Post Marketing Studies of New Medications: Implications for Patient Safety

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Should the FDA require all drugs to undergo post-marketing studies?

- 44% of Americans take at least one prescription drug in any given month.
- Adverse drug reactions (ADRs) are one of the leading causes of serious health problems in the United States.
- ADR’s kill more than 100,000 people every year and injure more than 2 million.
Need for Post Marketing Studies

- Instances of delayed discovery of an adverse reaction from several drugs that were approved and marketed.
  - Avandia, Vioxx and Redux.
- FDA & pharmaceutical companies enter into an agreement to study drugs after they are approved.
- Out of 1,259 post marketing commitments, 71.1% were not started and 18% were ongoing.
History & Background

- 1962 Kefauver-Harris Amendment required that safety and efficacy of a drug should be proved prior to being approved.

- In 1992, Congress enacted the Prescription Drug Users Fees Act (PDUFA) which requires manufacturers to pay user fees for new drug applications.
<table>
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<th>Year</th>
<th>Legislation and FDA Policy &amp; Procedure</th>
<th>Purpose</th>
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<tr>
<td>1997</td>
<td>Food &amp; Drug Modernization Act (FDMA)</td>
<td>Established fast track approval of certain drugs</td>
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<td>1998</td>
<td>FDA introduced the Adverse Event Reporting System</td>
<td>Computerized database to store and study safety reports of marketed drugs</td>
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<td>2003</td>
<td>Pediatric Research Equity Act</td>
<td>Gave the FDA the right to require drug companies to study the effectiveness of new drugs in children</td>
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<td>2005</td>
<td>Drug Safety Oversight Board established</td>
<td>Advises the FDA Center for Drug Evaluation and Research on potential drug safety issues</td>
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<td>2007</td>
<td>FDA Amendments Act (FDAAA)</td>
<td>Authorized FDA control over drug marketing and requires post market studies. Authorized prescription drug user fees for post marketing surveillance.</td>
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Process of Drug Testing & Approval

- Preclinical or lab testing
- Clinical testing
- Phase I – healthy volunteers (20-100)
  - Absorption, excretion, metabolism
  - Last from few days to few weeks
- Phase II – Drug testing in particular diseases
  - Includes 50-500 patients
  - Lasts several months to two years
- Phase III – Better understanding of the effectiveness of drugs. Placebo trials - about 70-90% of drugs entering Phase III complete phase.

- Total time for completion of clinical trials is about 2-10 years.
- 20% of drugs entering into Phase I are eventually approved and marketed
Limitations of Pre-Marketing Studies

- Design issues
- Co-morbid medical problems
- Size of the study
- Special population

Post marketing studies (Phase IV) becomes very important.

- FDA currently mandates post-marketing studies:
  - Fast-track products which are used to treat certain life threatening illnesses
  - Products for use in children
How are Adverse Drug Events Reported?

- MedWatch is an FDA reporting system founded in 1993.
- Reports can be done by phone or by submitting a form.
- Pharmaceutical companies are mandated to report adverse events.
- Physicians are not mandated to report: only 1 – 3% of adverse events are reported by physicians.
- This reporting system is inconsistent and somewhat incomplete.
Benefits of Post-Marketing Studies

- Can detect adverse reactions that occur while the drugs are being used on a long term basis.
  - E.g. HIV, protease inhibitors and risk of myocardial infarction
- Improved treatment and decreased toxicity – e.g. Interferon Alpha B in chronic Hepatitis C.
- Post-marketing studies can become the first point where pre-clinical drug safety issues can be analyzed.
- Reveal other disease treatment indications.
Limitations of Post-Marketing Studies

- Could be costly
- Length of study
- Who has the oversight?
- How do you determine which drugs undergo post marketing studies?
Cost of Post-Marketing Studies

- 2005 cost of developing a new drug was estimated at $51.3 billion
- Funding increased to obtain data from external sources about drug safety from $5 million to $28 million in 2007.
- In 2008, funding increased to about $9 million for contracting with companies for post-marketing studies.
- User fees increased to about $400 million in 2008 and of the $400 million, $300 million would fund post-marketing safety-related activities.
Cost of Post-Marketing Studies

- At FDA Center for Drug Evaluation and Research, funding for post marketing drug safety increased from $54 million in 2006 to $139 million in 2008.

- Of the $139 million, $55 million was revenue generated from the user fees.
Stakeholders Support of P-M

- Potential stakeholders who are in support of post marketing studies
- Food & Drug Administration
- OND – FDA Office of New drugs
- OSE – FDA Office of Surveillance and Epidemiology
- FDA provided guidance for industry on post-marketing studies and clinical trials.
- FDA has began “Safe Use Initiative.”
- Pharmacists
  - Improving quality of care and enhancing patient safety of reducing medication errors.
Stakeholders

- The House Energy and Commerce Committee are involved in drug safety.
- American Medical Association recommended that the government should increase funding levels to include post-marketing surveillance of prescription drugs.

Public Opinion
- Negative view of pharmaceutical industry.
Stakeholders – against P-M

- Health Insurance providers.
- Pharmaceutical industry.
- Other Legislation
  - Bills related to prescription drug safety and importation. No specific bills regarding post-marketing studies.
IOM Recommendations

- Institute of Medicine (IOM) has recommended to the Congress:
  - FDA to have increased authority at drug sponsors
  - FDA require companies to register all trials in Phase II – IV
  - Assign joint authority to OND & OSE for post marketing safety of drugs
Additional Recommendations

- All prescription drugs should undergo post-marketing studies. Prioritize which ones to be studied based on pre-marketing trials.

- Improve communication with physicians, hospitals, pharmacies for new drug release.

- Label drugs undergoing post-marketing studies.

- More oversight on drugs used in children because of the “off label” pre-trial use leading to serious consequences.