Assessing the Safety of Marketed Drugs

Current Issues and Controversies

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FDA Regulatory & Compliance Symposium
Cambridge, MA
August 24, 2006
Introduction

- Debates over drug safety have intensified in recent years:
  - Legislative – fundamental changes proposed
  - Congressional investigations
  - Investigative journalism
  - Medical journal editorials
  - Lawsuits

- Observation – poor understanding of current system, strengths & gaps; wide differences in views about risk
Overview of Drug Safety

- Current Status of Safety Assessment
  - Strengths & Challenges
- Issues in Drug Safety
  - Science/regulatory/public health perspective
- The Future
Safety in the Lifecycle of FDA-Regulated Products

- Pre-clinical Safety
- Phase 1 Safety
- Phase 2 Safety, Dose-Ranging
- Phase 3 Safety, Efficacy
- Approval
- Post-Marketing Safety Monitoring

Safety Concern

Risk Management Strategies
Current FDA – Operated Systems: Premarket Safety Evaluation

- Significantly more information generated about investigational drugs than in the past
- Common conditions: 5-6,000 patient exposures, 3-4 months of use. Some exposures of 1-2 years; common side effect profile
- Special studies: drug metabolism; studies in renal and liver failure; drug-drug interactions; cardiac repolarization effects
- Less common diseases: Fewer patients in trials
FDA Drug Safety: Premarket Review Process

Complete submission by industry required:

- All animal studies
- All safety results from all human trials
- Any relevant marketing experience
- Any relevant literature
FDA Premarket Drug Safety Review

- Assigned to medical reviewer or review team
- Thorough review of safety findings per “safety review guidance”
- Includes evaluation of remaining uncertainties
- Documented in written review—posted on FDA web page after drug approval
- Safety assessment is about 50% of FDA resources in premarket program
What Has Changed in Review Process in Past Decade?

- More rapid FDA review process means that many fewer drugs have a safety track record from marketing abroad—previously a big safety factor.

- Massive promotional efforts (primarily detailing-related) accelerate uptake and increase patient exposure – Billions spent vs FDA's resources.
What Has Changed in Review Process in Past Decade?

- Extensive DTC advertising has affected public expectations about drug safety and usage.
- Despite these factors, drug withdrawal rate has remained stable, although the rapidity of withdrawal has increased.
Safety of Marketed Drugs

- Continued evolution of understanding of benefits and risks after approval. Inevitable with current testing schemes.

- Drug label information usually updated multiple times in 5 years post-approval.
Postmarketing Commitments and Risk Management Plans

- Postmarket commitments about safety usually address specific issues or populations.

- Risk management plans – address specific preventable risks (e.g., use in contraindicated populations) identified during premarket workup.
  - FDA attempts to limit the number of such exceptional programs.

- Requirements for explicit randomized postmarket safety trials rare in drug development.
Current U.S. Pharmacovigilance System

- FDA operates “spontaneous reporting system” or “MedWatch”
  - Reporting and follow-up mandatory for manufacturers
  - Voluntary direct reporting to FDA by healthcare professionals and the public
  - More than 400,000 reports yearly

- This system generates signals for unusual drug-related adverse events: not very effective for detecting increased frequency of common events like MIs
Current U.S. Pharmacovigilance System

- Manufacturer may conduct studies in additional populations (e.g., pediatrics) or indications
- FDA may conduct population-based studies to follow up on Medwatch signal
- Comparative trials or explicit outcome studies (e.g., NIH-sponsored) are relatively uncommon
- FDA cannot mandate new safety trials
Summary: Capacities of Current System

- Generate profile of common adverse events in tested populations during drug development
- Understand drug metabolism and common metabolism-based drug-drug interactions
- Develop plans for managing/evaluating certain anticipated risks after marketing
- Identify rare serious adverse events after marketing
Current System May Not Identify

- Increased frequency of drug-related events that occur otherwise in population
- Time-dependent events
- Events occurring more frequently in populations not tested in trials: the very sick, those on polypharmacy, multiple medical problems, etc.
- Events that are much more frequent with off-label use
- Events related to medical errors or abuse
- Detailed understanding of who should take the drug and who should not
- Rare events, chronic use, complicated patients (co-morbidities, co-prescribing), pregnancy
Drugs Safety: The Big Picture

- 1.5 million preventable ADEs/year
- $3.5 billion among hospitalized patients
- Drug therapy for individuals still largely empiric
Sources of Harm From Medical Products – Systems Problem

- Known Side Effects
  - Unavoidable
  - Avoidable

Medication & Device Error

Product Defects

Preventable Adverse Events

Injury or Death

Remaining Uncertainties:
- Unexpected side effects
- Unstudied uses
- Unstudied populations
Balancing Benefits vs Risks

**FDA**
evaluates benefits/risks for the population

**Provider**
evaluates benefits/risks for a patient

**Patient**
evaluates benefits/risks in terms of personal values
The Future of Drug Safety: Improving the Quality of Healthcare

