



## Keeping Science on Top in Drug Evaluation

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In many sectors of American life — energy, defense, finance, pharmaceuticals — the government stands poised between powerful industry groups and the needs of the citizenry. But in only

one of these areas, prescription medications, is there a formal public mechanism for integrating science into the national decision-making process. At their best, U.S. drug-approval procedures include an open system in which outside scientists come together as advisory committees to the Food and Drug Administration (FDA), publicly evaluate the available evidence, and render opinions to guide the agency's decisions. The approach is based on the insight that a deep reservoir of knowledge and judgment exists in the academic and clinical communities about often arcane matters of drug benefits and risks — a kind of expertise that would be impossible to equal inside any government

agency. In theory, the FDA's advisory committee system aspires to the Platonic ideal of a group of disinterested experts giving freely of their wisdom to guide the republic's decision making.

Of course, the system doesn't always perform as well as it should. In recent years, the FDA has been less stringent about allowing the participation of committee members who have commercial conflicts of interest, despite evidence that such ties help shape opinions.<sup>1</sup> Science may also be defeated at later stages of the policymaking process, as when the FDA commissioner overruled the nearly unanimous recommendations of both internal and external scientists about the safety of emergency contraception

(the morning-after pill). Unfortunately, the upcoming reauthorization of user-fee funding at the agency will lock in 5 more years of dependence on support from pharmaceutical manufacturers to pay the salaries of the FDA's internal drug-review staff, renewing concern about the relationships between science, commerce, and federal policy and making the independence of external advisers even more critical.<sup>2</sup>

But though the quiet voice of science may often be no match for powerful vested interests or ideology, some encouraging signs may be in the air. The same reauthorization bill, disappointing in so many respects, may tighten somewhat the conflict-of-interest rules for outside advisers. In addition, some recent committee decisions provide interesting contrasts with recommendations made several years ago about similar drugs.

During the 1999 approval

Risk of Cardiovascular Events with Etoricoxib, as Compared with Naproxen.*			
Drug	No. of Patients	Risk of Cardiovascular Event, per 100 Patient-Years (95% CI)	Relative Risk as Compared with Naproxen (95% CI)
Etoricoxib	1960	1.09 (0.72–1.58)	2.72 (1.18–6.27)
Naproxen	1497	0.41 (0.16–0.83)	

\* Data are from an FDA presentation by Robert Shibuya ([www.fda.gov/ohrms/dockets/ac/07/slides/2007-4290s1-01-02-FDA-Shibuya.ppt](http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4290s1-01-02-FDA-Shibuya.ppt)). CI denotes confidence interval.

process for rofecoxib (Vioxx, Merck), FDA internal reviewers noted early signals of a possible increase in cardiovascular risk. But the advisory committee focused instead on the hope that the drug would have less gastrointestinal toxicity than other nonsteroidal antiinflammatory drugs (NSAIDs), though such an advantage had not yet been convincingly demonstrated. When a quadrupling of the rate of myocardial infarction was documented a year later in a clinical trial comparing rofecoxib with naproxen, the agency allowed the company to imply that this was because of the cardioprotective effect of naproxen.

Fast-forward to 2007, when the same company sought FDA approval for etoricoxib (Arcoxia), a new drug in the same class. Merck had initially proposed — and the agency had approved — a study comparing etoricoxib with diclofenac, an NSAID that many worried carried its own cardiac risk. Several years and millions of dollars later, Merck presented the FDA with trial evidence that etoricoxib caused roughly the same number of cardiac events as diclofenac. But this time, the FDA allowed its sharpest internal critic, David Graham, to present data to the advisory committee on the implications of approving another cyclooxygenase-2 inhibitor with potentially dangerous cardiac

side effects. Had the company used a more appropriate comparator, naproxen, Graham and the others argued, the increased cardiovascular risk would have been clear (see table). The committee voted overwhelmingly against approval. If diclofenac also presented a cardiac risk, the committee agreed, then the FDA should not approve a new product with no proven advantage that might confer the same hazard.<sup>3</sup> Not only did this decision fly in the face of the original study design, it was also a sharp departure from the conventional FDA view that a new drug in an established class need not be any safer or more effective than its predecessors. The committee's vote was so lopsided that the agency, still embarrassed at having missed the risk of myocardial infarction associated with rofecoxib during 5 years of widespread use, could not but agree with its recommendation.

A decision in the diet-drug category provides another indication of renewed assertiveness by the FDA's external advisers. In 1995, the FDA reviewed an application for dexfenfluramine, later marketed as Redux (Interneuron). Its parent compound, fenfluramine, led to negligible weight loss and caused potentially fatal pulmonary hypertension; there was no clear evidence that its new D-isomer would be

any better in either respect. In a single clinical trial, the manufacturer showed that patients randomly assigned to receive dexfenfluramine lost about 6 lb more than those given placebo — hardly a medical breakthrough. The company claimed that on a population basis, such weight loss could result in less hypertension, diabetes, and heart disease, but no trial data were presented to substantiate this hope. Only 2 months after an advisory committee recommended disapproving the drug, the FDA convened another meeting of the same group to reconsider the question. No important new data were presented, but several skeptical committee members couldn't attend the second meeting, and the drug was approved. Redux proved to be an unimpressive appetite suppressant; the expected pulmonary hypertension indeed occurred, along with unexpected heart-valve damage. The drug was withdrawn from the market after just 1 year; its manufacturer has since paid more than \$20 billion in damages to affected patients and their lawyers.<sup>4</sup>

