Improving FDA’s approach to new drug approval and post-marketing surveillance

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Conflicts of interest

• Neither I nor anyone in my division accepts personal compensation of any kind from any pharmaceutical manufacturers.

• Our unit does receive research support from several drug companies through unrestricted grants to the Brigham and Women’s Hospital.
Three clinical vignettes

• an otherwise healthy 60 year old man with mild arthritis unexpectedly has a heart attack and dies.
• an unmarried 16 year old girl has unprotected sex, can’t get emergency contraception, seeks an abortion, and has serious medical and psychological complications.
• after a storm, a family of four is trapped by rising flood waters in their home four feet below sea level in a major American city; all drown.
What do these events have in common?

- a failure of science-based infrastructure.

- In each case:
  - We had clear evidence pointing to the need for specific governmental action.
  - Better federal decisionmaking could have averted tragedy.
  - The right decisions were not made.
  - The resulting human and economic costs were enormous, far greater than doing it right the first time.
The “telephone” problem

• First-rate bench-level clin pharm research
• Rigorous but sometimes irrelevant review
• Non-scientific factors influence approval
• Inadequate post-marketing safety surveillance
• Distorted communication of benefits, risks – to prescribers and to patients
• Flawed reimbursement policies encourage suboptimal use
From a good beginning......


--- Proc Natl Acad Sci, 1994
Martinez B, Mathews AW, Lublin JS, and Winslow R.

"Merck pulls Vioxx from market after link to heart problems."

--Wall Street Journal, 2004
Benefits, risks, and cost-effectiveness do not reside exclusively within the drug molecule. They are also determined in large part by how prescribers and patients use a product.
Limits of clinical trial data

- small N’s
- volunteer patients
- short duration
- under-representation of important groups
- atypical clinicians, settings
- protocolized care: compliance, monitoring
- surrogate endpoints
- comparator is often placebo
Some notable withdrawals

- **Duract**: hepatotoxicity
- **Posicor**: hypotension, bradycardia
- **Fen-phen**: pulmonary htn, valvulopathy
- **Rezulin**: hepatotoxicity
- **Baycol**: rhabdomyolysis
- **PPA**: intracerebral hemorrhage
- **Vioxx**: MI, stroke
- **Bextra**: SJS, MI
- **[Avandia]**: CHF, ?MI?
Financial and practical issues

- cost of capital (a function of time) looms large in drug development expenses
- incentive for smaller, quicker trials
- motivation to avoid “messy” patients
- PDUFA:
  - faster approvals
  - problems later
**Efficacy and safety: a policy dilemma?**

- To make drugs available quickly, trials must:
  - be brief and have modest N
  - include easy-to-study patients

- To define all adverse events, trials would:
  - last longer
  - be larger
  - include more vulnerable, complex patients

- But beware the Heisenberg fallacy!
Needed changes in approval

- Inclusion of more representative patients
- Longer duration
  - a two-stage process?
- Better flagging of signals in need of followup
- More critical thinking about surrogate outcomes
Origins of FDA’s problems

- Anti-regulatory trends:
  - “Government is not the solution to our problem; government is the problem.”
    - President Ronald Reagan, 1st Inaugural Address
  - growing reliance on the marketplace to solve most social issues
  - the power of lobbying and $$ to shape policy

- Adverse effects of PDUFA
Post-marketing safety surveillance
Two views of an adverse drug event report:

- **Physician:**
  “This drug could be a real threat to the life of my patient!”

- **Manufacturer:**
  “This patient could be real threat to the life of my drug!”
Two industry perspectives

• ostrich view:
  - liability fears
  - marketing concerns

• enlightened view:
  - What we don’t know can hurt us
  - information could save drug
FDA problems

• Inadequate clout over manufacturers after approval
  - most “mandated” PMS “commitments” are never even begun
• Inadequate funds to do or commission studies
• Low staffing, expertise, morale among PMS staff
Fixing the three M’s

- Money
- Mandate
- Methodology
Money

• FDARA ???
  - not adequate
• CMS realizes that it has become the nation’s biggest drug purchaser
  - prudent use of its own $
  - more comparative trials
• Where are the other payors??
  - Medicaid, private insurers, VA
Mandate

• FDARA
  - one small step...
• FDA needs more power to compel studies to protect public health
• The marketplace
  - Will the sleeping giant ever awaken?
Methodology

- Pre-approval studies
  - innovative designs
  - more research on surrogate outcomes
- Post-marketing surveillance
  - less reliance on spontaneous reports
  - more ubiquitous databases
  - evolution of pharmaco-epi methods
- Large pragmatic post-approval trials
Head-to-head risk-benefit comparisons

• continuing coxib-NSAID confusion
  - about efficacy
  - about side effects

• a dozen other clinical areas
  - CHF, HTN, diabetes, depression, insomnia, Parkinson’s Disease, etc., etc.

• no-one’s in charge at present
“How can we ever afford this?!”

• The U.S. already spends more per capita on drugs than any other nation.

• Much of that is wasted.
  – Government (federal, state, VA) is footing a big part of the bill.
    - e.g., Medicaid spent $1 billion a year on Vioxx

• Publicly funded comparative drug trials and better PMS would pay for themselves quickly.
The future
Drivers of change

• Growing need to use powerful new medications appropriately
• Aging of the population
• Escalating drug costs
• Greater sophistication in data accessibility, informatics
• Changing political climate
  – the public / the Congress / 2008
"The lion shall lie down with the lamb...

...but the lamb won't get much sleep.

- Woody Allen
Katrina, 2 years later

• Ample data exist documenting the problem.
• Solutions are obvious, do-able, and relatively inexpensive, compared to inaction.
• What has thwarted intelligent policy?
  - governmental inertia and ineptitude
  - misguided ideology
  - interest-group politics
• We need to overcome all three.
A pharmacological New Orleans

• Every drug and every patient who takes it are potentially four feet below sea level.
• Category 3 to 5 medication disasters will occur inevitably, though we can’t predict each one in advance.
• Science-based public policies on drug evaluation and regulation are the levees that keep us all from drowning.
• The bad news: The levees are leaking.
• The good news: It won’t take that much to fix them.
For more information....


www.PowerfulMedicines.org

The BWH Division of Pharmaco-epi and Pharmaco-eco (“DOPE”):

www.DrugEpi.org