Ensuring Drug Safety: Where Do We Go From Here?
Bill Number:
Hearing Date: March 3, 2005, 10:00 am
Location: SD106
Witness:
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Testimony

Mr Chairman and members of the Committee,

Thank you for the opportunity to testify. My name is Bruce Psaty. As a practicing general internist and cardiovascular-disease epidemiologist, I have broad interests in public health and drug safety.

The COX-2 inhibitors, a new class of non-steroidal anti-inflammatory drugs, were supposed to have fewer serious side effects than other available non-steroidals. After more than 5 years on the market, an increased risk of heart attack and stroke has been confirmed for Vioxx, Celebrex, and Bextra (1-5). Some of the 20 million Vioxx users and 27 million Celebrex users have been injured. Indeed, the integrity of the American drug-safety system itself has been questioned. How can this problem be prevented in the future?

Recommendations.

1. Give balanced attention to risks and benefits in FDA decisions (6-8). To use a drug wisely, patients and physicians need to know about both risks and benefits. The design of the pre-approval trials of the COX-2 inhibitors minimized the possibility of uncovering evidence of cardiovascular harm. If manufacturers do not address the potential risks and benefits with equal scientific rigor, then in the interests of public health, the FDA must insist that they do so, both before and after approval.

2. Require large long-term trials (9). The limited pre-approval evaluation of the COX-2 inhibitors was not adequate. Medicines that will be used by millions of Americans for long periods of time are best evaluated in large long-term clinical trials that are started as early as possible in the drug approval process. These trials need not delay approval. This approach, used for the lipid-lowering statin drugs, has benefited patients, physicians and the pharmaceutical industry.

3. Create an independent Center for Drug Safety within the FDA to oversee drugs after marketing (10-14). In a commentary entitled, “Postmarketing surveillance--lack of vigilance, lack of trust,” the editors of JAMA, write: “It is unreasonable to expect that the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek evidence to prove itself wrong.” Other scientists and former FDA officials have also advocated a truly independent Center for Drug Safety.

4. Invest the Center for Drug Safety with new authority to regulate drugs that are on the

market (4,15). Revisions to the Vioxx product label in 2002 took more than two years to negotiate. The CDS must be able to compel manufacturers, in a timely fashion, to revise product labels, to conduct patient or physician education, to limit advertising, to complete promised studies, to conduct new studies, to suspend sales and to withdraw drugs. The Center for Drug Safety should be responsible for post-marketing evaluations, including determinations of the balance of risks and benefits for drugs that are on the market.

5. Provide the Center for Drug Safety with new resources (14,16,17). America has become the drug-safety testing ground for new medications, such as the COX-2 inhibitors. According to Dr David Kessler, former head of the FDA, "PDUFA should have had funding on the safety side from the beginning, but the industry refused to accept that…. We wanted it. The industry said no." Since 1992, FDA resources for drug safety have dwindled. In the Office of New Drugs, more than 1000 employees work to review a few dozen new drugs per year. In the Office of Drug Safety, 109 employees work to evaluate the safety of thousands of drugs currently on the market.

6. Strengthen US post-marketing safety systems (18-21). The FDA's MedWatch system, which has been characterized as "fundamentally a 1950s-era approach," lacks many of the features of high-quality epidemiologic studies, including validation of events by standard criteria, complete ascertainment of cases, population-based controls, comparable assessment of drug use and risk factors, and so forth. The state of this system stands in stark contrast to the enormous expansion of the pharmaceutical industry during the past several decades. In 2004, the three COX-2 inhibitors alone had combined sales more than $6 billion dollars. Several new mechanisms to conduct post-marketing surveillance rapidly and efficiently merit support.

Regardless of the speed of approval, toxic molecules occasionally make it to market as drugs. To protect the health of the public, the most important recommendation is an independent Center for Drug Safety with new authority and funding. On-going congressional oversight of the FDA, CDER, and the new Center for Drug Safety would afford an important forum for the public discussion of drug safety. Thank you.

dst15-16.rtf/doc
March 1, 2005
737 words

US Senate Committee on Health, Education, Labor and Pensions
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Biographical Sketch

