

HEALTH AND STRESS

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THE FDA = FAULTY, FEEBLE AND FUTILE DRUG ADMINISTRATION

KEYWORDS: Elixir sulfanilimide, Thalidomide, Omniflex, Rezulin, Fen-Phen, Redux, PPA, Trovan, Lotronex, Baycol, Seldane, Propulsid, Accutane, Arava, Naprosyn, Celebrex, *Forbes* "Face of the Year", AG-Immune, Fat Trapper, Exercise in a Bottle, Acceleron, Chitozyme, Sagee, Dr. Greg Cynaumon, Dr. Gary Adams

The History, Trials And Tribulations Of The FDA

Past issues of the Newsletter have been sharply critical of The Food and Drug Administration for approving dangerous drugs that subsequently had to be recalled. In many instances, approval was granted over the objections of their own internal experts or was based on the opinion of an Advisory Panel composed of individuals with strong financial ties to the company whose drug was being reviewed. Because of these and other clear conflicts of interest, rigorous reforms of current policies and practices have been urged by Congress as well as various public advocacy groups. While it is difficult for many to comprehend how such abuses arose or why they continue to be tolerated, the FDA has an enlightening history that helps to explain some of its present problems.

The agency was created in 1906 largely as a result of the publication of *The Jungle*, Upton Sinclair's startling exposé of the unsanitary conditions in the meatpacking industry. The vast majority of changes in FDA regulations and policies also appear to have been in response to some scandal or disaster involving drugs. The 105 known deaths due to elixir sulfanilamide in 1937 was responsible for the Food Drug and Cosmetic Act the following year, which mandated proof of safety before a new drug could be made available to the public. Prior to this, pre-marketing toxicity studies for foods and drugs were not required. This radically changed the

focus of the FDA from an organization primarily concerned with policing and confiscating adulterated drugs to a regulatory body increasingly involved with overseeing the evaluation of new drugs.

The thalidomide tragedy three decades later led to legislation that expanded the FDA's authority. The AIDS epidemic drew attention to the need for faster approval of new drugs in the 1980's. This was intended to expedite the availability of lifesaving medications but was quickly utilized by manufacturers to apply to any pharmaceutical,

ALSO INCLUDED IN THIS ISSUE

- Σ Dr. David Graham's Recent Senate Committee Hearing Testimony
- Σ The FDA Failed To Protect The Public From Vioxx Despite Negative Studies
- Σ FDA Officials Ignore Any Findings That Dispute Prior Approval of Drug Safety
- Σ Why The FDA's Deplorable State Of Affairs Is Not Very Likely To Change
- Σ Nutritional Supplement False Advertising Claims And Dangers
- Σ Promising That Cortislim Can Promote Weight Loss By Reducing Stress
- Σ Codex Alimentarius Commission

causing a backlog in the FDA because of the lack of qualified personnel and funding. The Prescription Drug User Fee Act of 1992, specifying that new drug sponsors pay user fees, was passed primarily to permit the agency to be more efficient in reviewing applications by increasing their resources. Further provisions in the FDA Modernization Act of 1997 included setting standards for priority drugs. After 9/11, Congress passed the Bioterrorism Preparedness and Response Act of 2002 that contained several more efficiency measures and token funding for post-marketing surveillance, which had been seriously neglected.

Dr. David Graham's Recent Senate Committee Hearing Testimony

Manufacturers and Congress want new drugs to be available more rapidly and most of the above alleged "improvements" were designed to facilitate this. The problem is that the faster a drug is approved, the more likely that safety concerns will be ignored. This was vividly illustrated in David Graham's testimony before a Senate Finance Committee hearing investigating the withdrawal of Vioxx. He did not mince any words in telling them that the FDA ignored his and other warnings that Vioxx had been responsible for causing thousands of deaths due to heart attack and stroke. He described the current system for determining drug safety as "completely broken" and warned that the agency was "incapable of protecting the public against another drug disaster." As he concluded, **"We are faced with what may be the single greatest drug safety catastrophe in the history of this country or the history of the world."**

A father of six, Graham is a deeply religious Catholic and taught himself biblical Greek so he would be able to read the New Testament in its original language. The following excerpts from his November 18 testimony leave little doubt about his superb medical and scientific qualifications/expertise with problems related to drug safety.

"Mr. Chairman and members of the Committee, Good morning. My name is David Graham, and I am pleased to come before you today to speak about Vioxx, heart attacks and the FDA. By way of introduction, I graduated from the Johns Hopkins University School of Medicine, and trained in Internal Medicine at Yale and in adult Neurology at the University of Pennsylvania. After this, I completed a three-year fellowship in pharmacoepidemiology and a Masters in Public Health at Johns Hopkins, with a concentration in epidemiology and biostatistics. Over my 20-year career in the field, all of it at FDA, I have served in a variety of capacities. I am currently the Associate Director for Science and Medicine in FDA's Office of Drug Safety.

