FDA Postmarketing Regulatory Activities – Drug Safety

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Postmarketing Focus on Safety

“The FDA rarely gets criticized for approving a safe but inefficacious drug...because safety errors are much more visible than efficacy errors”

Carpenter DP. Health Affairs 2004;23:53

Adverse Drug Reactions Discovered After Marketing

- Thalidomide - Phocomelia
- DES - Clear-cell Adenocarcinoma
- Zomepirac (Zomax) - Anaphylactoid Reactions
- Suprofen - Acute Flank Pain
- Isotretinoin - Psychosis
- Triazolam - CNS Effects
- Alosetron - Bowel ischemia
- Rofecoxib – Cardiovascular events

Marketed Products Impacted by Suspected Adverse Drug Reactions

- Bendectin - Birth Defects
- Depo-Provera - Breast Cancer
- Fluoxetine - Suicide
- β-agonist Inhalers - Asthma Deaths
Reasons for Delay in Discovery

- Small numbers in clinical trials
- Highly selected people in clinical trials
  - no other drugs used
  - no pregnant women
  - no children, elderly
  - no comorbid conditions
- Short observation period in clinical trials
- No denominators after marketing for perspective

Pressures on Regulatory Processes

- Aging population, ↑ prescription use
- Managed care → high volume of prescribed drugs
- High rate of new drugs entering market
- Popularity of pharmacologically-active dietary supplements
- Direct-to-consumer advertising
- Advocacy groups

Drug Regulation as a Dance

- Tension between government and industry
- Congress has mandate to protect public’s health (oversees FDA)
- Congress controls FDA through funding, laws
- Members of Congress have accountability to constituents (industry, patient advocates)
- The dance: accessibility (drug availability) vs. safety
- Note: cost is not address by Congress or FDA

Uncertainty aided by FDAMA

- May approve on data from one clinical trial
- Allows dissemination of information about off-label use of products, including economic information
- Codifies expedited review of “fast-track” drugs
- Public access to NIH clinical trials info
PDUFA II - 1997

- Effected through FDAMA
- Extended a second five years, with more restrictions
- Objective: reduce drug development time
- Prescribes periodic sponsor-FDA meetings
- Significantly increased FDA workload, pulled staff from other areas, including safety monitoring

Five Products Withdrawn from Market in 1998

- Fenfluramine (Pondimin) - cardiac valves
- Dexfenfluramine (Redux) - cardiac valves
- Terfenadine (Seldane) - cardiac arrhythmia
- Mibefradil (Posicor) - liver toxicity
- Bromfenac sodium (Duract) - liver toxicity

PDUFA III - 2002

- Authorized use of funds for postmarketing surveillance
- Risk Management Goals
  - Conduct premarketing risk assessment
  - Develop and implement risk minimization action plans (RiskMAPs)
  - Perform postmarketing pharmacovigilance and pharmacoepidemiologic assessments.

Key Elements of Risk

- Identification of unwanted outcome for patient and physician
- Permanence: temporary or permanent
- Timing: when will it occur?
- Probability: likelihood
- Value: how much does it matter to the patient?
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Regulation Regarding ADE

- The postmarketing adverse drug experience (ADE) regulations (21 CFR 310.305, 314.80 and 314.98) cover prescription drugs and Rx-to-OTC switched drugs
- The purpose of postmarketing ADE surveillance is to obtain information on rare, latent or long term drug effects not identified during premarket testing.

Basic Regulations

- Sponsors, manufacturers, packers and distributors are required to report all serious, unexpected (not listed in the drug product’s current labeling) ADEs to FDA within 15 calendar days.
- For ADEs not meeting these criteria, periodic reports must be submitted to FDA quarterly during the first three years following approval of the drug and annually thereafter.
FDA Tools for Ensuring Safety

- Labeling (primary risk management tool)
- Spontaneous ADR reporting system – MedWatch and sponsor generated
- Studies required of sponsors
- Database contracts – longitudinal and ad hoc
- Drug Safety and Risk Management (DSaRM) Advisory Committee

Risk Minimization Action Plans (RiskMAP)

- Seeks specified health outcome in presence of known risk
- Three types of “tools” described by FDA
  - Targeted education and outreach
  - Reminder systems
  - Performance – linked access systems
- Goal of widest access to product with least burden on system

Targeted Education and Outreach

- Aimed at prescribers: CME programs, “Dear Health Professional” letters, articles, editorials in selected medical journals, public health advisories
- Aimed at patients: Medication Guides, “patient package inserts”, website information including video programs, press releases, DTC advertising

Reminder Systems

- Registries, consent forms, physician attestation schemes or qualifying tests
- Specialized packaging or formulation, restriction of quantity or frequency of availability
- Prescription stickers
Performance-linked Access Systems

- Restriction to prescribers or pharmacies with particular qualifications
- Documentation of negative lab test or other required prior safety-related performance

Epidemiologic Studies in Databases

- Case reports
- Case series
- Analyses of secular trends
- Cross-sectional studies
- Case-control studies
- Cohort studies

Drug Development and Approval Issues Affecting Safety

- Study in “special populations” - children, women, minorities
- Requirement of “Phase IV” studies for fast track approvals or pre-market signals
- Use of surrogate endpoints
- Direct-to-consumer advertising
- Rx-to-OTC switch

Regulatory Requirements for Rx-OTC Switch

- Safety without medical monitoring
- Wide therapeutic index
- Low abuse/misuse potential
- Indicated symptoms easily recognized
- Indications readily treatable
- Labeling claims accurate
- Clarity of labeled instructions, precautions
- Advantage to consumer of OTC availability
Caution!

- Many studies have shown that FDA communications, e.g., through “Dear Health Professional” letters do not result in change or improved outcome
- Some databases are known to contain biases that require careful handling in analyses
- Regulations are quite clear about expectations, not clear about enforcement options
- Some interventions may have unintended consequences

Additional Resources for Information about the US FDA

- http://www.fda.gov/