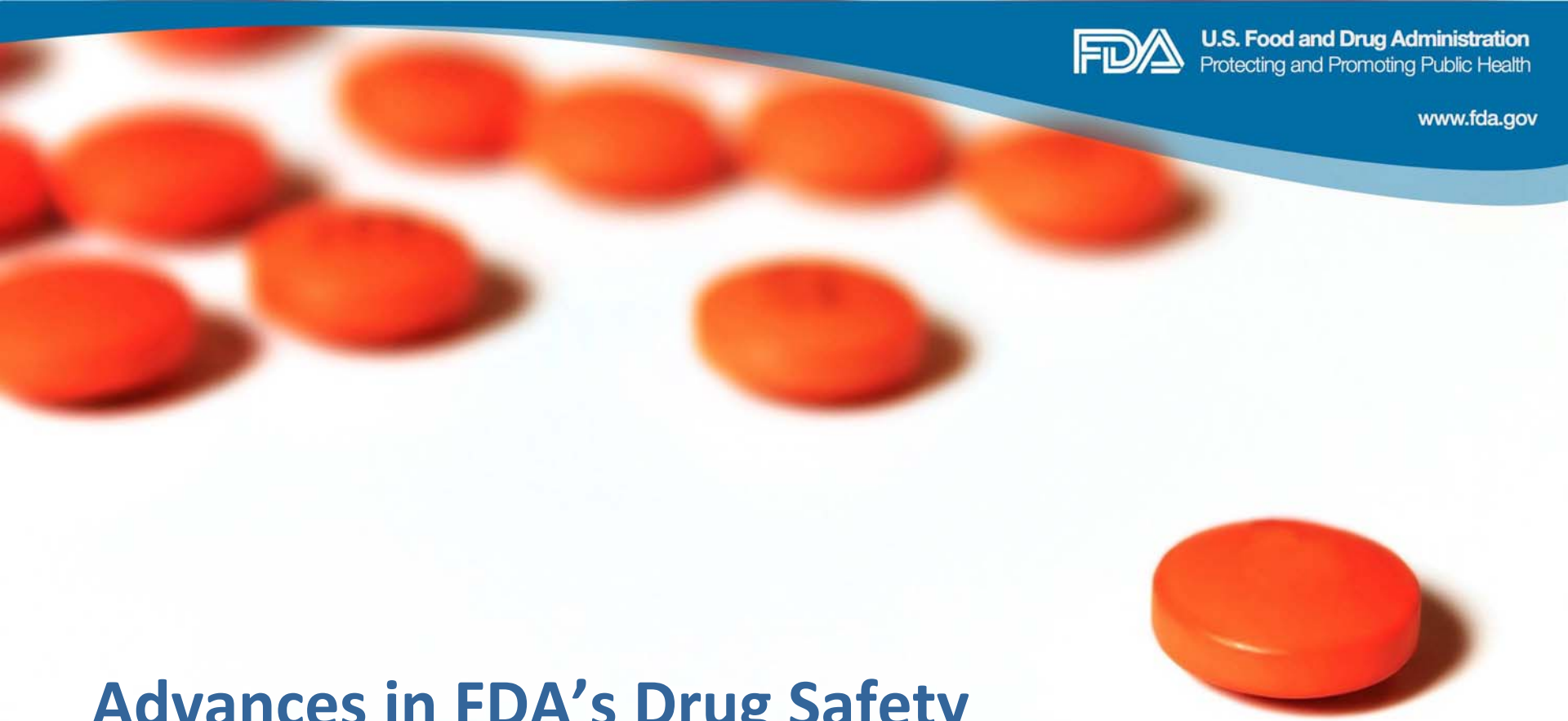

Advances in FDA's Drug Safety Program

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Food and Drug Administration

For the Association of Health Care Journalists
Health Journalism: 2012 Program
Saturday, April 21, 2012

Topics

- Announcing a milestone in FDA's drug safety program
- Future directions for drug safety science
- Current Congressional activity: considering user fee programs for prescription generic, and biosimilar drugs, and associated legislation

DRUG SAFETY

"Unshackle the FDA From Rules That Kill Innovation"

