Public Health, Epidemiology and the Regulation of Pharmaceuticals

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Role of the drug regulator

• Access to medicines
  – Assess efficacy, safety, quality

• Protection of the public
  – During clinical trials
  – Postapproval

• Information to the public
Drug Regulation

- Public health-focused
- Science-based
- Regulatory activity
Drug Development Timeline

Pre-Human Research

Submit IND

Phase 1

Submit Application

Phase 2

Phase 3

FDA Review

Marketing and Phase 4
The Drug Lifecycle

Knowledge about Effects in Humans

Approval

Ongoing post-approval drug safety monitoring and benefit-risk assessment

Pre-Human Research  |  Phase 1  |  Phase 2  |  Phase 3  |  FDA Review  |  Marketing and Phase 4

Time
Goals of Drug Safety Surveillance

• Identify previously unknown drug-related adverse events
• Learn more about known drug-related adverse events
• Learn more about how drugs are used in ways that may not promote safe use
Growing Volume of Medication Usage - US

Total number of prescriptions dispensed from U.S. outpatient retail pharmacies, Years 2000 - 2011

Public Concern

Failing the Public Health — Rofecoxib, Merck, and the FDA

Eric J. Topol, M.D.

On May 21, 1999, Merck was granted approval by the Food and Drug Administration (FDA) to market rofecoxib (Vioxx). On September 30, 2004, after more than 80 million patients had taken this medi-
dial infarctions associated with rofecoxib and the numerical, albeit not statistically significant, ex-
cess associated with celecoxib, was that “it is mand-
datory to conduct a trial specifically assessing car-

Rosiglitazone and the need for a new drug safety agency

PERSONAL VIEW Silvio Garattini, Vittorio Bertele’

The recent news about the suspension of rosiglitazone, a blockbuster that had underestimated or overlooked it. The usual true Europe-wide network such as the current
Increased Focus on Postmarket Drug Safety

- Agency actions to strengthen postmarket drug safety systems
- Institute of Medicine Report 2007
- Passage of the Food and Drug Administration Amendments Act (FDAAA) – September 2007
FDAAA

Public Law 110–85
110th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the “Food and Drug Administration Amendments Act of 2007”.

Landmark legislation
Increased funding for postmarket drug safety
Increased transparency

New authorities allowing FDA to require:
- Postmarketing safety studies and clinical trials
- Safety labeling changes
- Risk evaluation and mitigation strategies

Sept. 27, 2007 [H.R. 3580]
Pharmacoepidemiology

“Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people.”

(Strom B. Pharmacoepidemiology 5th Ed., 2012)
Some Features About Pharmacoepidemiology

- Exposure is intentional (usually)
- Medicines are usually given to people with an illness
- Prescribing decisions may (and often do) take into account factors that are related to outcomes of interest
- Confounding and bias can be big problems in observational data
  - Confounding by indication
  - Channeling bias
Historically....

- Individual case safety reports were the main source of drug safety information
  - Good for rare events that are usually the result of drug or toxin exposure
    - Acute liver failure
    - Stevens-Johnson Syndrome
    - Torsades de pointes
- Most drug withdrawals and major safety actions are related to one of these events
Today….

- Large databases are available for drug safety studies
- We can detect much more subtle adverse drug effects including increases in relatively common events
  - Common in the population
  - Manifestation of the disease being treated
Major Methods in Pharmacoepidemiology

- Case Reports
- Case Series
- Observational Studies
- Clinical Trials
Case Reports and Case Series - Challenges

- Case reports, as a whole, often lack important clinical details
- Need to involve stakeholders
- Need refinement of signal detection methods, as numbers of reports increase
- Can this be automated?
Growing Number of Adverse Event Reports - US

Number of ISRs
nonexpidited
expedited
direct

Calender Year

Clinical Trial Data Are Important for Adverse Events That Have a High Background Prevalence

- Tegaserod
  - Myocardial infarction
- Sibutramine
  - Myocardial infarction
- Anti-depressants
  - Suicidal behavior
- Anti-epileptics
  - Suicidal behavior
Clinical Trials for Drug Safety - Challenges

• Proper endpoint selection
• Relevant patient population
  – May be different from population used for efficacy studies
• Choice of comparator
  – Active vs. placebo
  – Clinical relevance
• Adequate sample size
• Ethical issues
  – Institute of Medicine Report 2012
Observational Studies Have Revealed Important Safety Findings

- Combined Hormonal Contraceptives
  - Arterial thrombosis
  - Deep venous thrombosis
- Phenylpropanolamine
  - Cerebral hemorrhage
- Pergolide
  - Valvulopathy
Observational Studies in Large Databases - Challenges

• Measurement uncertainty
• Methodologic questions
• Confounding
• Many more
• Missing key information
  – BMI, smoking
Using Large Databases

• Potential source of data for large observational studies
  – Case-control studies
  – Cohort studies
• Need to understand the output of such systems
• Not a replacement for careful clinical evaluation
Observational Studies - Challenges

• Need good data sources
  – Large data sources are not always the best sources

• Need robust methods to adjust for confounders
  – Residual confounding can still be a problem

• If the database is large enough, ANY finding can be statistically significant
  – Need careful interpretation
Effect Measures -- A Not-so-random Sample of Some Recent Drug Safety Issues

Rosiglitazone - MI – FDA RTC meta-analysis – OR

PPI - Hip Fracture – Case-Control Study #1 – OR

PPI - Hip Fracture – Case-Control Study #2 – OR

Oral Bisphosphonates - Esophageal Cancer – Nested Case-Control Study – RR

Oral Bisphosphonates - Esophageal Cancer – Cohort Study – HR

Drosperinone - VTE – Cohort Study – HR

Sources:
Active Surveillance - Sentinel Initiative

- FDA initiative
- Response to FDAAA mandate
  - Active risk identification and analysis system
- Use large databases from multiple sources
- Cover a large number of lives
  - 25 million in 2010
  - 100 million in 2012
- Two components:
  - Mini-Sentinel
  - Federal Partners Collaboration
Governance

What are the keys to a successful public-private partnership?

Data

Which types of data? administrative claims, electronic health records
Which sources? healthcare providers, insurers, data aggregators

Performance

What are appropriate analyses for:
- hypothesis generating?
- hypothesis strengthening?

Architecture

What is the appropriate infrastructure:
- hardware?
- software?
- processes?
- policies?

Methods

How to maintain collaborations and engage research community?

Technology

What are best practices for protecting data?

What are viable data access models:
- centralized?
- distributed?
FDAAA’s Hierarchy for Post-Approval Data

- FDA may require studies only if:
  - adverse event reports and active surveillance system are insufficient to meet purposes
- FDA may require clinical trials only if:
  - study or studies are insufficient to meet purposes
- For already-approved drugs, FDA must have new safety information
Current Challenges

- Deciding what questions need to be answered
- Deciding the best way to answer them
- Understanding the trade-offs in various approaches
- Ethical considerations
- Communications
- Regulatory actions
Traditional Hierarchy of Evidence
From Traditional Hierarchy to Synthesis of Evidence

Traditional hierarchy

Observational Studies

Clinical Trials

Clinical Pharmacology
Toxicology
Other Data

Synthesis of evidence
Drug Safety Communications

Cumulative Number of Drug Safety Communications

Month
No. of DSCs

2011
2010

No. of DSCs

0 10 20 30 40 50 60 70 80

Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec

2011
2010

68
39
Building Capacity

- As drug safety science becomes more important and more complex
  - Need to build more capacity
  - Need to increase collaborations
  - Need to share best practices
- A global endeavor
Thank you