

Written testimony before the
United States House of Representatives
Committee on Appropriations
Subcommittee on Agriculture, Rural Development,
Food and Drug Administration, and Related Agencies

In Public Hearings on
FDA Oversight of Drug Safety

Wednesday, February 27, 2008

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I am honored to testify in these hearings on the drug safety and the Food and Drug Administration. Since the Merck Company voluntarily withdrew its pain reliever Vioxx from the U.S. and other markets worldwide on September 30, 2004, the FDA has come under intense criticism for its handling of drug safety. Much of this criticism arose from a series of events involving the Cox-2-inhibitor class of pain relievers (Vioxx, Celebrex, and Bextra), the SSRI class of antidepressants (where the possibility of suicidal behavior is the main issue), the diabetes drug Avandia (involving excess adverse cardiovascular events in clinical trials), the antibiotic Ketek, and others.

Some observers have suggested that we face an ongoing crisis in drug safety and that the FDA lacks the determination and institutional tools necessary to deal adequately with drug safety (Avorn 2007; Curfman, et al. 2006; Fontanaros, et al., 2004; Furberg, et al., 2006; Hennessy and Strom 2007; Kohn and Bor 2004; *New York Times*, September 28, 2006; Okie 2005; Psaty and Furberg 2005; Smith 2007; Strom 2006; Topol 2004b). Among the FDA's alleged problems are weak leadership, weak incentives to give due weight to drug safety, an institutional structure ill-designed to deal with drug safety before and after drug approval, and a lack of resources. Although the FDA Amendments Act of 2007 (FDAAA) was designed to address many of the problems, vigorous criticism of the FDA continues.

I believe these criticisms are largely unfounded. On the whole, the FDA is giving adequate, and indeed, more than adequate weight to safety in its deliberations over drug development and approval and in its handling of approved drugs in the marketplace. This was true before passage of FDAAA and it remains true today. To be sure, changes at the FDA and in the entire health care sector could improve drug safety at reasonable cost, but that does not mean that the FDA has been neglectful.

Is There a Drug Safety Problem?

Perhaps the oddest part of the past few years' debate of over drug safety is that so far as I am aware, no one has adduced systematic data indicating that drug safety is in a crisis or has even significantly worsened. Probably the most cited report on drug safety is *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, released in September 2006 by the Institute of Medicine, a part of the National Academy of Sciences (NAS 2006; all citations are to the "uncorrected proofs" released at that time). That report did not even attempt to assess whether there is indeed a drug safety crisis: "The committee did not attempt to document whether or not a drug safety crisis exists, and this report should not be interpreted as commenting on that claim one way or the other" (p. 1-1). Nonetheless, the report generally assumed that the FDA's handling of drug safety was seriously endangering the American public, and the authors strongly recommended numerous changes.

In reaching its conclusions, however, the IOM authors relied upon deeply flawed evidence and reasoning. For one thing, the report was notably unscholarly. On direct-to-consumer advertising of prescription drugs, for example, the authors cited a few largely irrelevant older articles while ignoring a flood of recent econometric research (Berndt 2006; Calfee 2007b) and a much-cited randomized trial that revealed large health benefits from antidepressant advertising (Kravitz et al. 2005). On another crucial topic – "off-label" prescribing for uses not explicitly approved by the FDA – the only citation (pp. 2-7) was to a *Washington Post* article (Boodman 2006) instead of the *Archives of Internal Medicine* article (Radley et al. 2006) that the Post article was about. On yet another central issue – whether FDA drug warnings are effective – the report (pp. 2-16) cited a trade press report (*Medical News Today* 2006) rather than the *Archives of Internal Medicine* study it was about (Lasser et al. 2006). What the *Archives of Internal Medicine* study actually found was that medical harm from prescriptions that violated warnings was extremely rare (an estimated total of sixteen such events among the 324,548 patients in the study). In general, the IOM report adduced little systematic evidence for its criticisms or in support of the efficacy of its many recommendations for change.

