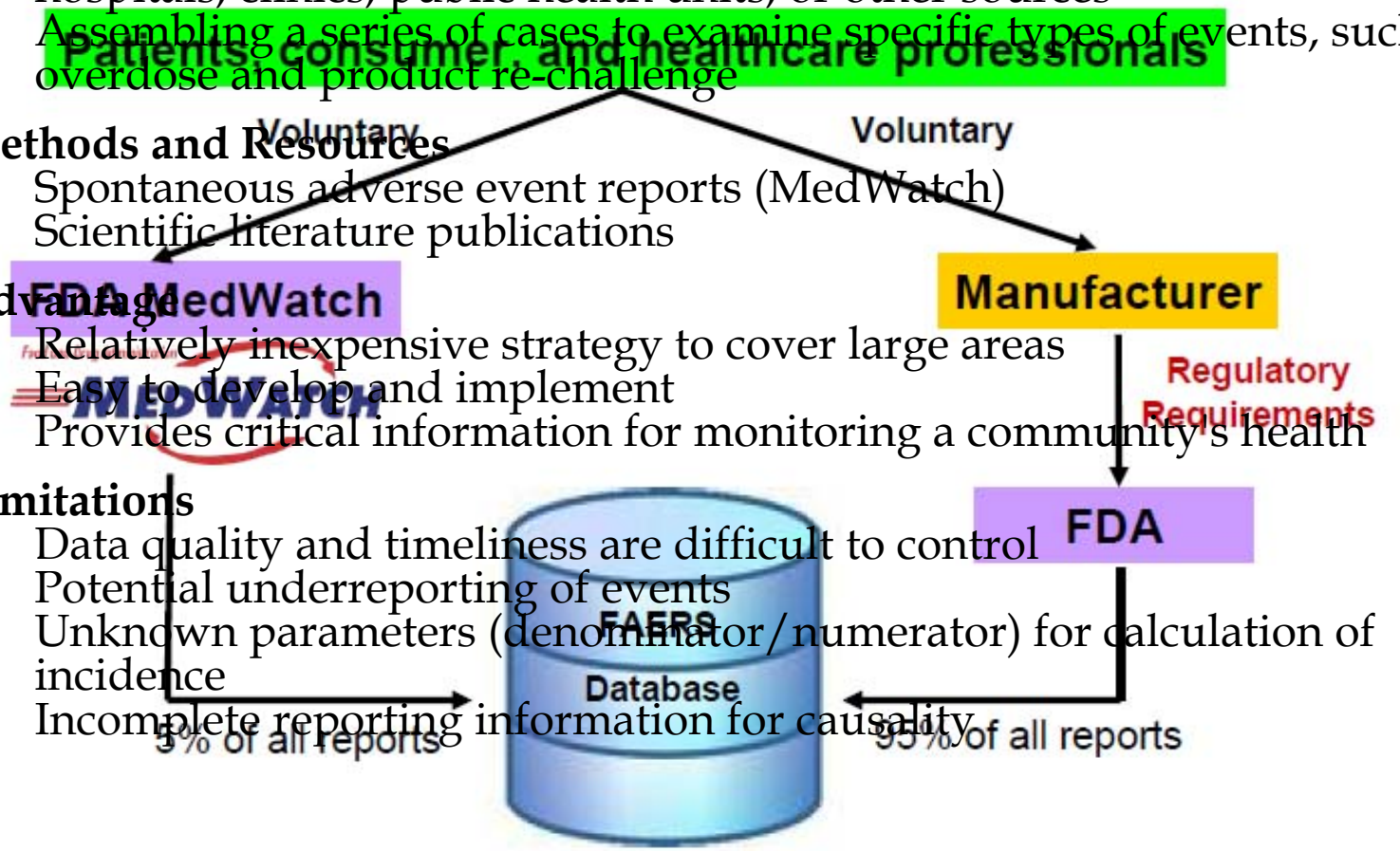
Challenge: Not ideally set up to directly assess generic:brand therapeutic equivallance

