FDA Oversight Of Drug Safety: What Works, What Doesn't

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FDA Oversight of Drug Safety: The Stakes

- 100,000 deaths/year from ADEs; “huge” # of hospitalizations
- Drug withdrawal rate about 2.5%
  - Unchanged over last 30 years
- Drug safety a core issue from preclinical research through postmarketing
- Most recent attention focused on postmarketing phase

The Problem: Loss of Trust

- FDA taking too long to tell physicians and patients about new safety information
- FDA not acting quickly enough on evidence of safety risks
- Disagreements within FDA about how to address safety issues
- FDA organizational structure underweights postmarket safety considerations

The Problem: Loss of Trust

- FDA lacks clear, effective process for decisions about postmarketing drug safety
- FDA lacks authority and funding for adequate oversight of postmarketing drug safety
- Drug safety system has “broken down”
- “We are defenseless”

Underlying Issues

- Communication
  - Not fast enough
- Structure
  - Not clear enough
- Authority
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Fixes: Communication

- Get emerging safety information out faster: DrugWatch (May 2005)
- Drugs for which FDA is “actively evaluating early safety signals”
  - Newly observed SAEs
  - New risk minimization measures
  - Significant emerging risks that may be avoided by proper countermeasures

DrugWatch: Concerns

- FDA imprimatur on unvalidated safety information
  - Potential for confusion, overreaction
  - Irreparable damage to drug's reputation
  - No sponsor input
  - Undermines status of drug label as key source of safety information

DrugWatch: FDA Response

- FDA heeds criticisms, puts DrugWatch on hold (Nov. 2005)
- But continues lower-key communication of drug safety information
  - Public Health Advisories
  - Patient, HCP Information Sheets
  - MedWatch

Fixes: Communication

- Hearing on Risk Communication (Dec. 2005)
- Communication tools covered:
  - Patient and HCP info sheets
  - Safety-related Talk Papers
  - Public health advisories
  - MedWatch updates

Hearing on Risk Communication

- Public comment requested on:
  - Strengths and weaknesses
  - Awareness and use by intended audiences
  - Right kind and amount of risk info
  - Acessibility and understandability
  - Special populations

Hearing on Risk Communication

- Key messages:
  - Simplify risk communications
  - Improve HCP and patient access
  - Develop consistent approaches
  - Engage HCP organizations
  - Address limited-literacy populations
  - Maintain risk-benefit balance

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Fixes: Structure

- Drug Safety Oversight Board
  - Identify, track, and oversee important safety issues and establish policies
  - Adjudicate organizational disputes
  - Ensure that drug safety decisions receive input of experts not involved in primary review or pre-market evaluation
  - [Oversee DrugWatch]

DSOB: Membership

- Fifteen voting members
  - Three each from OND and ODS
  - Five from other CDER offices
  - One each from CBER and CDRH
  - One from non-FDA HHS agency (NCI)
  - One from non-HHS health agency (VA)
- Deputy Director CDER is non-voting chair

DSOB: Procedures

- DSOB decisions are recommendations to CDER Director
- Should be reached by consensus but if necessary vote will be taken; 2/3 majority of quorum (11 members)
- Members involved in primary review of data or regulatory decision-making for drug at issue recused from voting

DSOB: Activities

- Meetings closed; brief written summaries posted to web
- Relate mostly to selection of drugs for patient or HCP information sheets or public health advisories

Proposed Fixes: Structure

- Raise profile of drug safety operations
  - Enhance role of FDA drug safety office in premarket reviews and postmarket safety deliberations
  - Take drug safety office out of CDER, reporting directly to Commissioner
  - Take drug safety function out of FDA altogether (NTSB model)

Proposed Fixes: Reaction

- So far FDA has taken no major steps to restructure drug safety operations (DSOB aside)
- IOM evaluating agency's internal safety organization and operations
- Some bills have called for independent drug safety board
- Most recent major bill relies on DSOB

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Authority: Issues

- Labeling
  - authority to compel safety changes
- Postmarketing studies
  - authority to enforce commitments
  - authority to require new studies
- IOM review: Consider FDA's legal authorities for identifying and responding to drug safety issues

Authority: Is there an issue?

- Existing Authority Over Labeling
  - Power to issue patient/HCP information sheets, public health advisories, Talk Papers, etc.
  - Authority to declare drug misbranded for omitting material safety information
  - Ability to withdraw approval over safety concern, suspend marketing if “imminent hazard”
  - Not always easy or practical to utilize

Authority Over Label: Proposed Fixes

- Basic idea: Give FDA power to order safety changes to drug label; avoid lengthy talks, sponsor foot-dragging
- Sanctions for non-compliance may include misbranding charge, civil money penalties

Post Marketing Study Commitments

- Key element of drug approval process: 73% of drugs approved since 1998 carried PMCs
- FDAMA, FDA regs require annual sponsor status reports
- Enforcement of existing PMCs: Is there a problem?
  - FDA: Four percent of confirmatory studies for accelerated approval drugs are delayed; one percent of all pending postmarket studies for drugs

Authority over PMCs: Is there a problem?

- Rep. Hinchey: “Conspiracy of silence;” majority of companies benefiting from accelerated approval are failing to complete PMCs on a timely basis
- 68% of public companies failed to disclose PMCs in SEC filings

Authority over PMCs: Proposed Fixes

- Little to no direct FDA authority over completion of PMCs
- Little to no direct FDA authority to impose new postmarketing study requirements
- Pending legislation would make failure to complete postmarketing studies a violation under FDCA, allow for civil money penalties
  - Would also give FDA limited authority to require new postmarketing studies

Net Result: Enhanced Drug Safety?

- Expedite risk communication
- Clarify safety structure
- Strengthen safety authority
- Trust restored?
- Better drug safety?
- Healthier population?

Drug Safety: A Different Perspective

- Drug safety concerns: “part real – part hype – part hysteria”
- Risk vs. Benefit
- “Statistical myopia”
- Patients are dying while waiting for approval of new treatments

Drug Safety: How to Balance

- Pendulum has clearly swung toward caution/safety
- Some strengthening of safety tools a foregone conclusion
- Harder part is to strike the right balance, not lose sight of benefit as well as risk