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Bruce M. Psaty, MD, PhD, is co-director of the Cardiovascular Health Research Unit and professor of medicine, epidemiology, and health services at the University of Washington, Seattle, WA. As a practicing general internist and cardiovascular-disease epidemiologist, Psaty has broad interests in public health and drug safety. For the past 10 years, all funding for his research, including numerous drug-safety studies, has come from the National Heart, Lung, and Blood Institute (NLHBI), the National Institute on Aging (NIA), or the American Heart Association (AHA). His primary research interests include the study of drug treatment for high blood pressure, hormone replacement therapy in postmenopausal women, and new or emerging risk factors for heart disease and stroke. Several current projects, funded by the National Institutes of Health (NIH), focus on drug-gene interactions and represent efforts to translate findings from the Human Genome Project into clinical practice and, thus, improve the safety and efficacy of commonly used medications. In addition to serving as the principal investigator on 4 large epidemiologic studies, Psaty has major roles in several multi-center NHLBI- or NIH-funded epidemiologic studies and clinical trials, including the Cardiovascular Health Study, the Multi-Ethnic Study of Atherosclerosis, and the Women's Health Initiative. With 250 peer-reviewed publications, Psaty publishes regularly, including a number of articles and editorials in the Journal of the American Medical Association and the New England Journal of Medicine. Psaty also reviews research in several capacities. Currently, he is the chair of the NIH Epidemiology of Chronic Disease Study Section and chair of the Group Health Cooperative Research Committee. Psaty has chaired or participated in a large number of committees and review groups constituted by the AHA, the NIH, and the World Health Organization. He also teaches and mentors students, fellows and junior faculty in medicine and epidemiology. Psaty has no financial interest in the matters now before the committee.

US Senate Committee on Health, Education, Labor and Pensions
“Ensuring drug safety: where do we go from here?”
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Supplementary information

Post-marketing surveillance. When drugs are approved as “safe and effective” for their intended use, the known benefits appear to outweigh the known risks (20). At the time of regulatory approval for most drugs, a number of issues remain unknown--the occurrence of rare but serious adverse drug events, drug interactions, late events during treatment or after the discontinuation of treatment, effects in pregnancy or differential effects in subgroups that may be defined by age, sex, race, or other factors. In contrast to the highly structured pre-marketing evaluation, post-marketing surveillance has little structure. According to Gale, “the regulatory process creates an evidence-free zone at the time of launch of new drugs” (20). Pharmaceutical companies often promise post-marketing clinical trials as a condition of approval. In practice, however, more than half of these promised studies, according to an FDA report, have not been started (15). The FDA lacks authority to insist that these promised studies be completed or to compel new post-marketing studies. The FDA post-marketing regulations require only that pharmaceutical companies collect, review and report to the FDA all suspected adverse drug reactions (ADRs) thought to be associated with the drug (22,23). While both companies and the FDA can analyze the ADR data and recommend actions such as label changes, additional warnings, or new studies, the FDA regulations largely focus on reporting procedures and thus leave unclear who is required to initiate these actions.

US post-marketing surveillance system. MedWatch, the FDA safety information system and adverse event reporting program, encourages physicians to report ADRs on a voluntary basis (18). Although the FDA received 286,755 ADR reports in 2001 (24), these data have major well-known limitations. The MedWatch ADR data are suitable only to identify rare serious adverse drug events that occur early in treatment and that are unrelated to the indication of the drug. For example, the lipid-lowering statin drug, Baycol (cerivastatin), was withdrawn from the market in 2001 because it was associated with high rates of rhabdomyolysis, a breakdown of muscle cells that causes pain, kidney failure and sometimes death (19,21,25). The MedWatch ADR data lack many of the features of high-quality epidemiologic studies, including validation of events by standard criteria, complete ascertainment of cases, population-based controls, comparable assessment of drug use and risk factors, and so forth. It would not have been possible to use the MedWatch system to detect reliably, for instance, the increased risk of cardiovascular events associated with the COX-2 inhibitors. One recent commentator characterized the MedWatch system as “fundamentally a 1950s-era approach” (26).

Growth of drug sales. The lack of development in post-marketing surveillance systems stands in stark contrast to the enormous expansion of the pharmaceutical industry during the past several decades. Although the costs of drug development are high, spending on prescription drugs between 1997 and 2001 increased by about 18% per year; and in 2001, the total prescription drug expenditures in the US reached $154.5 billion dollars (27). In 2004, despite the withdrawal of Vioxx in September, the three COX-2 inhibitors alone--Vioxx, Celebrex, and Bextra--had combined sales more than $6 billion dollars, or an average of about $16 million per day (28). The recent growth of the pharmaceutical industry has outstripped the safety systems that were developed when the industry was young.