Quite aside from the IOM report, the leading drug safety anecdotes of the past few years have been treated in a largely misleading manner, greatly exaggerating safety problems and especially, the adverse nature of FDA actions. The triggering event was Merck's withdrawal of Vioxx on September 30, 2004, after an ongoing clinical trial revealed excess heart attacks among Vioxx users (Psaty and Furberg 2005). As the FDA presciently pointed out at the time, it was far from clear that Vioxx or its competing Cox-2 inhibitor, Celebrex, was significantly riskier than the much older non-steroidal anti-inflammatory drugs (NSAIDs) they replaced, given that these older drugs had never been subjected to rigorous clinical trials like the one that brought Vioxx down. Subsequent research has largely vindicated that view, with the entire class of NSAIDs (old and new, Cox-2s or not) now bearing heart attack warnings (Calfee 2005; Kearney et al. 2006; Warner and Mitchell 2008).

The second-ranking triggering event was controversy over previously non-public clinical trial results in which children and adolescents taking one of the SSRI class of antidepressants (Prozac or Zoloft, for example) were more likely to exhibit suicidal "ideation" or thoughts (but not to attempt or commit suicide). Faced with relentless criticism from litigators, politicians, popular press editorialists, and elite medical journals, the FDA implemented its strongest warning (a "black box," which appears on the FDA-approved label) for all antidepressants, not just SSRIs (because again, there was little reason to think that older drugs, which can cause fatal overdoses, are safer). Subsequent research taking a variety of approaches has found that SSRI use is strongly associated with lower, not higher, suicide rates, and that the highly publicized warnings probably did more harm than good by reducing antidepressant use. In particular, a series of reports has found that there is a striking, inverse relationship between SSRI prescriptions and youth suicides in a variety of data sets and that the imposition of new FDA warnings (beginning with public health alerts) is strongly associated with reduced antidepressant prescribing for children (and younger adults) and higher suicide rates (Shogren 2004; McKeown, Cuffe, and Schulz 2006; Ludwig, Marcotte, and Norberg 2007; Brent 2007; Gibbons et al. 2007; Lubell et al. 2007; Bridge et al. 2007; Pfeffer 2007).

Finally, there is Avandia, a popular diabetes drug first approved in 1999 (see Calfee 2007a for more details on this and other matters). On May 21, 2007, the *New England Journal of Medicine* published a meta-analysis of adverse cardiovascular events in clinical trials of Avandia (Nissen and Wolski 2007). Coauthored by a prominent critic (Nissen) of the FDA's handling of Vioxx, the meta-analysis revealed excess heart attacks and strokes among Avandia users. Accompanying the meta-analysis was an editorial by two well-known advocates of FDA reform (Psaty and Furberg 2007), one of whom (Psaty) was among the IOM authors. They declared that the Avandia meta-analysis revealed FDA neglect and was reason enough to implement one of the more radical reforms, the creation of an independent drug safety board (something the IOM report declined to recommend).

We soon learned that the meta-analysis authors and the journal editors were politically motivated (Usdin 2007b, Gottlieb 2007b [May 29]). Dissent quickly emerged from the academic medical community regarding both policy and research methods (*Lancet* 2007). FDA staff, researchers at Glaxo-Smith-Kline (the manufacturer of Avandia), and others pointed out that significant cardiovascular risk had not been revealed by large randomized trials, including the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, which was designed to address cardiovascular safety (Krall 2007; Home et al. 2007). In July 2007, an editorial in the journal *Nature Clinical Practice* vigorously attacked the Avandia meta-analysis on methodological grounds and criticized the *New England Journal* for rushing it into print and causing confusion among patients (Fuster and Farkouh 2007).

Academic and scholarly debate has continued, with one meta-analysis finding, again, excess heart attacks (but slightly fewer deaths) for Avandia users (Singh et al. 2007), and another, slightly reduced cardiovascular risk for Actos, Avandia's chief competitor (Lincoff et al. 2007). The imprecision and questionable reliability of meta-analyses have been made clear, as articles have demonstrated how modest changes in data and statistical methods (which involve considerable judgment even on such basic matters as whether to include trials in which no adverse events occurred) can dramatically alter

the results. Many, if not most, endocrinologists clearly want to maintain treatment options for a condition (diabetes) that is notoriously variable among patients and correspondingly difficult to treat. Thus a July 30, 2007, joint meeting of two FDA advisory committees voted 23-1 that Avandia involves an elevated risk of (minor) heart attacks compared to placebos, but also voted 21-3 in favor of keeping Avandia on the market while asking for new label warnings (but not the FDA's strongest "black box" warning) (Usdin 2007c). In the meantime, Avandia clinical trials continue, under FDA oversight as always. Obviously, experts can disagree over such matters as the nature and timing of cardiovascular warnings for Avandia, but that is very different from a finding that the FDA tended to downplay risks while approving Avandia and monitoring its risks afterward. In fact, the debate has come to focus mainly on the use of "surrogate markers" (in this case, glycemic control) instead of "clinical outcomes" (such as heart attacks or amputations) in approving new drugs. Critics of FDA policy want to avoid surrogate markers, but as the FDA and others have pointed out, this would drastically increase research costs and delay new drug approvals by several years (Joffe, et al., 2007).