Passive Surveillance

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

How Postmarketing Reports Get to FDA

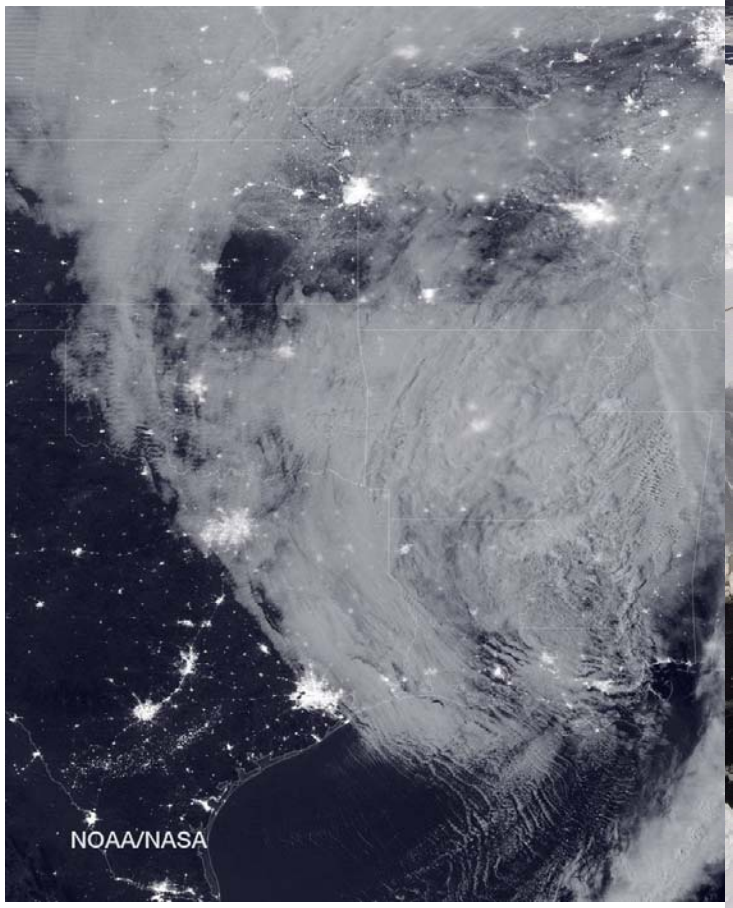
- **Definition and objectives**
  - A system by which a health jurisdiction receives reports submitted from hospitals, clinics, public health units, or other sources
  - Assembling a series of cases to examine specific types of events, such as overdose and product re-challenge
- **Methods and Resources**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