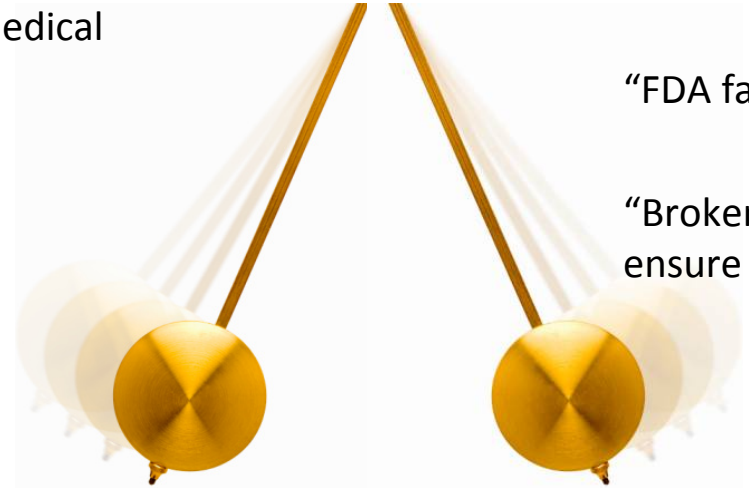
"FDA: Innovation or Stagnation?"

"Is the FDA killing innovation?"

"FDA's new policies threaten innovation"

"FDA should encourage medical innovation"

INNOVATION



"Rush decisions by FDA may subvert drug safety"

"FDA and Drug Safety: A proposal for sweeping reforms"

"FDA's drug safety system fails to protect public"

"FDA failing in drug safety"

"Broken government: FDA failure to ensure drug safety"

