Use of Targeting in Drug Development: Regulatory Viewpoint

Douglas C. Throckmorton MD
Deputy Director for Regulatory Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
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Tension

- Need for targeted approaches to patient enrollment to improve medical product development
  - Predicting and managing specific drug safety issues
- Need for broad approaches to patient enrollment as a part of medical product development
- Larger context of development

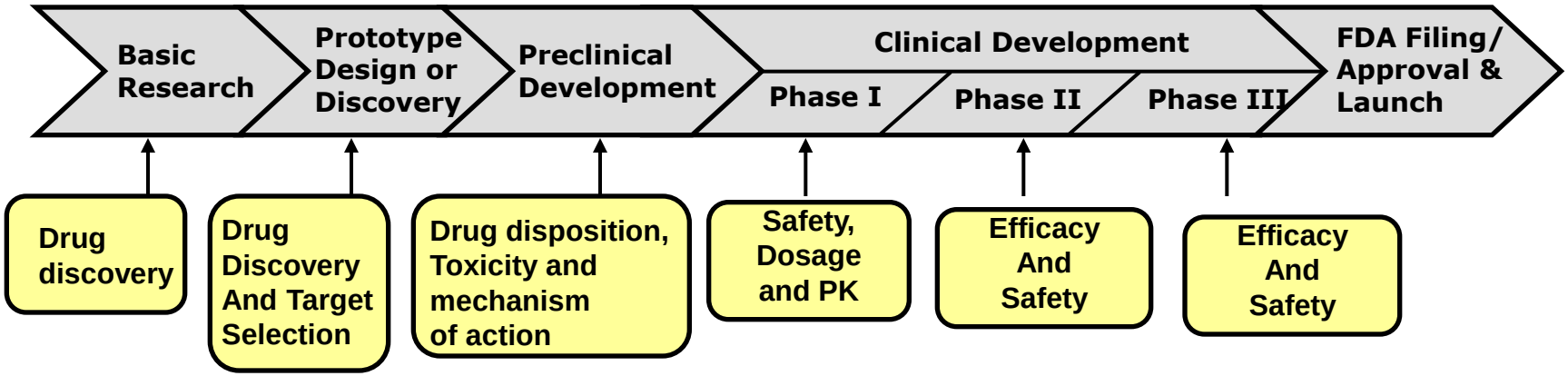
Need for Targeted Approaches to Development

New Drug Success Rates

- New drug success rates in Phase II trials: 18% (2008-2009)*
  - 51% insufficient efficacy
  - 19% safety concerns
- New drug success rates in Phase III trials: 50% (2007-2010)*
  - 66% insufficient efficacy
  - 21% safety concerns

* *Arrowsmith (2011) Nature Reviews Drug Discovery,10:87*
** *Arrowsmith (2011) Nature Reviews Drug Discovery,10:328-329*

Causes for Failure of Drugs



- 30% due to lack of efficacy
- 41% due to ADME
- 29% due to toxicity

Needed: Evaluative and Predictive Tools

- Targeted development supports public health goal of efficient and predictive drug development
- Efficacy: identify the population who will respond to a new drug earlier to speed development
- Safety (focus of this session): predict adverse events earlier to allow their prevention or mitigation


WARNING
CHALLENGES
AHEAD

Challenges in Identifying Safety Signals During Drug Development

- Targeting to assess CV safety efficiently requires you know what to target….
  - QT
  - Blood Pressure
  - Thrombosis
  - Heart Failure
  - Valvulopathy

Challenges in Identifying Safety Signals During Drug Development

- Mechanistic inferences from non-clinical data sometimes misleading
- Disease heterogeneity
  - Inter-individual variability
  - Idiosyncratic serious adverse events in a small group of patients
- Data often limited during development
  - Rare adverse events not seen in development program
  - Rates of adverse events seen in selected population may not translate to broader populations
  - More common adverse events not always attributable to drug during development

Unexpected Drug Safety Toxicity

A.M. FOG
HIGH 78, LOW 62 - 820

The Washington Times FINAL

www.washingtontimes.com FRIDAY, OCTOBER 1, 2004 ★★ SUBSCRIBER SERVICE: (202) 636-3333 Prices may vary outside metropolitan Washington area 25 cents

Merck recalls Vioxx

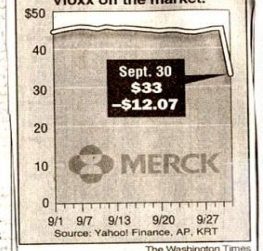
Heart risk found in arthritis drug

TRENTON, N.J. (AP) — Vioxx, the blockbuster arthritis drug taken by 2 million people, was pulled from the market by its maker yesterday after a study found it doubled the risk of heart attacks and strokes.

Experts advised patients to immediately stop taking Vioxx and talk to their doctors about alternatives.

"Given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take," said Raymond V. Gilmartin, chairman, president and chief executive officer of Merck & Co.

PAINFUL
Merck's stock plunged after the pharmaceutical company said it was taking its arthritis drug Vioxx off the market.



The Washington Times

The news of Vioxx's dangers came five years after Merck put the drug on the market with great fanfare. Vioxx has become one of the world's most aggressively marketed drugs, advertised in magazines and in TV commercials, with celebrity endorsements from former athletes Dorothy Hamill and Bruce Jenner.