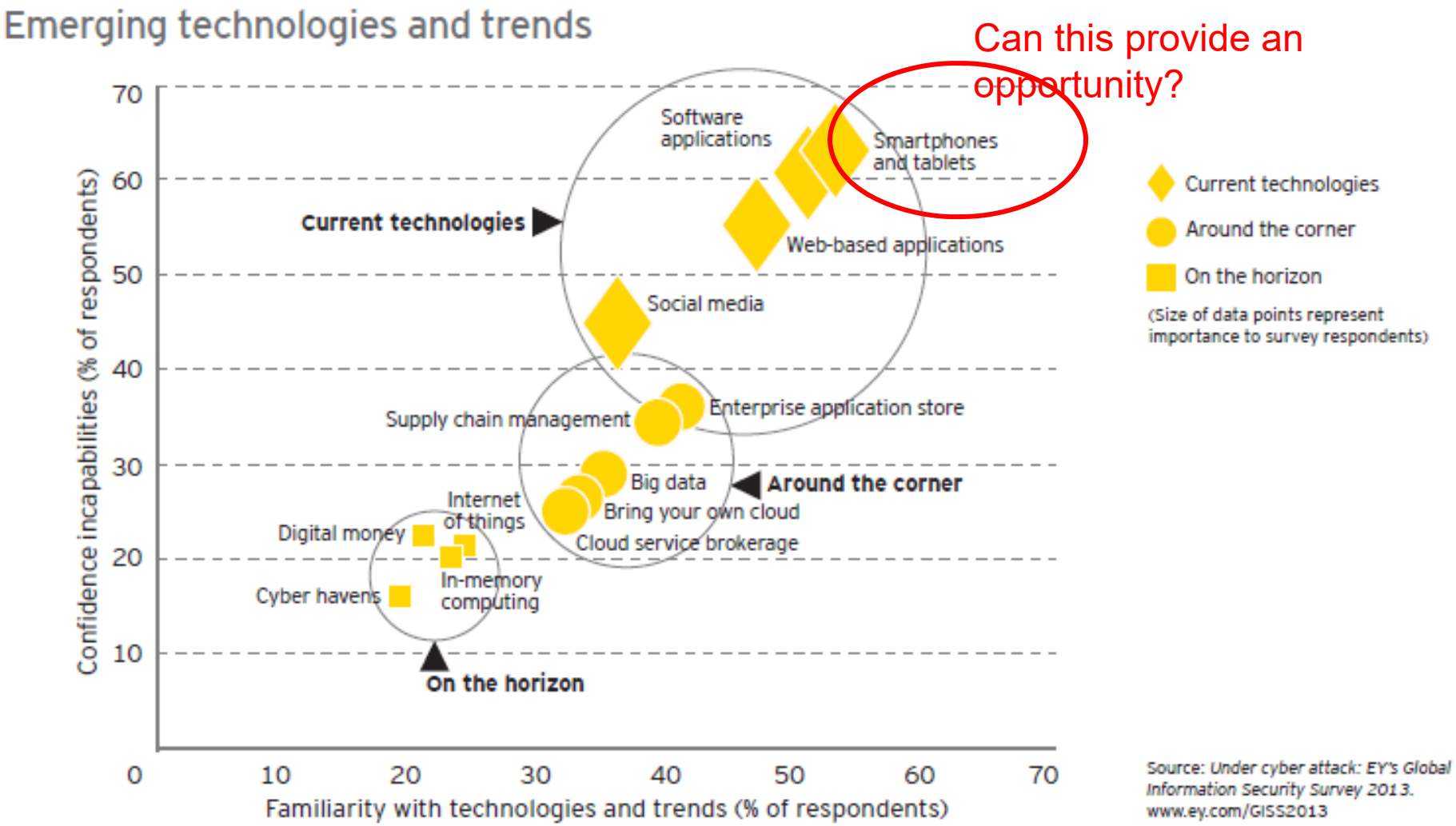
Component of a Good Report/Documentation in AE Report

- 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

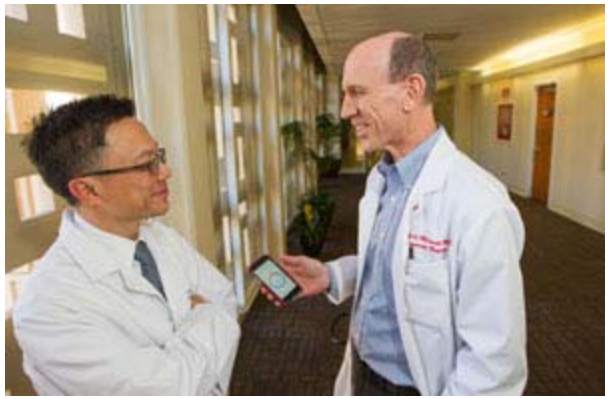
Realization of Information Collection in a Modern Data Era