SAFETY

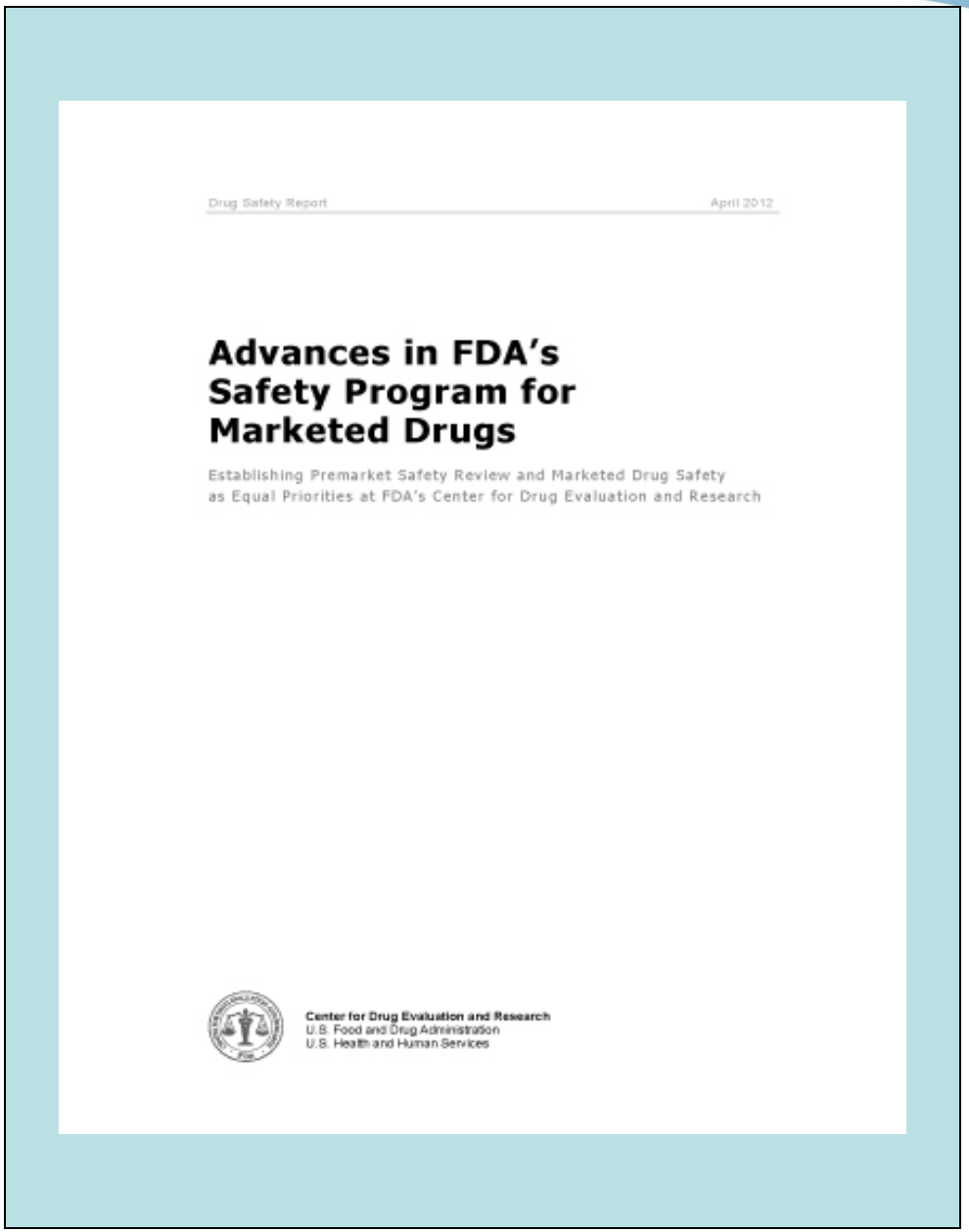
NOT A DICHOTOMY: PATIENTS WANT NEW THERAPIES AND ASSURANCE OF SAFETY

Early 2000's: Drug Safety

- Vioxx and other safety problems emerged
- Traditional approach: Careful premarket review, then launch into healthcare system and await results from spontaneous reporting
- FDA (and the health care system generally) lacked the needed tools for intensive postmarket surveillance:
  - Scientific
  - Regulatory/legal
  - Communication

Today's announcement

- We have reached an important goal in managing the safety of marketed drugs
- Building on new legislation and resources, new scientific tools, new procedures, better communications, and organizational changes
- FDA now applies the same emphasis and intensity to marketed drug safety that is used for premarket review

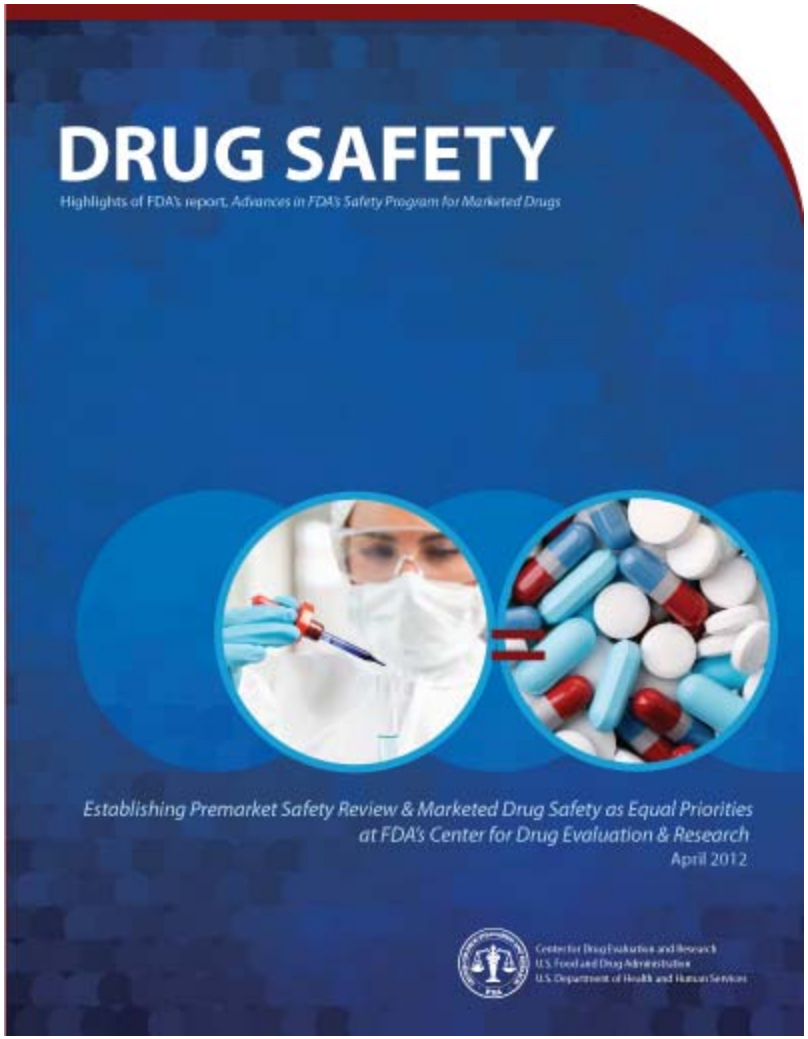


Reporting positive change in protecting public health through advances in drug safety

Priority on safety…

<u>throughout the product life cycle</u>

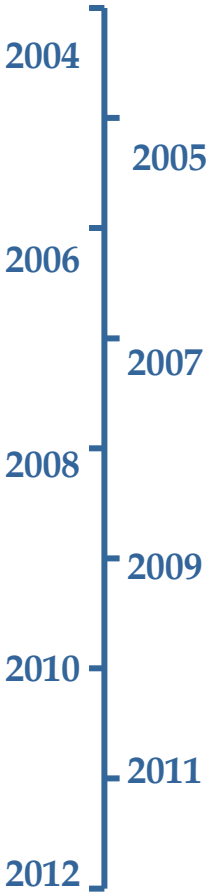
Also available:



Report Highlights Document

Regulatory Science Document

Long-term fundamental change



FDA recognizes need to balance focus on drug safety throughout the product lifecycle

Institute of Medicine provides recommendations

FDA Amendments Act (FDAAA) provides FDA with a wide array of new drug safety authorities and resources

Launched Safety First, Safe Use, and Equal Voice Initiatives

Strengthening Drug Safety Science

Improved Drug Safety Communications

Increased resources

Made organizational changes

FDA Implemented:

- **Safety First**: Enhancing the quality, timeliness, and transparency of safety decisions throughout the drug's life cycle
- **Safe Use**: Reducing preventable harm from medications
- **Strengthening drug safety science**: New capabilities for detecting, investigating, managing, and monitoring drug safety issues
- **Enhanced Communications**: Earlier and more useful communication about drug safety

safetyFIRST

- Prioritizing postmarket safety issues according to their degree of risk to patient safety
- Enhancing quality and timeliness of specific drug safety decisions
- Ensuring drug safety decisions are made collaboratively, using a team model that considers all relevant scientific viewpoints
- Implementing drug safety authorities and responsibilities authorized by Congress in FDAAA

Safe Use

- Collaborating to reduce preventable harm from medications
  - With other federal agencies, health care professionals, consumers, and others interested in drug and patient safety

- Examples:
  - Preventing acetaminophen toxicity
  - Safe use of antipsychotic drugs in elderly
  - Avoiding errors in prescribing and using opioid products

Strengthening Drug Safety Science

- Developed a system for postmarket risk identification and analysis
- Secure access to electronic health care information of more than 125 million patients

Sentinel Initiative

- Personalized medicine – "Pharmacogenomics"
- Enhanced statistical analysis and epidemiology studies

Enhanced Communications

- Communicating safety issues to the public as early as possible
- Single format for communicating drug safety issues
  - "Drug Safety Communication"
- Research most effective methods for communicating drug safety issues
- Increasing publications in medical journals to explain FDA evidence and analyses
- Seeking advice from federal partners and outside risk communication experts on how to communicate risk

Growing evidence of change…

- With new FDAAA authorities:
  - Over 385 drug safety studies or clinical trials required for drugs already on the market
  - 65 times we have required manufacturers to make safety labeling changes to their products
  - Required manufacturers to implement risk evaluation and mitigation strategies

Growing evidence of change…

- Organizational changes have included:
  - Doubled the size of staff in CDER's Office of Surveillance and Epidemiology, the office primarily responsible for postmarketing drug safety at FDA
  - Established specific safety positions in each of our 18 drug product review divisions
- Increasing communications about drug safety issues:
  - 68 drug safety communications in 2011 (up from 39 in 2010)

Our announcement

In summary…

- Our efforts in recent years have contributed to reaching parity between premarket and postmarket priorities
- We apply a team-oriented approach to drug safety issues
- We provide an atmosphere that encourages all relevant disciplines an equal voice
- …and drug safety science is dynamic and evolving!

Future drug safety science

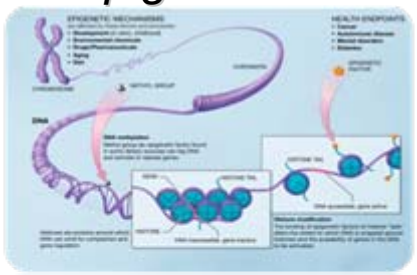
Systems Biology; Personalized Medicine; Pharmacogenomics: what will they do for drug safety?

- Prediction of clinical adverse drug reactions before they happen
- Identification of patients who are particularly susceptible to adverse reactions
- Systems pharmacology: understand potential mechanisms of possible adverse reaction

