APPROACHES TO STUDYING SAFETY OF MEDICAL TREATMENTS

• Monitoring spontaneous reports to FDA and/or product manufacturer
• Studying drug-outcome associations in existing cohorts
  - Claims data bases
  - Large research cohorts with ongoing follow-up
  - General Practice Research Database (UK)
• Formal studies
  - Observational study of those using treatment
  - Case-control study
  - Randomized comparison of two treatments
  - Meta-analysis of previously conducted studies
ISSUES IN CONSIDERING VALUE OF STUDY APPROACH

- Susceptibility to bias
- Coverage of all relevant populations
- Resources required
- Assurance of accuracy
- Feasible study size
SPONTANEOUS REPORTING

- Possible drug side effect may be observed by patient and/or physician
- Effect may be known (ie, already mentioned in drug label) or unknown
- Physician or patient may report event to FDA (or to drug company, which is then required to convey report to FDA)
SPONTANEOUS REPORTING SYSTEM (SRS)

- A SRS is a data base of all such reports
- FDA maintains multiple such systems
  - Drugs
  - Vaccines (with CDC)
  - Medical devices
  - Foods and cosmetics
  - Veterinary drugs
- Safety surveillance using such systems is called “passive surveillance”
FDA’s ADVERSE EVENT REPORTING SYSTEM

In 2009: 580,904 reports to AERS
• 330,476 from manufacturers (expedited)
• 216,255 from manufacturers (non-expedited)
• 34,173 directly from individuals
FDA AND THE SRS

• Historically the SRS has been the primary focus of FDA safety surveillance efforts
• The worst type of data base imaginable
  - No numerator—reporting is voluntary, and no evidence except (perceived) temporal association that drug caused event
  - No denominator—don’t know how many were exposed
  - No quality control—all reports submitted get put in data base “as is”
  - Subject to influence by publicity
SOME POSITIVES

• Relatively inexpensive to maintain
  - System maintenance
  - Reviewers
  - No expenses for data collection
• Broadest possible net
• Could be the fastest way to identify a newly emerging serious problem
MONITORING A SRS

- For some serious events, temporal association with drug administration alone is highly suggestive or even definitive
  - Anaphylactic reaction within seconds or minutes of exposure
  - Stevens-Johnson syndrome
  - Sudden liver or kidney failure
  - Q-T interval prolongation
MONITORING A SRS

• For serious events that occur “in background,” independently of medication use, SRS less likely to help
  - Suicide and suicide ideation
  - Emergence of autoimmune disease (MS, arthritis)
  - Myocardial infarction and stroke in older populations
  - Autism
SIGNAL EVALUATION

• Early approach at FDA
  - Individual review of reports by physician or pharmacist
  - Reviewer judgment regarding when one or more reports constituted a signal

• More recently
  - Attention to automated approaches
  - Interest in statistically-based procedures
DATA MINING

• DuMouchel: Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system, *American Statistician*, 1999 (with commentaries)

• Innovative step in automated signaling of potential problems
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IMPLEMENTATION COMPLEX

• Many drug-event associations will be artifactual
  - Events more common in older populations will be more frequently temporally associated with drugs given to older people
  - If unsafe medication is commonly given to people also receiving a safe medication, the latter will also be associated with events

• Can account for some known confounding issues in the signal-generating algorithm
ARE SRS DATA WORTH THE EXPENSE OF MAINTAINING THE SYSTEM AND MONITORING THE DATA?
FINDINGS BASED ON SRS DATA: BIOLOGICS

• Hemolysis following plasmapheresis due to errors in diluting albumin with sterile water
• IGIV-associated adverse effects
  - Renal insufficiency
  - Aseptic meningitis
  - Thromboembolic events
• TB and other opportunistic diseases associated with TNF inhibitors
• Hair loss following vaccination
• Hemoglobinuria following anti-D immunoglobulin for ITP
• Pure red cell aplasia associated with erythropoetin
• Neurological effects of yellow fever vaccination
• Thromboembolic events following recombinant human coagulation factor Viia
OTHER REPORTS BASED ON SRS DATA: BIOLOGICS