Epidemiologic studies and new opportunities. In the past, data sources used to conduct high-quality observational studies of the risks and benefits of drugs have included existing cohort studies (29), administrative data from health maintenance organizations (30,31), Medicaid data (32,33), Medicare data linked to cancer registries (34), and international databases with drug data (35,36). In addition to AHRQ-funded Centers for Education and Research in Therapeutics (26), the FDA has had cooperative agreements with several institutions to investigate drug safety, but the available funds have diminished in recent years. Several new opportunities are on the horizon. First, data from new Medicare drug benefit can be linked with hospital and ambulatory care data to create a new resource for the study of drugs in older adults. With appropriate protections for privacy, these data should be available to the FDA and independent scientists interested in drug safety. Secondly, as part of the NIH Roadmap Project, the HMO-Research Network--Coordinated Clinical Studies Network will create an infrastructure for conducting studies on substantial numbers of the US population, and the movement toward an EPICcare based electronic record among the network members should soon provide the opportunity to conduct post-marketing surveillance rapidly and efficiently.

Post-marketing clinical trials. The pharmaceutical industry supports a number of post-marketing clinical trials, often for new indications. The cardiovascular harm associated with the COX-2 inhibitors became apparent in studies that were conducted for new indications such as the prevention of non-cancerous tumors in the colon (1-3). For the lipid-lowering statin drugs, for instance, the large long-term clinical trials have provided robust evidence about their health benefits in preventing cardiovascular complications of high levels of cholesterol (37-40). On the basis of this evidence, the indications for the statin drugs have expanded, statin drug sales have increased, and the health of the public has improved. Rapid publication and widespread dissemination of favorable findings is standard practice.

Failure to publish trials with unfavorable results. Unfavorable results tend not to get published. In the manufacturer's trial of 1.6 mg of Baycol, about 12% of patients developed signs and symptoms compatible with rhabdomyolysis (25). The high rate of adverse effects, with a dose that was only twice as high as the approved dose of 0.8 mg, "led to a consensus by the [company's communications] committee not to publish the results of this study" (25). Similarly, in 2000, Pfizer completed a randomized trial of celecoxib in Alzheimer's patients, but never published the unfavorable cardiovascular results and only made them publicly available in January 2005 (41). The results of this Alzheimer's study were not submitted to the FDA until June 2001, several months after a safety review that established labeling for Celebrex. Human subjects participate in studies to contribute to science and public health. Failure to publish findings not only violates their trust, but it also misrepresents the evidence about risks and benefits for patients and physicians. Federal action to assure that all clinical trials are registered and reported in a timely fashion is important.

Prescription Drug Fee Users Act (PDUFA) of 1992. In the late 1980s and early 1990s, the pressure from companies and patients alike was not for additional safety evaluations, but for shorter approval times (42). In response to the criticism that the FDA approval

times were too long, Congress introduced user fees in 1992. Pharmaceutical companies seeking drug approvals paid fees that enabled the FDA to hire additional staff, and the FDA was expected to meet new requirements for the timeliness of new-drug approvals (16). According to Dr David Kessler, head of the FDA from 1990 to 1997, “PDUFA should have had funding on the safety side from the beginning, but the industry refused to accept that…. We wanted it. The industry said no” (17). The 1992 user fee act and its reauthorization in 1997 prohibited the agency from spending users fees “on post-marketing surveillance or other drug-safety programs" (14). The reauthorization in 2003 included some provisions for safety. During the period 1992 to 2003, this approach--more and faster new approvals without additional funds for safety surveillance--relied increasingly on the honesty, trustworthiness, and integrity of the pharmaceutical industry in the conduct of its own post-marketing safety evaluations.

PUDFA, review times, and funding for safety. The PUDFA act in 1992 and its reauthorizations in 1997 and 2003 reduced the time required for review of a new drug application by the FDA from 33 months in 1992 down to about 13 or 14 months in 2001 (17). As a result, the proportion of new molecular entities that are first introduced in the US has increased from 2 to 3% in the early 1980s up to 60% in 1998 (43). New medicines are now indeed available to Americans more quickly. At the same time, US patients also became the first to receive new medications, some of which, such as COX-2 inhibitors, are subsequently discovered to have serious adverse effects. The Office of Inspector General 2003 Report on the FDA's Review Process for New Drug Applications has assessed the impact of the new review process at the FDA (16). Funding for safety has also been affected. In 1992, 53% of the budget of the FDA Center for Drug Evaluation went to new drug reviews, and the rest went to surveillance, laboratories and other safety efforts. In 2003, 79% went to new drug reviews. Resources available for safety have dwindled (44). Drug recalls following approval increased from 1.56% in 1993-1996 up to 5.35% for 1997-2001 (10).