The withdrawal is a serious blow for the New Jersey company, the world's third-largest drug maker. Vioxx accounted for $2.5 billion in worldwide sales in 2003 and has been taken by 84 million people worldwide since its introduction.

Merck stock fell $12.07, or nearly 27 percent, to $32.90 in heavy trading on the New York Stock Exchange yesterday. Merck dragged down the Dow Jones Industrial Average, which was off by 56 points.

Merck's recall of its Vioxx painkiller surprised pharmacies in the United States and Canada, leaving them unprepared to handle questions from concerned patients and doctors looking for alternatives and trying to get information about reimbursement.

Vioxx, which is also prescribed for acute pain and disorders such as carpal tunnel syndrome, is seen as a potential cancer-prevention medicine. In fact, the recall was prompted by a three-year study aimed at showing the drug could prevent the recurrence of potentially cancerous polyps in the colon and rectum.

Participants taking Vioxx for more than 18 months were found to be twice as likely as those given placebos to have a heart attack, stroke or other heart complications.

The Food and Drug Administration said there were early signs of potential problems with Vioxx. A Merck study led to warnings about heart risks being placed on the drug's label in 2001, and the FDA has been monitoring problems that have been reported since then.

"This is not a total surprise," said Dr. Steven Galson, acting director of the FDA's Center for Drug Evaluation and Research.

Vioxx is part of a class of anti-inflammatory drugs called cox-2 inhibitors that have been heavily touted by the pharmaceutical industry as being more effective and having fewer side effects, particularly on the stomach, than older drugs. Pfizer's Celebrex and Bextra are also cox-2 inhibitors. But so far there has been no evidence that these other drugs pose any dangers to the heart.

Officials do not know how Vioxx may be causing the increased risk.

Alternatives to Vioxx include generic pain relievers such as ibuprofen and aspirin, as well as Celebrex.

"There are very few patients for whom there won't be a good alternative drug," said Dr. Steven Abramson, director of rheumatology at New York University Hospital for Joint Diseases. Dr. Abramson said there is no reason for those who used Vioxx in the past to panic; he said there is no evidence that the elevated risk of heart attack persists after a patient has stopped taking the drug.

Personal-injury lawyers already have begun circling Merck. Trial lawyer Wayne Cohen said the decision has opened the company up to tremendous legal jeopardy.

Besides possibly knowing about the harmful effects and not acting quickly enough, the company is also vulnerable to huge settlements because the injuries — cardiovascular problems and stroke — are debilitating and costly, said Mr. Cohen, the president for the D.C. branch of the Association of Trial Lawyers of America.

"One hundred million people have used Vioxx and therefore the potential for claimants is monumental," he said. "You also have users of Vioxx that are not injured now but may need to get monitored."

A law firm in Oklahoma City, Federman & Sherwood, said it had filed the first lawsuit subsequent to Merck's recall of the drug. Within hours of the recall announcement, lawyer Barry Slotnick of New York announced plans to file an unspecified number of federal lawsuits on behalf of Vioxx users.

"It's a disaster for Merck, coming at the worst time," said health care analyst Hemant Shah of HKS & Co. in Warren, N.J.

Need for Broad Approaches to Development

Gains for Inclusion of Broad Population

- Supports public health goal of representative exposure pre-marketing
- Enables fuller characterization of risks and benefits
  - Adverse events profile more reflective of intended population
  - Forest plot of efficacy
- CFR requirement to analyze results by sex, age and race
  - Sufficient representation of both sexes in clinical trials to permit detection of important differences

Regulatory Advice: CDER MaPP on Good Reviewer Practices*

- Sponsors should be encouraged to consider collection of DNA samples in a substantial proportion of their trial population to allow examination of data in relevant pharmacogenetic subsets

*http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm118777.htm

Regulatory Advice: CDER MaPP on Good Reviewer Practices (cont)

- In general, the choice of the trial population in a phase 2 or phase 3 clinical trial should reflect the intended use of the drug
- There are powerful reasons to include heterogeneous populations in a trial
- In particular, reviewers should closely examine exclusions in phase 3 trials to consider whether they are really needed

Regulatory Advice: CDER MaPP on Good Reviewer Practices (cont)

- Decisions on whether to require evaluation in both the enriched and nonenriched population involve many complex factors and must be carefully considered before providing advice to sponsors

My Translation: Period of Scientific Transition

- 'Omics and other tools promise substantive improvements in predictive toxicology and efficacy assessment
  - More and more can be learned with fewer subjects in targeted populations
  - Supports efficiency in drug development
- Interests in generalizability remain as the promise is realized

Summary

- Strong rationale for use of targeting strategies to enrich efficacy assessment and predict/manage potential toxicities
- Generalizability of data is a key goal to support broader use, and exclusions in late-phase trials should be carefully justified

- The art of progress is to preserve order amid change and to preserve change amid order

---Alfred North Whitehead

In general, apart from enrichment attempts, sponsors should be encouraged to conduct major efficacy trials in demographically heterogeneous patient populations and in patients with a wide range of concurrent illnesses and treatments to ensure that the results are reasonably generalizable. Within those trials, subset analysis can help identify important differential treatment effects. In particular, reviewers should closely examine exclusions in phase 3 trials to consider whether they are really needed. It has been common, for example, to exclude patients older than 75, but there is no good reason to do this. Similarly, exclusions of patients with a history of psychiatric or cardiovascular illness, unless dictated by the drug's pharmacology, decrease the opportunity to detect important drug-drug interactions and should be discouraged.