During my career, I believe I have made a real difference for the cause of patient safety. My research and efforts within FDA led to the withdrawal from the US market of Omniflox, an antibiotic that caused hemolytic anemia; Rezulin, a diabetes drug that caused acute liver failure; Fen-Phen and Redux, weight loss drugs that caused heart valve injury; and PPA (phenylpropanolamine), an over-the-counter decongestant and weight loss product that caused hemorrhagic stroke in young women. My research also led to the withdrawal from outpatient use of Trovan, an antibiotic that caused acute liver failure and death. I also contributed to the team effort that led to the withdrawal of Lotronex, a drug for irritable bowel syndrome that causes ischemic colitis; Baycol, a cholesterol-lowering drug that caused severe muscle injury, kidney failure and death; Seldane, an antihistamine that caused heart arrhythmias and death; and Propulsid, a drug for night-time heartburn that caused heart arrhythmias and death. I have done extensive work concerning the issue of pregnancy exposure to Accutane, a drug that is used to treat acne but can cause birth defects in some children who are exposed in-utero if their mothers take the drug during the first trimester. During my career, I have recommended the market withdrawal of 12 drugs. Only 2 of these remain on the market today-Accutane and Arava, a drug for the treatment of rheumatoid arthritis that I and a

co-worker believe causes an unacceptably high risk of acute liver failure and death."

The FDA Failed To Protect The Public From Vioxx Despite Negative Studies

Dr. Graham went on to point out that prior to its approval in 1999, a Merck study had shown an almost 7-fold increase in risk for heart attacks with low dose Vioxx but that this was completely ignored in the approved label. The VIGOR clinical trial in 2000 found a five-fold increase with higher doses but the company stated that this was because it had been compared to naproxen (Naprosyn), which they claimed had cardioprotective effects. In 2002, a large study found that high doses of Vioxx doubled heart attack risk and another showed that naproxen was not cardioprotective. Some 18 months after the publication of the VIGOR study the FDA finally made a labeling change that mentioned heart attack risk with high-dose Vioxx. However, it did not place this in the "Warnings" section or ban the high-dose formulation and its use, as Graham and others had urged. As a result, the label change had absolutely no effect on how often high-dose Vioxx was prescribed. In March 2004, another article found that both high and low doses of Vioxx significantly increased heart attack risk compared to Celebrex, its leading competitor. This was confirmed by Graham in another study reported in August that was posted on the FDA web site. Despite this, the FDA not only took no action, but also announced on Sept. 22 that it had now approved Vioxx for use in children with rheumatoid arthritis. It was only by coincidence that around this date, a Merck study designed to show that Vioxx could prevent colon polyps in patients without evidence of cardiovascular disease was halted after it was found that those on Vioxx suffered almost twice as many heart attacks or strokes compared to controls on a placebo. Faced with these facts, the company voluntarily halted Vioxx sales worldwide on September 30. By then, over 80 million patients had taken the drug and annual sales exceeded \$2.5 billion, due largely to the more than \$100 million/year spent in direct to consumer TV and print ads. An even greater amount likely went to pay for sales personnel who visited doctors to provide free samples and gifts in return for their prescribing Vioxx. Recent figures are not available but back in 2000, Merck spent \$161 million on advertising for Vioxx, which was much more than was spent for Pepsi or Budweiser. An October *New England Journal of Medicine* article estimated up to 160,000 cases of heart attacks and strokes in Americans due to Vioxx.

FDA Officials Ignore Any Findings That Dispute Prior Approval of Drug Safety

In an effort to determine Vioxx risks, Graham had worked with California's Kaiser Permanente in reviewing 1.4 million patient records that took three years to complete. The results, which he hoped to present at an August International Conference on Pharmacoepidemiology in France, concluded that high dosage Vioxx significantly increased risk of heart attacks and sudden death and that high doses should not be prescribed or used by patients. Instead of being applauded by his superiors for this important contribution, he recounts their reactions as follows:

"This conclusion triggered an explosive response from the Office of New Drugs (OND) which approved Vioxx in the first place and was responsible for regulating it post-marketing. The response from senior management in my Office, the Office of Drug Safety (ODS), was equally stressful. I was pressured to change my conclusions and recommendations, and basically threatened that if I did not change them, I would not be permitted to present the paper at the conference. One Drug Safety manager recommended that I should be barred from presenting the poster at the meeting, and also noted that Merck needed to know our study results. An email from the Director for the entire Office of New Drugs, was revealing. He suggested that since FDA was "not contemplating" a warning against the use of high-dose Vioxx, my conclusions should be changed. The Center For Disease Evaluation and Research (CDER) and the Office of New Drugs have repeatedly expressed the view that ODS should not reach any conclusions or make any

recommendations that would contradict what the Office of New Drugs wants to do or is doing. Even more revealing, a mere 6 weeks before Merck pulled Vioxx from the market, CDER, OND and ODS management did not believe there was an outstanding safety concern with Vioxx.