Calls for an independent Center or Office of Drug Safety. In a recent commentary, the JAMA editors advocate an independent center or office of drug safety: “It is unreasonable to expect the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek evidence to prove itself wrong (ie, that the decision to approve the product was subsequently shown to be incorrect)” (10). Other recent commentaries in JAMA (13) and the New England Journal of Medicine have recommended the creation of an independent drug-safety board “to monitor drug safety, investigate reports of drug toxicity, and recommend actions to minimize the risks of drug therapy” (14). The new Advisory Board on Drug Safety announced by Michael O. Leavitt, secretary of health and human services on February 15 is not adequate. According to Dr William Schultz, FDA deputy commissioner for policy from 1994 to 1998, “The FDA should separate the monitoring of drugs after they have been approved from the drug review function” (12).

Need for additional authority in the Center for Drug Safety. In March 2000, Merck was aware that compared with naproxen, Vioxx increased the risk of heart attacks (45). In February 2001, an FDA Advisory Committee reviewed the safety data, but revisions to

the “Precautions” section of the VIOXX product label were delayed until April 2002. The public health rationale for the two-year delay in revising the product label remains unclear. Although the FDA can call Advisory Committee meetings or issue press releases, talk papers, guidances, and requests to manufacturers, these powers are not adequate to regulate drugs that are on the market. For an approved drug, the FDA currently engages in protracted negotiations with manufacturers rather than mandating manufacturers: to change a product label, to conduct patient or physician education, to limit advertising to patients or physicians, to modify approved indications, to restrict use to selected patients, to complete post-marketing studies agreed upon at the time of approval, to conduct additional post-marketing studies or trials, to suspend marketing or withdraw a drug. At least one pharmaceutical executive has advocated providing the FDA with additional authority to mandate studies after drugs are approved (46). Moreover, provisional approval for the first two or three years would provide an opportunity to re-review the balance of risk and benefit.

Elements required to protect the health of the public. The failure to pose a question often precludes the possibility of obtaining an answer. Pharmaceutical companies generally lack enthusiasm for aggressively pursuing questions about the safety of their drugs. In science, only those questions that are investigated with well-designed studies have a decent chance of producing a solid answer. If the pharmaceutical industry does not pose critical questions about drug safety, the FDA must do so in an effort to protect the health of the public. Key elements related to the study of drug safety include: (1) the generation of ideas about a drug’s risks as well as its benefits; (2) a sustained effort to investigate or document risks as well as benefits; (3) the availability of high-quality surveillance systems or the conduct of specifically designed studies to assess risks as well as benefits; and (4) the willingness to publish findings about risks as well as benefits. If manufacturers do not provide support for a vigorous and balanced scientific evaluation of safety signals for drugs that are already on the market, the Center for Drug Safety must do so to protect the health of the public.

Activities of the Center for Drug Safety. At the time of approval for each new drug and on the basis of information available in the NDA and other studies, the Center for Drug Safety needs to identify a set of studies required to address the key unanswered questions, particularly the pursuit of potential safety “signals” or “plausible biologic hypotheses” on behalf of the health of the public. Depending on the drug, the indication and the known safety profile, the studies may include Phase IV trials, epidemiologic studies, pharmacokinetic-pharmacodynamic studies, close surveillance of ADR reports, or a combination of several approaches. Specific post-marketing trials or studies should be designed, conducted and completed in a timely fashion. The Center for Drug Safety should be responsible for assessing the balance of risk and benefit of drugs that are on the market.

References

1. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005; 352; Epub.
2. Solomon SD, McMurray JJV, Pfeffer MA, et al. for the Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005; 352: Epub.
3. Bresalier RS, Sandler RS, Quan H, et al. for the APPROVe Trial Investigators. Cardiovascular events associated with rofecoxib in a 3-year randomized colorectal adenoma chemoprevention trial. N Engl J Med 2005; 352: Epub.
4. Psaty BM, Furberg CD. COX-2 inhibitors--lessons in drug safety. N Engl J Med 2005; Epub February 15, 2005.
5. Drazen JM. COX-2 inhibitors: a lesson in unexpected problems. N Engl J Med 2005; Epub Feb 15, 2005.
6. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci 1999;96:272-277.
7. Villalba ML. FDA Medical Officer Review of VIOXX (rofecoxib), NDA 21-042 (capsules) and NDA 21-052 (oral solution). Http://www.fda.gov/cder/foi/nda/index.htm.
8. Writing Group for the Women's Health Initative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-333.
9. Psaty BM, Weiss NS, Furberg CD, et al. Surrogate endpoints, health outcomes, and the drug approval process for the treatment of risk factors for cardiovascular disease. JAMA 1999;282:786-790.
10. Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing surveillance--lack of vigilance, lack of trust [editorial]. JAMA 2004;292:2647-2650.
11. Harris G. FDA to create advisory board on drug safety. New York Times, February 16, 2005.
12. Schultz WB. How to improve drug safety. Washington Post (washingtonpost.com), December 2, 2004, page A35.
13. Moore TJ, Psaty BM, Furberg CD. Time to act on drug safety. JAMA 1998;279:1571-1573.
14. Wood AJJ, Stein CM, Woosley R. Making medicines safer--the need for an independent drug safety board. N Engl J Med 1998;339:1851-1854.
15. Steinman M. FDA reports more than half of post-approval prescription drug studies not begun. California Healthline, May 23, 2003.
16. Department of Health and Human Services Office of Inspector General. FDA's review process for new drug applications: a management review. Department of Health and Human Services; OEI-01-01-00590; March 2003.
17. Graham J, James F. Flaws in drug agency put consumer at risk. The Chicago Tribune, February 20, 2005.
18. Kessler DA. Introducing MEDWatch: a new approach to reporting medication and device adverse effects and product problems. JAMA 1993;269:2765-2767.
19. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004;292:2585-2590.
20. Gale EA. Lessons from the glitazones: a story of drug development. Lancet