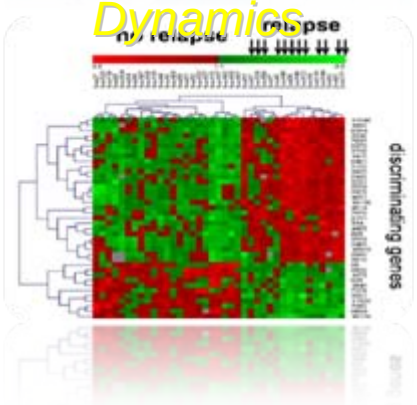
Enhancing the Analysis Model

Genetics

Epigenetics



Cell Dynamics



Cell

DNA | Protein | Membrane

Phenotype

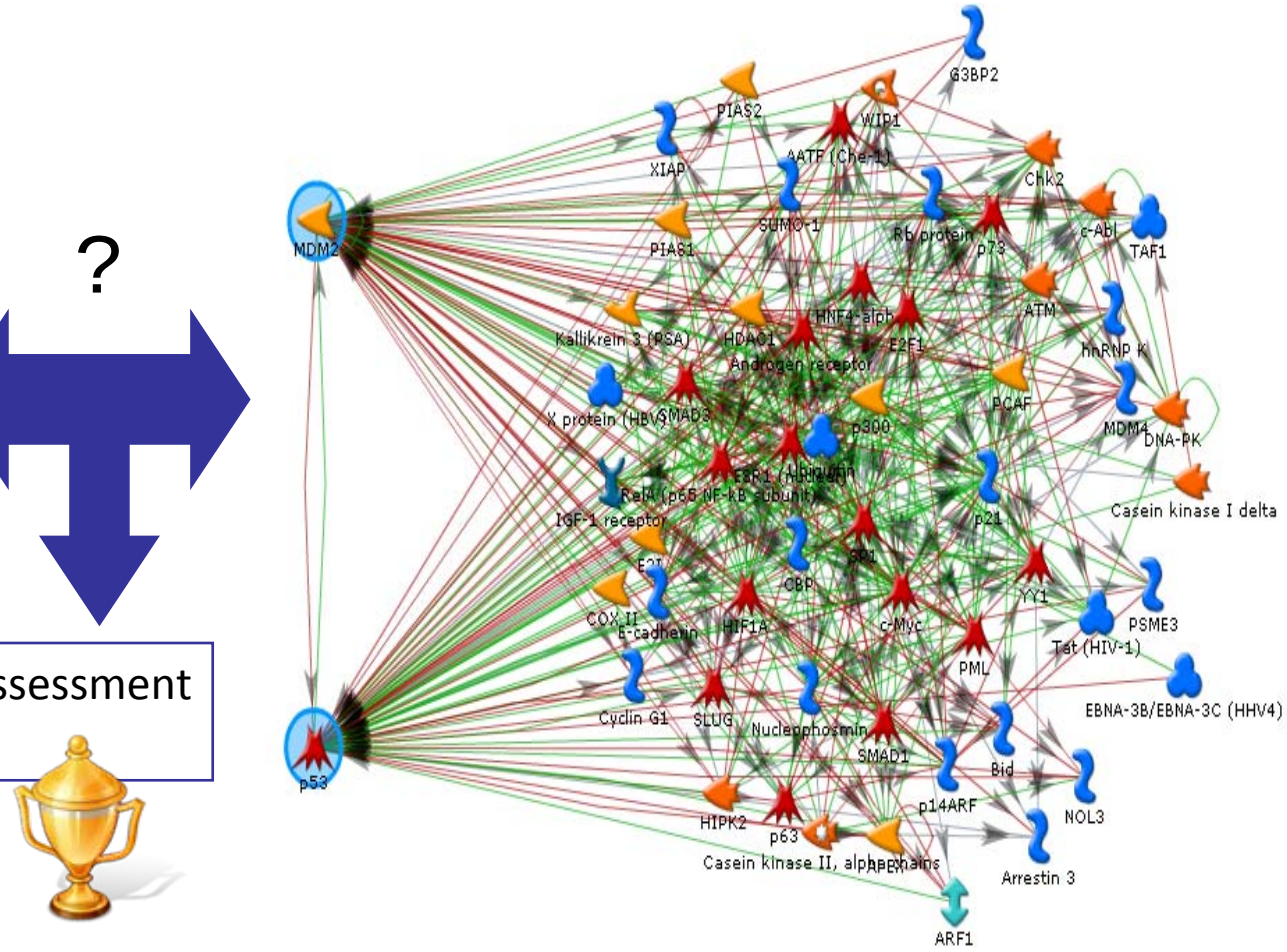
The Challenge

Systems biology-based assessment of target-related toxicity and understanding of mechanisms of toxicity

Structure related toxicity assessment

?