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

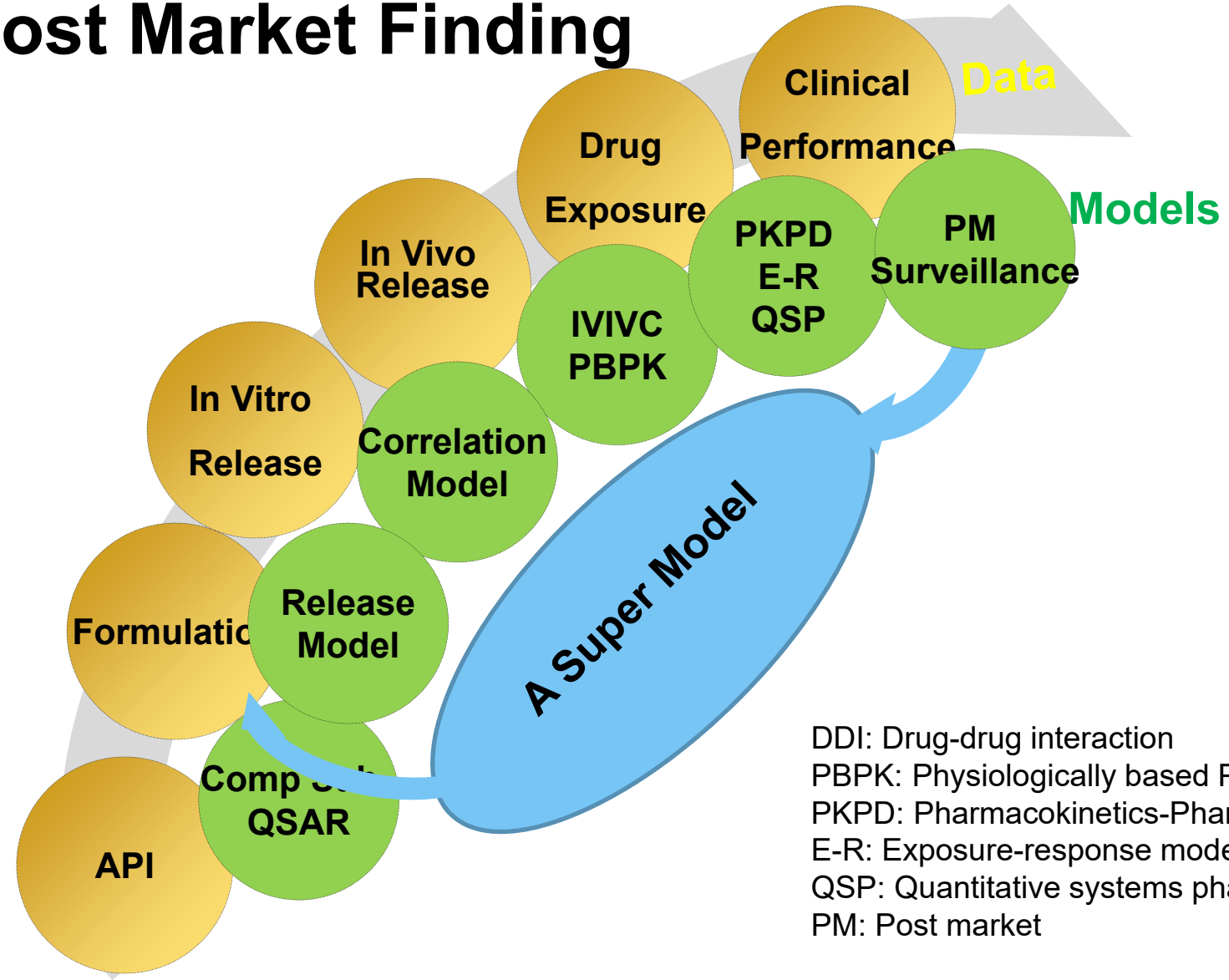
http://www.surveyswipe.com/passive-data-collection.html



http://stanfordmedicine.org/communitynews/2015summer/app.htm

- Use information/model to confirm study finding

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?

Acknowledgement

ORS IO

- Robert Lionberger PhD
- Wenlei Jiang PhD

DQMM (in alphabetical order)

- Sarah Dutcher PhD
- Xia Pu PhD
- Meng Hu PhD
- Zhong (John) Wang PhD