In mid-August, despite our study results showing an increased risk of heart attack with Vioxx, and despite the results of other studies published in the literature, FDA announced it had approved Vioxx for use in children with rheumatoid arthritis. Also, on September 22, at a meeting attended by the director of the reviewing office that approved Vioxx, the director and deputy director of the reviewing division within that office and senior managers from the Office of Drug Safety, no one thought there was a Vioxx safety issue to be dealt with. At this meeting, the reviewing office director asked **why had I even thought to study Vioxx and heart attacks because FDA had made its labeling change and nothing more needed to be done.** At this meeting a senior manager from ODS labeled our Vioxx study "a scientific rumor." Eight days later, Merck pulled Vioxx from the market. Finally, we wrote a manuscript for publication in a peer-reviewed medical journal. Senior managers in the Office of Drug Safety have not granted clearance for its publication, even though it was accepted for publication in a very prestigious journal after rigorous peer review by that journal. Until it is cleared, our data and conclusions will not see the light of day in the scientific forum they deserve and have earned, and serious students of drug safety and drug regulation will be denied the opportunity to consider and openly debate the issues we raise in that paper. My experience with Vioxx is typical of how CDER responds to serious drug safety issues in general. This is similar to what Dr. Mosholder went through earlier this year when he reached his conclusion that most SSRIs should not be used by children. I could bore you with a long list of prominent and not-so-prominent safety issues where CDER and its Office of New Drugs proved to be extremely resistant to full and open disclosure of safety information, especially when it called into question an existing regulatory position. In these situations, the new drug reviewing division that approved the drug in the first place and that regards it as its own child, typically proves to be the single greatest obstacle to effectively dealing with serious drug safety issues. The second greatest obstacle is often the senior management within the Office of Drug Safety, who either actively or tacitly go along with what the Office of New Drugs wants."

Why The FDA's Deplorable State Of Affairs Is Not Very Likely To Change

I wish we had space to include Dr. Graham's entire testimony, which, like the previous comments, also illustrate the tremendous clout that powerful pharmaceutical companies have over the FDA in addition to influential members of Congress. He cites numerous examples to support how the agency's ineptitude and failure to act responsibly have harmed the public and why it is quite likely that nothing will be done to correct this tragic and serious situation. A few additional excerpts:

"Rezulin was a drug used to treat diabetes. It also caused acute liver failure, which was usually fatal unless a liver transplant was performed. The pre-approval clinical trials showed strong evidence of liver toxicity. The drug was withdrawn from the market in the United Kingdom in December 1997. With CDER and the Office of New Drugs, withdrawal didn't occur until March 2000. Between these dates, CDER relied on risk management strategies that were utterly ineffective and it persisted in relying on these strategies long after the evidence was clear that they didn't work. **The continued marketing of Rezulin probably led to thousands of Americans being severely injured or killed by the drug. And note, there were many other safer diabetes drugs available. During this time, I understand that Rezulin's manufacturer continued to make about \$2 million per day in sales.**"

"I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless. . . . Simply put, FDA and its Center for Drug Evaluation and Research are broken. . . . Now, I'm sure you have read the recent proposal to have the Institute of Medicine perform a review of CDER and its drug safety program and make recommendations for fixing things up. Don't expect anything meaningful or effective from this exercise. Over the history of CDER's drug safety program, a number of similar reviews have been done. In the late 1970's, I believe that a blue ribbon panel recommended that there be an entirely separate drug safety operation in FDA with full regulatory authority. It wasn't implemented. During the 1980's and early 1990's, CDER organized its own 'program reviews' of drug safety. The basic premise underlying each of these reviews was that the 'problem' was with the drug safety group; it didn't fit into the Center. So, the charge given to the review panel members was always framed as 'figure out what's wrong with drug safety, and tell us what to do to get it to fit in.' There was and is an implicit expectation that the status quo will remain unaltered. The organizational structure within CDER is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division approves a new drug, it is also saying the drug is 'safe and effective.' When a serious safety issue arises post-marketing, their immediate reaction is almost always one of denial, rejection and heat. They approved the drug so there can't possibly be anything wrong with it. The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest. At the same time, the Office of Drug Safety has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs. The corporate culture within CDER is also a barrier to effectively protecting the American people from unnecessary harm due to prescription and OTC drugs. The culture is dominated by a world-view that believes only randomized clinical trials provide useful and actionable information and that post-marketing safety is an afterthought. This culture also views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety."