Integrated assessment of toxicity



Examples

- Abacavir (HIV drug): can screen patients to remove those at high risk for hypersensitivity reactions BEFORE they are treated

- Targeted cancer drugs: Don't treat people who have a low chance of response

- Stevens-Johnson syndrome:
  - Life threatening skin reaction
  - Now can screen out patients at high risk

USE OF ELECTRONIC HEALTH DATA

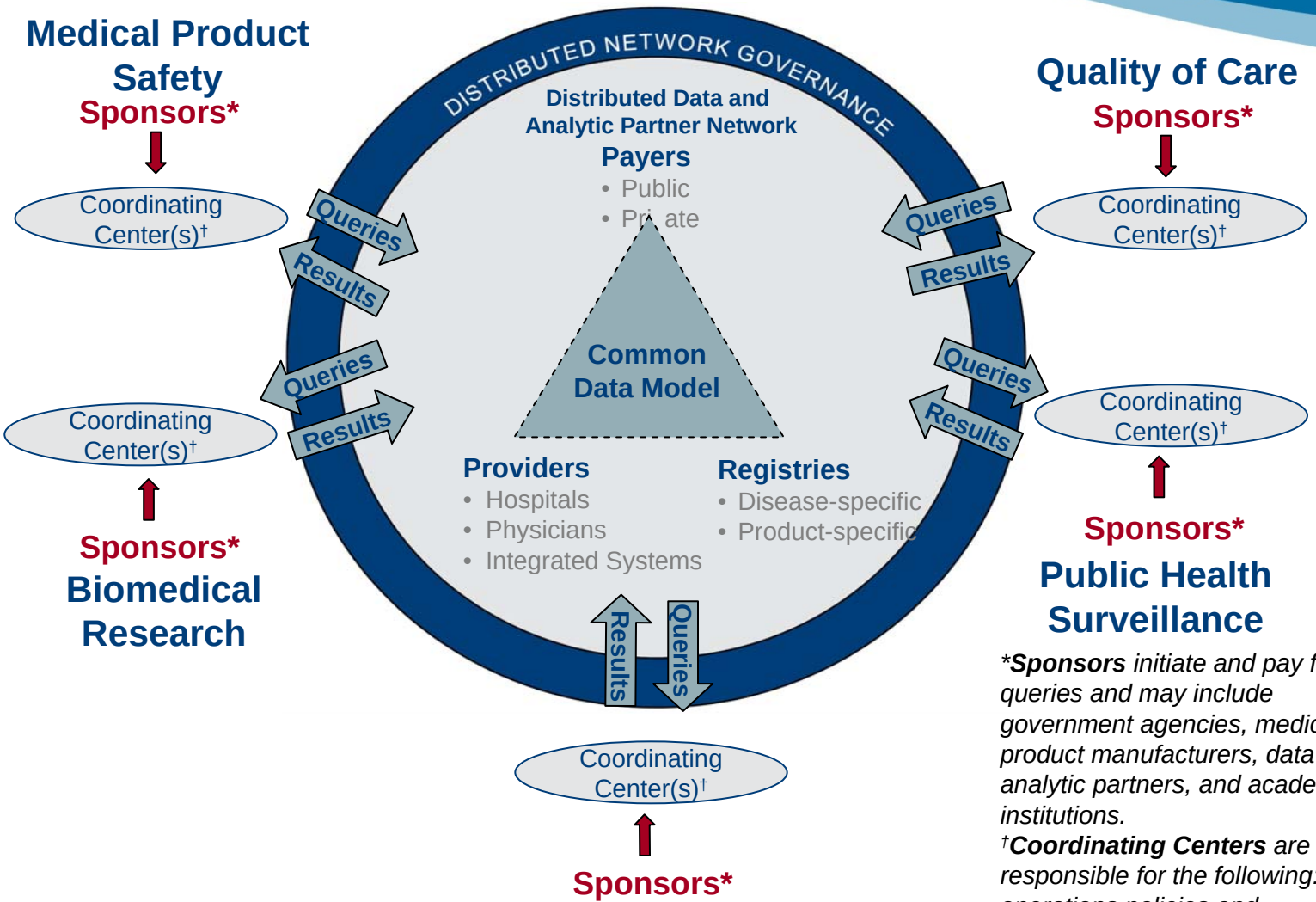
FDA Amendments Act of 2007

Section 905: Active Postmarket Risk Identification and Analysis

- Establish a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including
  - at least 25,000,000 patients by July 1, 2010
  - at least 100,000,000 patients by July 1, 2012
- Access a variety of sources, including
  - Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs)
  - Private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data)

The Sentinel Initiative

- Data Partners
  - Private: Mini-Sentinel pilot
  - Public: Federal Partners Collaboration
- Industry
  - Observational Medical Outcomes Partnership
- All Stakeholders
  - Brookings Institution cooperative agreement on topics in active surveillance