• Overview of reports following introduction of new vaccines
• Overview of reports associated with new biological therapies
  - Botulinum toxin
  - Palivizumab
• Description of syndromes of interest
  - Hypotonic-hypo responsiveness syndrome following childhood vaccination
  - Anaphylaxis following vaccination
  - Injection site reactions following interferon beta-1b treatment for multiple sclerosis
HEALTH CARE DATABASES

• **Advantages**
  - Data already collected for financial purposes
  - Definable numerators and denominators

• **Limitations**
  - Medical information restricted; chart review often required
  - Little information on outpatient events (including deaths)

• **Examples**
  - Kaiser
  - Partners
  - Medicaid
GENERAL PRACTICE RESEARCH DATABASE

- Different kind of database
  - Data from 400 UK medical practices
  - Established 1987; managed by UK regulatory authority
  - About 3 million patients currently followed
- Information specifically collected for public health research purposes
- Increasingly used by epidemiologists to study drug AEs
POPULATION COHORTS

- Specific populations followed over time with active data collection
  - Nurse’s Health Study
  - Multicenter AIDS Cohort Study
  - Framingham Study
  - National Child Development Study (UK)
  - Collaborative Perinatal Project
MANY REPORTS ON SAFETY ISSUES USING DATABASES

• Typically motivated by emerging safety concern
  • Anecdotal case reports
  • Litigation
  • Theoretical concern

• Rarely produce definitive answers due to concerns about confounding
  • Same confounding issue can affect multiple studies

• Substantial research into methods to limit confounding
HEALTH CARE DATABASES

• Basis for FDA’s new Sentinel System
• FDA will contract for query capability to a number of health care databases
• Pilot under development by Harvard Pilgrim
• Capabilities will include
  - Evaluating signals arising from SRS, clinical trials, or elsewhere
  - Monitoring for new adverse drug effects
  - Development of improved methodology
Companies sometimes agree to conduct further studies as part of drug approval negotiations.

These may be randomized studies; more often, observational studies:
- Incidence of adverse effects
- Outcomes in specific subgroups inadequately studied in pre-market trials

Difficult to control for confounding variables in observational studies—even large ones.
RANDOMIZED TRIALS

- Randomized trials are less susceptible to bias and confounding than other approaches
- FDA has not typically requested randomized comparative studies post-licensure
- Increasing interest in larger pre-market studies with safety focus
  - Second rotavirus vaccine was studied in 70,000 children to rule out intussusception risk
  - New guidance requiring studies with adequate power (more subjects, longer followup) to detect excess cardiovascular risk associated with new diabetes drugs
META-ANALYSIS

- FDA requires and reviews an “integrated safety summary” including most or all studies submitted in an application
- Less quantitatively rigorous than meta-analysis
- Many consider meta-analysis of randomized trials as a “platinum standard” but there are many issues that affect reliability and can introduce bias
  - Identification and selection of studies
  - Choice of outcomes to analyze
  - Statistical approach to analysis
MAJOR POLICY ISSUE

- In considering approaches to safety evaluation, must address how to handle emerging signals
  - If action is late, more people may be harmed if the problem is real
  - If action is early, people may stop taking medications unnecessarily if false alarm
  - False signals may lead to unwarranted public concerns and can have major financial consequences that should not be discounted
    - Bendectin for morning sickness
    - Silicone breast implants
CONCLUDING REMARKS

• FDA is moving away from primary reliance on spontaneous reporting for safety surveillance

• Methodological work is needed in many areas to improve reliability of findings and support optimal decision-making
  - Monitoring and analysis of spontaneous reports
  - Monitoring and analysis of claims data bases
  - Design of ongoing studies or databases to provide additional safety data
  - Design of economically feasible large RCTs