Other frequently cited examples of FDA failure also do not withstand scrutiny. An example is the pioneer antibiotic Ketek. Far from rushing to approve Ketek, the FDA was actually slow, mainly because of fraud in one of the pivotal clinical trials, and it finally approved Ketek partly on the basis of five years of experience in Europe, where it remains in use to this day. This unorthodox process provoked much criticism, but any new class of reasonably safe and effective antibiotics is a valuable addition, and despite the controversy, there is little reason to think this particular drug is especially dangerous (Usdin 2006a, 2006b).

Why the FDA Tends Toward Over-caution in Drug Safety

Clearly, there is little persuasive evidence of FDA neglect of drug safety in recent years. On the other hand, there are compelling reasons to think that in balancing safety against the benefits of new drugs, the FDA tends to give too much weight to safety and not enough to benefits. The reasons lie in the biased incentive structure facing the FDA

staff. The unrelenting criticism visited on the FDA since the Vioxx withdrawal illustrates a profound disparity how the public penalizes two different kinds of regulatory error. When FDA staff members decide whether the benefits of a proposed new drug exceed its risks, they know that if they commit what is often called a Type I error – the approval of a drug that turns out to be insufficiently safe once marketing begins – their error will usually become known (a “public error”). This can and often does lead to impassioned criticism of the agency and to correction of the error (although more often than not, critics fix upon something that was probably not an error at all). On the other hand, a Type II error – the failure to permit marketing of a drug that would in fact provide benefits in excess of harms – is typically detected by relatively few people (a “private error”), and its deleterious effects can persist more or less indefinitely.

The effect is to bias even the most conscientious FDA regulators toward exercising excessive caution and requiring excessive drug testing. This first became apparent in a stream of research on the “drug lag” of the 1960s and 1970s, when FDA approvals trailed far behind those in European nations. This research revealed no consumer benefit in terms of safer drugs, yet similar approval lags continued for years afterward (Peltzman 1973, 1974; Wardell and Lasagna 1975; Katin and Brown 1995). Yet slow drug approvals here did not bring extra safety. An analysis of the United States, Spain, and the United Kingdom yielded essentially identical drug-withdrawal rates despite the more rapid drug-approval timelines in the European countries (Bakke, et al. 1995). Also, research has made clear that the advent of user-fee funding via the 1992 Prescription Drug User Fee Act has worked to the benefit of patients by accelerating the arrival of new drugs (Philipson, et al., 2005).

There is anecdotal evidence that soon after the Vioxx withdrawal and ensuing criticism, the FDA became even more cautious in approving new drugs and new indications (Harris 2005). Last year, for example, the FDA refused to approve the pain reliever Arcoxia and the weight-loss drug Accomplia even though both had been approved by the European Union and many other nations (Gottlieb 2007a [April 17]; Wadman 2007). The FDA has also been unreceptive to some promising new drugs for

advanced cancer, including Provenge, Genasense, and others (Usdin 2007a; Miller and Henderson 2007; Miller 2007; Pardoll and Allison 2004). The 2007 FDAAA legislation, which rooted in the view that the FDA staff has consistently neglected drug safety, has probably reinforced the FDA's innate tendency toward over-caution (Calfee 2007).

Neither Congress nor the IOM report has paid much attention to another potent force: market-driven manufacturer incentives to maintain drug safety. Such incentives operate with powerful effect in far less regulated high-tech industries such as automobiles, petroleum, and electronics. As in other industries, pharmaceutical manufacturers rely heavily upon maintaining their reputation among customers (especially physicians) for product safety and efficacy. Post-approval clinical trials play a central role in this process. These trials are undertaken to expand markets, but they necessarily open the door to new and possibly alarming (as well as reassuring) safety information. Often, post-approval trials are bigger, longer, and more informative than the trials undergirding drug approvals. Often, they force revisions in accepted views of such basic matters as, for example, the benefits of lowering serum cholesterol or the safety of all NSAID pain relievers (Topol 2004a; Wadman 2007).