2001;357:1870-1875.
21. Pauley III WH. Memorandum and order in re: Bayer AG securities litigation. . Southern District of New York, No 03 Civ 1546, Sept 30, 2004: http://www.nysd.uscourts.gov/courtweb/public.htm.
22. Food and Drug Administration, Department of Health and Human Services. Expedited safety reporting requirements for human drug and biologic products, 21 CRF Parts 20, 310, 312, 314 and 600, final rule. Federal Register Oct 7, 1997;62:52237-52253.
23. Food and Drug Administration, Department of Health and Human Services. Safety reporting requirements for human drug and biological products, 21 CFR Parts 310, 312, 314, 600, 601, and 606, proposed rule. Federal Register March 14, 2003;68:12406-12497.
24. Food and Drug Administration. CDER 2001 report to the nation: improving public health through human drugs. Rockville, Maryland, 2002. http://www.fda.gov/cder/reports/rtn/2001/rtn2001.pdf.
25. Psaty BM, Furberg CD, Ray WA, Weiss NS. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. JAMA 2004;292:2622-2631.
26. Strom BL. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: a counterpoint. JAMA 2004;292:2643-2646.
27. The National Institute for Health Care Management Research and Education Foundation. Prescrption drug expenditures in 2001: another years of escalating costs. NIHCM Foundation, Washington, DC, April 2002; http://www.nihcm.org/index2.html.
28. Berenson A, Feder B. A reminder that no drug is risk-free. New York Times, February 19, 2005.
29. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: method and initial results in the Cardiovascular Health Study. J Clin Epidemiol 1992;45:683-692.
30. Psaty BM, Koepsell TD, Siscovick D, Wagner EH, Wahl P, LoGerfo JP, Inui TS. An approach to several problems in the use of large databases for population-based case-control studies of the therapeutic efficacy and safety of anti-hypertensive medicines. Stat Med 1991;10:653-662.
31. Graham DJ, Campem D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005; Epub Jan 25, 2005.
32. Ray WA, Griffin MR. Use of medicaid data for pharmacoepidemiology. Am J Epidemiol 1989;129:837-84.
33. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-flammatory drugs and risk of serious coronary heart disease. Lancet 2002;360:1071-1073.
34. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154-164.
35. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerized data resources in the United Kingdom. BMJ 1991;302:766-8.
36. Herings RMC. Pharmo: a record linkage system for postmarking surveillance of prescription drugs in The Netherlands [Thesis, University of Utrecht, The Netherlands]. Elinkwijk BV, Utrecht: 1993.

37. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-1389.
38. Shepherd J, Cobbe SM, Isles CG, et al for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-1307.
39. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279:1615-1622.
40. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA). Lancet 2003;361:1149-1158.
41. Pfizer Inc. A double-blind randomized placebo-controlled comparative study of celecoxib (SC-58635) for the inhibition of progression of Alzheimer's Disease, protocol IQ5-97-02-001. Http://www.clinicalstudyresults.org/documents/company-study_76_0.pdf; last accessed Jan 29, 2005.
42. Meadows M. Why drugs get pulled off the market. FDA Consumer 2002; Jan/Feb, 11-17.
43. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines: do recent market removals mean there is a problem? JAMA 1999;281:1728-1734.
44. Harris G. Regularlation rededined: At FDA, strong drug ties and less monitoring. New York Times, December 6, 2004.
45. Bombardier C, Laine L, Reicin A, et al for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of Rofecoxib and Naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-1528.
46. Anonymous. FDA needs more teeth, says GSK [GlaxoSmithKline] head Jean-Pierre Garnier. The Daily Telegraph [United Kingdom newspaper], December 5, 2004.