Sponsors *initiate and pay for queries and may include government agencies, medical product manufacturers, data and analytic partners, and academic institutions.*

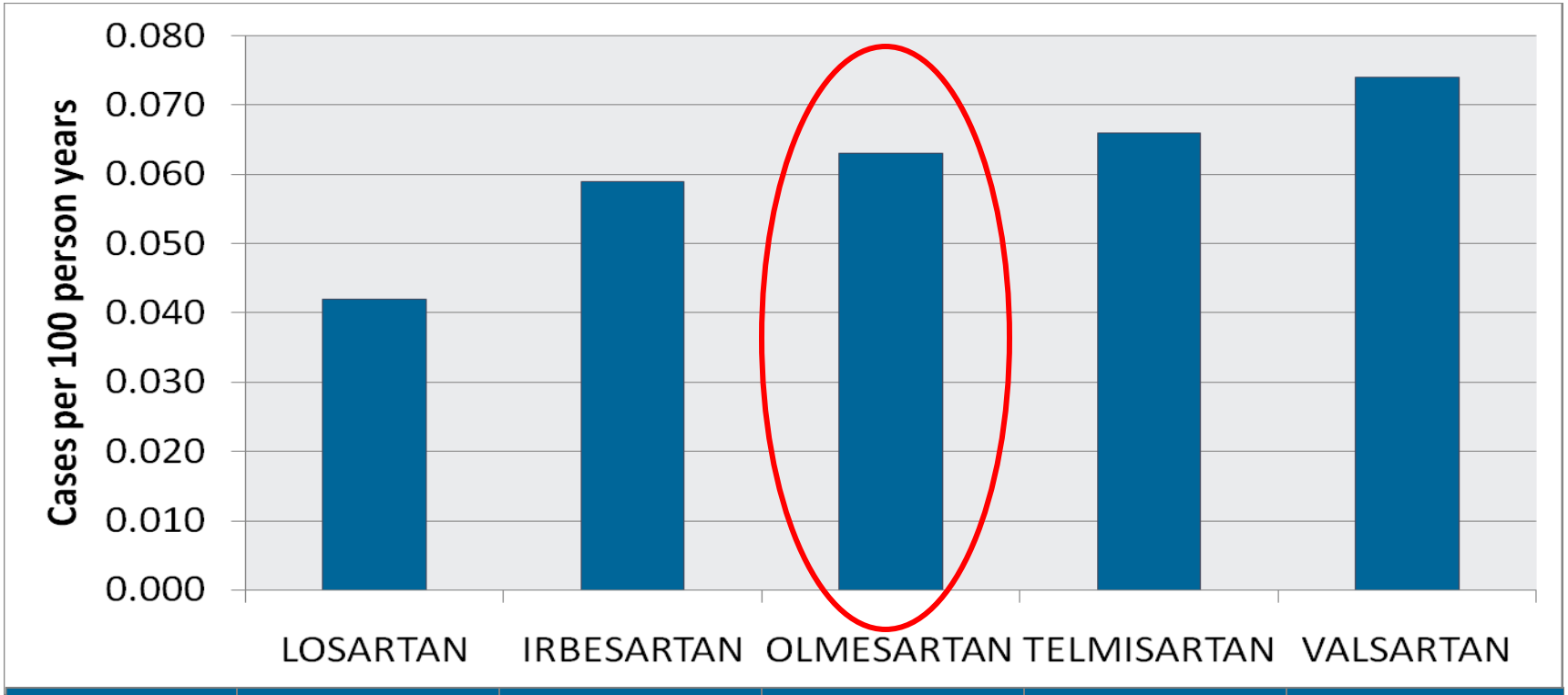
†**Coordinating Centers** *are responsible for the following: operations policies and procedures, developing protocols, distributing queries, and receiving and aggregating results.*

Sentinel in Action - Olmesartan

- Potential "signal" identified from FDA reports that **olmesartan** might cause more celiac disease than other drugs in its class

- Sentinel question: How many patients taking olmesartan had developed celiac disease compared to those taking other drugs for high blood pressure?

Cases of Celiac Disease



Cases	63	10	17	5	50
New users	235,630	40,071	81,560	24,596	153,159

ARBs: New users after ≥365 day washout; Celiac Disease: 1st dx code after >365 day without diagnosis.