What Can Be Done to Improve Drug Safety

Much could be done to improve drug safety without making the FDA even more cautious in approving new drugs and new uses for old drugs. The FDA clearly needs more resources, especially in information technology and in personnel with strong training in basic biological sciences and related fields. As former Commissioner Mark McClellan and others have pointed out, there are fruitful opportunities to collaborate with the private sector – not the pharmaceutical industry but also health insurance and other industries – in order to make far better use of the voluminous and ever-improving databases that are already in place (McClellan 2007). Carefully targeted increases in FDA funding could open up numerous under-exploited pathways to improved drug safety as well as better use of pharmaceuticals generally.

References

- Avorn, Jerry (2007) "Paying for Drug Approvals: Who's Using Whom?," *New England Journal of Medicine*, posted Ap. 13.
- Bakke, Olav M., Michael Manocchia, Francisco de Abajo, Kenneth I. Kaitin, and Louis Lasagna (1995) "Drug Safety Discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: A Regulatory Perspective," *58 Clinical Pharmacology and Therapeutics*, v. 58, p. 108-117.
- Berndt, Ernst R. (2006) "The United States Experience with Direct-to-Consumer Advertising of Prescription Drugs: What Have We Learned?," in Frank A. Sloan and Chee-Ruey Hsieh, eds., *Promoting and Coping with Pharmaceutical Innovation: An International Perspective*, Cambridge University Press.
- Boodman, SG (2006) "Many Drug Uses Don't Rest on Strong Science," *Washington Post*, May 23.
- Brent, David (2007) "Editorial: Antidepressants and Suicidal Behavior: Cause or Cure?," *American Journal of Psychiatry*, v. 164, p. 989-991 (July).
- Bridge, Jeffrey A., Satish Iyengar, Cheryl B. Salary, Rémy P. Barbe, Boris Birmaher, Harold Alan Pincus, Lulu Ren, and David A. Brent (2007) "Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials," *Journal of the American Medical Association*, v. 297, n. 15, p. 1683-1696 (Ap. 15).
- Calfee, John E. (2005) "The Vioxx Fallout," *AEI Health Policy Outlook*, Sept.-Oct. 2005.
- Calfee, John E. (2006) "Playing Catch-up: The FDA, Science, and Drug Regulation," *Health Policy Outlook*, American Enterprise Institute, Washington, D.C., March 2006.
- Calfee, John E. (2007a) "Reform Without Reason," *Health Policy Outlook*, American Enterprise Institute, Washington, D.C., September 2007. Available at http://www.aei.org/publications/pubID.26859/pub_detail.asp. Accessed February 24, 2008.
- Calfee, John E. (2007b) "An Assessment of Direct-to-consumer Advertising of Prescription Drugs," *Clinical Pharmacology and Therapeutics*, v. 82, n. 4, p. 357-360 (October).

Curfman, Gregory D., Stephen Morrissey, and Jeffrey M. Drazen (2006) “Editorial: Blueprint for a Stronger Food and Drug Administration,” *New England Journal of Medicine*, v. 355, n. 17, p. 1821 (Oct. 26).

Fontanarosa, Phil B., Drummond Rennie, and Catherine D. DeAngelis (2004) “Editorial: Postmarketing Surveillance: Lack of Vigilance, Lack of Trust,” *Journal of the American Medical Association*, v. 292, p. 2647-2650 (Dec. 1).

Furberg, Curt D., Arthur A. Levin, Peter A. Gross, Robyn S. Shapiro, Brian L. Strom (2006) “The FDA and Drug Safety: A Proposal for Sweeping Changes,” *Archives of Internal Medicine*, v. 166, p. 1938-1942 (Oct. 9).

Fuster, Valentin, and Michael E. Farkouh (2007) “Editorial: Faster Publication Isn’t Always Better,” *Nature Clinical Practice*, v. 4, n. 7, p. 345 (July).