- Implement Quality Improvements outlined in landmark IOM reports
- Decrease “medication errors” and inappropriate prescribing through modifying prescriber behavior and automation
- Improve recognition and management of emerging side effects
- Improve training/education of physicians on pharmacology & best practices
The Future of Drug Safety: Improving Surveillance

- Utilization of emerging electronic medical record systems for surveillance
- Studies or registries conducted in practice settings after marketing
- More surveillance systems in specialized settings: e.g., ER, nursing homes, etc.
These Approaches Should Be Implemented, But They are Not Sufficient

- Traditional focus on detection, communications, (warnings, precautions), management
- Need to add where possible: prediction; prevention; monitoring; mitigation
- Avoid treatment of individuals at high risk for event: serious side effects occur in only a small fraction of patients
- Develop new ways of monitoring for emerging toxicity before it becomes severe
Drug development (e.g., animal & human testing) is largely empirical in nature.

This tradition focuses on population means & observations of outliers.

Directly translated into “trial and error” approach in clinical medicine.

Major loss of information, eg. Why did drug fail to work in patient?
The Future of Drug Safety

- These are significant limitations on the number of questions that can be answered via empirical testing (imposed by # of patients, changing practice patterns, cost, etc).

- Despite hundreds of millions of dollars invested in a development program – we often lack key information at approval.

- Many of the patients subsequently exposed will not benefit from the Rx.

- Some will be exposed unnecessarily to risks.
FDA’s Critical Path Initiative and Drug Safety

- Incorporate cutting-edge science into clinical drug development
- Better predictive tools for safety outcomes (e.g., side effects such as liver or renal toxicity)
- Genomic or other tools to identify the subgroups with high probability of positive response (targeted therapy)
Example: Drug Metabolism in Drug Development

- Development of in vitro human cell models and animal models over last 15 years have enabled manufacturers to predict human metabolism.
- Avoid candidates with problematic metabolism/drug-drug interactions.
- These have dropped in same timeframe from leading cause of late clinical failures to minor cause.
- Many fewer products pulled from market because of interactions.
Example: New Technologies

- Genomic, proteomic, metabolomic markers
- Status in patients with serious side effects vs those without?
- Study in prospective trials and from MedWatch reports
- Develop ability to avoid high risk patients or monitor for development before overt toxicity occurs
Improving Drug Safety: Possibilities

- Improve current surveillance systems
- Access additional data sources as they develop
- Improve quality of healthcare system
- Move clinical drug development from empirical, trial and error approach towards mechanistic “personalized” approach
Drug Safety – Specific Actions

- Institute of Medicine (IOM) Study of the Drug Safety System
- Established Drug Safety Oversight Board
  - Emerging information for providers & patients
- Published three guidance documents – March 2005
  - Premarketing Risk Assessment
  - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
  - Development and Use of Risk Minimization Action Plans (RiskMAP)
IOM Study

- Study began in January 2005
- Committee has had public meetings (June, July, October, Jan)
- Detailed information about each of the meetings
  [http://www.iom.edu/CMS/3793/26341.aspx](http://www.iom.edu/CMS/3793/26341.aspx)
- Have interviewed large number of stakeholders, including many FDA staff
- Final report - Fall 2006
Societal Disputes on Risk/Benefit Contributing to Debate

- Even with perfect information there will be sharp disagreements
  - Isotretinoin & SSRI antidepressant examples

- Differing views about:
  - Who should make risk decisions
    - Role of government regulators, practitioners, patients
  - Regulatory policy/constitutional issues
    - Power vested in FDA by Congress
    - Role of states

- Risk/benefit: analytic and communications methodology limits ability to communicate
Lively Public Debate

- Changing development paradigm
  - Conditional approval pending completion by sponsors of required post-approval studies (Strom)

- New institutions/organizations
  - Independent institute dedicated to post-marketing studies funded by healthcare insurers (Reidenberg)

- Expanding role for public health agencies
  - Increase funding/authority for agencies such as FDA/AHRQ/CMS/CDC to conduct studies
Summary of Recent Actions

- FDA responsive to concerns about drug safety decision-making and communication

- While comprehensive review underway, we will implement important changes to improve public knowledge, internal management and outside involvement
  - Reorganization, Congress increased drug safety budget $10 million

- Changes will not be free of controversy and may raise important new issues for resolution

- Clinicians must stay informed and involved
Improving Overall Drug Safety is a Systems Problem

- Many of the risks of drugs related to use patterns—e.g., prescribing habits, drug-drug interactions, errors, etc.

- No entity—government or otherwise—is charged with investigating and resolving safety issues—i.e., comparative safety, long term outcomes of therapy, etc.

- Focus on drug withdrawals and high profile AEs obscures many components of systems problem

- To a large extent – drug safety is a function of the safety of the healthcare system
Questions?

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