Sentinel in Action -- Rapid Postmarket Assessment of Varenicline Cardiovascular Safety

- Background
  - FDA Drug Safety Communication – "Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease" http://www.fda.gov/Drugs/DrugSafety/ucm259161.htm
  - Singh et al. Meta-analysis of CVD AEs in varenicline RCTs (Canadian Medical Assn J – July)

Cohort	New users	Follow-up (in years)	Composite CV outcome	Incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)	Mantel-Haenszel incidence rate ratio (95% CI) *
All initiators						
Varenicline	260,660	32,070.43	109	0.42 (0.34, 0.50)	3.40 (2.79, 4.10)	**1.52 (1.21 1.91)**
Bupropion	745,004	209,477.70	452	0.61 (0.55, 0.66)	2.16 (1.96, 2.37)	
Initiators with a tobacco use code						
Varenicline	89,519	11,197.01	56	0.63 (0.47, 0.81)	5.00 (3.78, 6.49)	**1.02 (0.71, 1.47)**
Bupropion	113,378	22,942.15	118	1.04 (0.86, 1.25)	5.14 (4.26, 6.16)	
Initiators of smoking cessation products						
Varenicline	260,660	32,070.43	109	0.42 (0.34, 0.50)	3.40 (2.79, 4.10)	**0.98 (0.43, 2.23)**
Bupropion	11,203	1,462.38	6	0.54 (0.20, 1.17)	4.10 (1.51, 8.93)	

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* Adjusted for age, sex, and health plan

Varenicline Conclusions

- Assessment of cardiovascular disease (CVD) risk associated with smoking cessation drugs, restricted to likely smokers, provided one piece of evidence against a major public health concern

- The higher risk of cardiovascular disease events observed among new users of varenicline compared with all bupropion new users was likely largely attributable to confounding by smoking status.
  - Most varenicline new users would be smokers while many bupropion new users might be non-smokers being treated for depression, a probable, but weaker risk factor for CVD events than smoking.

Current legislative activity: new user fee programs and associated policy riders

Prescription Drugs – “PDUFA V”

Generic Drugs

Biosimilars

PDUFA

- Began in 1992
- Innovator industry pays fees for government services
- Cut FDA review times by more than half
- Must be re-authorized every 5 years by Congress
- PDUFA 3 and 4 included money to support postmarket drug safety activities
- Currently PDUFA 5 up for re-authorization; current program expires September 30
- Extensive negotiation with broad public input resulted in recommendations sent to Congress in Jan 2012

PDUFA 5 Proposals

- "Patient centered drug development"
  - Meetings to collect information on patient's view of disease burden and acceptable benefit/risk tradeoffs
  - Develop patient reported outcome measures
  - Semi-quantitative benefit/risk framework
- Improve drug safety
  - Support for Sentinel and work on drug meta-analyses
  - Pharmacogenomics
  - Standardize REMS
- Small business and new innovator assistance
  - Staff to interact with inexperienced sponsors
  - Rare disease development assistance

Generic Drug User Fee Program
Negotiation Process

- Multiple Public Meetings and Stakeholder Updates
- Docket FDA-2010-N-0381 open for entire period
- 90% of comments support some type of generic user fee
- 18 face-to-face negotiating sessions with 3 industry trade associations, from February 28 to September 7
- Participants: FDA, GPhA, EFCG and SOCMA's BPTF
- Materials from negotiating sessions, public meetings, FDA speeches and presentations posted to the web

http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

Proposed Generic Fee Program

The program advances:

- Timely access to generic drugs
- Confidence in the quality of generic drugs, wherever they are sourced around the world; would pay for inspections worldwide
- Level playing field for competitors in US and outside US
- Regulatory science for bioequivalence methods

BIOSIMILAR User Fee Program

Industry and FDA agreed to a meeting structure that reduces uncertainty in development programs

Biosimilar Initial Advisory Meeting	BPD Type 1 Meeting	BPD Type 2 Meeting	BPD Type 3 Meeting	BPD Type 4 Meeting

Policy Proposals

- Innovation: "Breakthrough therapies" and clarifying accelerated approval pathway
- Antibiotic development: GAIN act—incentives for developing therapies for drug-resistant organisms
- Drug supply chain security and "track and trace" for distribution chain
- Proposals for changing FDA procedures and reporting
- Medical gas regulation
- Multiple others

Summary

- FDA announcing major milestone in managing the safety of marketed drugs
- Still more work to do
- Scientific advances will continue to help us learn more, faster and perhaps predict safety issues BEFORE they happen
- Electronic health data, particularly EHR data, will continue to boost our ability to find out what happens in the real world more quickly
- Meanwhile, Congress considering major legislation on drug user fees, and related policy matters