Gibbons, Robert D., C. Hendricks Brown, Kwan Hur, Sue M. Marcus, Dulal K. Bhaumik, Joëlle A. Erkens, Ron M.C. Herings, and J. John Mann (2007) “Early Evidence on the Effects of Regulators’ Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents,” *American Journal of Psychiatry*, v. 164, p. 1356-1363 (Sept.).

Gottlieb, Scott (2007a) “Drug Danger,” *Wall Street Journal*, April 17.

Gottlieb, Scott (2007b) “Journalist Malpractice,” *Wall Street Journal*, May 29, p. A15.

Harris, Gardiner (2005) “F.D.A. Responds to Criticism With New Caution,” *New York Times*, August 6.

Hennessy, Sean, and Brian L. Strom (2007) “Perspective: PDUFA Reauthorization — Drug Safety’s Golden Moment of Opportunity?,” *New England Journal of Medicine*, posted Ap. 13, 2007.

Home, Philip D., et al., for the RECORD Study Group (2007) “Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis,” *New England Journal of Medicine*, v. 357, n. 1, p. 28-38 (July 5).

Joffe, Hylton V., Mary H. Parks, Robert J. Meyer, John K. Jenkins, and Robert Temple (2007) “Letter: Rosiglitazone and the FDA,” *New England Journal of Medicine*, v. 357, . 17, p. 1775-1777 (Oct. 25).

Kaitin, Kenneth, and Jeffrey Brown (1995) “A Drug Lag Update,” *29/2 Drug Information Journal* 361-374.

Kearney, Patricia M, Colin Baigent, Jon Godwin, Heather Halls, Jonathan R Emberson, and Carlo Patrono (2006) “Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials,” *British Medical Journal*, v. 332, p. 1302-1308 (June 3).

Kohn, David, and Jonathan Bor (2004) “Scientist’s warnings on drugs stir debate: Some doctors question FDA’s assessment of 5 popular prescriptions,” *Baltimore Sun*, November 19, 2004.

Krall, Ronald L. (2007) “Cardiovascular Safety of Rosiglitazone ,” *Lancet*, v. 369, posted May 30.

Lancet (2007) “Editorial: Rosiglitazone: Seeking a Balanced Perspective,” v. 369, posted May 23.

Lasser, Karen E., Diane L. Seger, D. Tony Yu, Andrew S. Karson, Julie M. Fiskio, Andrew C. Seger, Nidhi R. Shah, Tejal K. Gandhi, Jeffrey M. Rothschild, and David W. Bates (2006) “Adherence to Black Box Warnings for Prescription Medications in Outpatients,” *Archives of Internal Medicine*, v. 166, n. 3, p. 338-344.

Lincoff, A. Michael, Kathy Wolski, Stephen J. Nicholls, and Steven E. Nissen (2007) “Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Trials,” *Journal of the American Medical Association* v. 298, n. 10, p. 1180-1188 (Sep. 12).

Lubell, K.M., S.R. Kegler, A.E. Crosby, and D. Karch (2007) “Suicide Trends Among Youths and Young Adults Aged 10--24 Years – United States, 1990-2004,” *Morbidity and Mortality Weekly Reports*, v. 56, n. 35, p. 905-908 (Sep. 7).

Ludwig, Jens, Dave E. Marcotte, and Karen Norberg (2007) “Anti-depressants and Suicide,” NBER Working Paper No. 12906.

McClellan, Mark (2007) “Drug Safety Reform at the FDA — Pendulum Swing or Systematic Improvement?,” *New England Journal of Medicine*, posted Ap. 13, 2007.

Medical News Today, Feb. 16, 2006, “Drugs” Black Box Warning Violations In Outpatient Settings Putting Patients At Risk.”

Miller, Henry I., and David R. Henderson (2007) “Governmental Influences on Drug Development: Striking a Better Balance,” *Nature Reviews Drug Discovery*, v. 6, p. 532-539 (July).

Miller, Richard (2007) “Cancer Regression,” *Wall Street Journal*, Aug. 1, 2007.

National Academy of Sciences, Institute of Medicine (2006) *The Future of Drug Safety: Promoting and Protecting the Health of the Public*.

New York Times, September 28, 2006, “Editorial: Prescription for a Stronger F.D.A.”

Nissen, Steven E., and Kathy Wolski (2007) “Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes,” *New England Journal of Medicine*, published online May 21, 2007.

Okie, Susan (2005) “What Ails the FDA?” *New England Journal of Medicine*, v. 352, p. 1063-1065 (Mar. 17).