A different fate has met the most recent entry into the lucrative diet-drug market, rimonabant. Advocates said it could reduce appetite, improve lipid levels, and help people quit smoking. Faced with such a potential embarrassment of riches, its manufacturer, Sanofi-Aventis, entered the blockbuster lottery by trying for an appetite suppressant indication. Rimonabant worked slightly better than dexfenfluramine — clinical trials demonstrated a weight loss of 13 lb more than that achieved with placebo — but the drug also seemed to raise the risk of depression (sometimes severe), suicidality, anxiety, and insomnia. Despite these ad-

verse effects, FDA staff issued an encouraging “approvable” letter in February 2006. But when an advisory committee reviewed the evidence in June 2007, it voted unanimously against the drug.<sup>5</sup> Soon thereafter, the manufacturer withdrew its application.

The agency is now addressing yet another follow-on drug as the glitazone story evolves. In 1997, the first entry in this class of antidiabetic agents, troglitazone (Rezulin, Parke-Davis), was observed to cause fulminant hepatic necrosis, sometimes fatal. Regulatory authorities throughout the world quickly concluded that the product had an indefensible risk-benefit ratio, and it was withdrawn from the market, often within just a few months of approval. Yet the FDA and its advisory committee were swayed by the arguments of the manufacturer and kept it in use in the United States for 2 years after it had been made unavailable in nearly every other country.<sup>4</sup> Now, a decade later, troglitazone’s younger sibling, rosiglitazone (Avandia, GlaxoSmithKline), has been implicated in raising the risks of congestive heart failure and myocardial infarction, without impressive evidence of a coun-

tervailing advantage in clinical outcomes. An advisory committee meeting on July 30, 2007, did not fuel hopes for a new era of data-driven reform. The committee voted, 20 to 3, that rosiglitazone increases cardiac ischemic risk in type 2 diabetes but then recommended, by a 22-to-1 vote, that the drug remain in use. The decision was more suggestive of Rezulin redux (and of Redux) than it was of resolve. Although Avandia has been prescribed widely since 1999, several participants noted that neither the manufacturer nor the FDA had carried out enough safety studies to permit a clear conclusion.

The approval, prescribing, and safety surveillance of prescription drugs involve a complicated mix of science, regulatory law, clinical judgment, business, and politics. It is not easy to ensure that science dominates in such a heady brew, but despite missteps such as the latest move with respect to rosiglitazone, an open model holds more promise for data-driven public decision making than those followed in the energy, finance, and defense sectors, among others. As Congress persists in allowing industry funding to dominate the FDA budget

(and, many fear, its perspective as well), it will be especially important for the scientific community to remain independent, conduct rigorous analyses, and make its voice heard clearly to ensure that drug-review decisions are driven solely by the data.

Dr. Avorn reports having served, pro bono, as an expert witness for plaintiffs in Vioxx-related lawsuits.

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1. Harris G, Berenson A. 10 Voters on panel backing pain pills had industry ties. *New York Times*. February 25, 2005:A1.
2. Wood S. Reauthorizing the Prescription Drug User Fee Act: how are PDUFA, the FDA budget, and drug safety related? Washington, DC: George Washington University School of Public Health and Health Services, April 2007. (Accessed July 26, 2007, at [http://www.gwumc.edu/sphhs/about/rapidresponse/download/RapidResponse\\_PDUFA.pdf](http://www.gwumc.edu/sphhs/about/rapidresponse/download/RapidResponse_PDUFA.pdf).)
3. FDA Arthritis Advisory Committee. Arcoxia (etoricoxib). Rockville, MD: Food and Drug Administration, April 12, 2007. (Accessed July 26, 2007, at <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4290t1-Part4.pdf>.)
4. Avorn J. Powerful medicines: the benefits, risks, and costs of prescription drugs. New York: Alfred A. Knopf, 2005.
5. Center for Drug Evaluation and Research. NDA 21-888, Zimulti (rimonabant). Rockville, MD: Food and Drug Administration, June 13, 2007. (Accessed July 26, 2007, at <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4306t1-Part1.pdf>.)

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## When Doctors Become Terrorists

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We were lucky in London in June. A large car bomb was left just outside a crowded nightclub near Piccadilly Circus, and a second car bomb was parked nearby to catch those fleeing from the first bomb. Neither bomb went off, but if either had exploded, we would have seen casualties similar to those of the Bali nightclub bombings.

The following day, two men tried to drive a car loaded with gasoline and gas cylinders into the main terminal of the Glasgow airport but were thwarted by the bollards outside the entrance. One man then set fire to himself, and both were overpowered by police and bystanders. The wealth of forensic evidence left behind in the three cars was

sufficient for the police to swiftly detain six further suspects.

British security services are reported to be alarmed because the alleged perpetrators were people not well known to the police and intelligence community beforehand. But that is not what has caught the public’s attention. Seven of the eight arrested are physicians, the eighth is a medical