Pardoll, Drew, and James Allison (2004) “Cancer Immunotherapy: Breaking the Barrers to Harvest the Crop,” *Nature Medicine*, v. 10, n. 9, p. 887-892 (Sept.).

Peltzman, Sam (1973) “An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments,” *Journal of Political Economy*, v. 81, n. 5., p. 1049-1091 (Sept.-Oct.).

Peltzman, Sam (1974) *Regulation of Pharmaceutical Innovation: The 1962 Amendments*, Washington DC: American Enterprise Institute for Public Policy Research.

Pfeffer, Cynthia R. (2007) “Editorial: The FDA Pediatric Advisories and Changes in Diagnosis and Treatment of Pediatric Depression,” *American Journal of Psychiatry*, v. 164, p. 843-846 (June).

Philipson, Tomas J., Ernst R. Berndt, Adrian H. B. Gottschalk, and Matthew W. Strobeck (2005) “Assessing the Safety and Efficacy of the Fda: the Case of the Prescription Drug User Fee Acts,” NBER Working Paper 11724.

Psaty, Bruce M., and Curt D. Furberg (2005) “Cox-2 Inhibitors—Lessons in Drug Safety” *New England Journal of Medicine*, v. 352, p. 1133-1135 (Mar. 17).

Psaty, Bruce M., and Curt D. Furberg (2007) “Editorial: Rosiglitazone and Cardiovascular Risk,” *New England Journal of Medicine*, v. 356, p. 2522-2524.

Radley, David C., Stan N. Finkelstein, and Randall S. Stafford (2006) “Off-label Prescribing Among Office-Based Physicians,” *Archives of Internal Medicine*, v. 166, p. 1021-1026 (May 8).

Shogren, Elizabeth (2004) “FDA Sat on Report Linking Suicide, Drugs: Officials ordered more studies after their own expert found children on antidepressants were twice as likely to show suicidal behavior,” *Los Angeles Times*, April 6.

Simon, Gregory E. (2006) “The Antidepressant Quandary — Considering Suicide Risk When Treating Adolescent Depression,” *New England Journal of Medicine*, v. 355, p. 2722-2733 (Dec. 28).

Singh, Sonal, Yoon K. Loke, and Curt D. Furberg (2007) “Long-term Risk of Cardiovascular Events With Rosiglitazone: A Meta-analysis,” *Journal of the American Medical Association*, v. 298, n. 10, p.1189-1195 (Sep. 12).

Smith, Sheila Weiss (2007) “Sidelining Safety — The FDA's Inadequate Response to the IOM,” *New England Journal of Medicine*, v. 357, n. 10, p. 960-963 (Sep. 6).

Strom, Brian L. (2006) “How the US Drug Safety System Should Be Changed,” *Journal of the American Medical Association*, v. 295, n. 17, p. 2072-2075 (May 3).

Topol, Eric (2004a) “Intensive Statin Therapy: A Sea Change in Cardiovascular Prevention,” (editorial), *New England Journal of Medicine*, early release April 8, 2004, v. 350, n. 15, p. 1562-1564 (April 8).

Topol, Eric J. (2004b) “Failing the Public Health: Rofecoxib, Merck, and the FDA,” *New England Journal of Medicine*, v. 351, n. 17, p. 1707-1709 (October 21, 2004).

Usdin, Steve (2006a) “Ketek Politics,” *BioCentury*, June 26, 2006, p. A1.

Usdin, Steve (2006b) “Science Friction,” *BioCentury*, Dec. 18, 2006, p. A1-A5.

Usdin, Steve (2007a) “Blockbusted at ODAC” *BioCentury*, May 14, 2007, p. A1.

Usdin, Steve (2007b) “Political Defibrillator” *BioCentury*, May 28, 2007, p. A1-A8.

Usdin, Steve (2007c) “A Vote Against Panic”, *BioCentury*, Aug. 7, 2007, p. A1-A7.

Wadman, Meredith (2007) “The Pain Game,” *Nature*, v. 448, p. 400-401 (July 26).

Wardell, William M., and Louis Lasagna (1975) *Regulation and Drug Development*, American Enterprise Institute.

Warner, Timothy D., and Jane A. Mitchell (2008) “Viewpoint: COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs,” *Lancet*, v. 371, p. 270-273.