"When it comes to safety, the OND paradigm of 95% certainty prevails. Under this paradigm, a drug is safe until you can show with 95% or greater certainty that it is not safe. This is an incredibly high, almost insurmountable barrier to overcome. It's the equivalent of 'beyond a shadow of a doubt.' And here's an added kicker. In order to demonstrate a safety problem with 95% certainty, extremely large studies are often needed. And guess what. Those large studies can't be done. There are 2 analogies I want to leave you with to illustrate the unreasonableness of CDER's standard of evidence as applied to safety, both pre- and post-approval. If the weatherman says there is an 80% chance of rain, most people would bring an umbrella. Using CDER's standard, you wouldn't bring an umbrella until there was a 95% or greater chance of rain. The second analogy is more graphic, but I think it brings home the point more clearly. Imagine for a moment that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets into those chambers. The gun represents a drug and the bullets represent a serious safety problem. Using CDER's standard, only when you have 95 bullets or more in the gun will you agree that the gun is loaded and a safety problem exists. Let's remove 5 bullets at random. We now have 90 bullets distributed across 100 chambers. Because there is only a 90% chance that a bullet will fire when I pull the trigger,

CDER would conclude that the gun is not loaded and that the drug is safe."

It took considerable courage for Dr. Graham to be so frank and honest in his criticism of superiors, given the fate of other whistleblowers who were also motivated more by a desire to tell the truth than monetary rewards. He has received widespread supportive media exposure and enthusiastic public approval for his testimony. *Forbes* magazine named him their "Face of the Year" for his "steadfast advocacy of drug safety and his willingness to blow the whistle on his bosses." Although nobody has disputed the accuracy of his charges, the director of Center for Drug Evaluation and Research said that Dr. Graham's new numbers "constitute junk science" and were "irresponsible". Since the FDA operates as an autonomous fiefdom, retaliation is certain and his lawyer recently confirmed that Graham will be exiled from his duties of reviewing drugs and placed in the office of the commissioner. This position was described as "filling space under the scrutinizing watch of a babysitter." However, as Graham told *Forbes*, he has "been getting heat from his bosses for his entire career and you don't get rewards for doing the work that gets a drug taken off the market." **Things are not likely to change since the FDA appears to be a law unto itself. Indeed, on February 20, an FDA Advisory Panel investigating whether Celebrex and other Cox 2 inhibitors should be banned because of evidence that they also had adverse effects not only voted against this but recommended that Vioxx should be made available again.** (Dr. Graham's entire testimony can be found at <http://news.findlaw.com/hdocs/docs/vioxx/111804graham.pdf>)

Nutritional Supplement False Advertising Claims And Dangers

Unlike drugs, nutritional supplements do not have to provide proof of safety or efficacy before they can be marketed. As a result, manufacturers frequently make false claims and consumers have no guarantee that a supplement has the correct dosage or even any of the active ingredients specified on the label. The FDA can intervene when there is proof that a product is not safe, as was done for those containing ephedra. The FTC can also levy fines if advertisements state that a supplement can be used to treat a disease. However, there are ways to get around this with carefully crafted wording with the same implication that makes enforcement difficult. In addition, both of these agencies are understaffed and have more important priorities to deal with.

It is therefore encouraging to report that efforts to protect the public have significantly increased over the past year. Last January 18, Body Wise International agreed to pay over \$3.5 million for unsubstantiated claims that its AG-Immune dietary supplement could prevent, treat, or cure cancer, AIDS, asthma and other diseases. In 1995, Body Wise settled FTC charges that the company made unsubstantiated claims for weight loss and cholesterol products. The resulting order barred Body Wise from making unsubstantiated claims for any dietary supplement, misrepresenting tests or studies, or failing to disclose any material connection between Body Wise and persons endorsing their products. Body Wise violated this FTC order by making such claims for AG-Immune, misrepresenting that scientific research had demonstrated the alleged benefits, and failing to disclose the financial connection between AG-Immune and its expert endorser, Dr. Jeese Stoff. The settlement included a judgment of \$358,000 against Dr. Stoff that was suspended because of an alleged inability to pay but will become due immediately if the court finds that he misrepresented his financial condition. The latter seems likely since Body Wise, which sold AG-Immune for approximately \$50 for a one-month supply, had over \$14 million in sales.

On the same date, the makers of "Fat Trapper" "Fat Trapper Plus" and "Exercise in a Bottle" were banned from advertising weight-loss supplements in a settlement that required them to pay \$300,000 in consumer redress. It also contained an avalanche clause under which \$4,000,000 would become due immediately if the court finds they misrepresented their financial condition. The settlement resolved prior FTC contempt charges in 2000 and 2002 for violating the terms of a final order to desist from making false claims regarding these

purported weight-loss products and others like Accelaron and Chitozyme. Both these settlements illustrate that even when the FTC has issued "final" warnings to stop deceptive and illegal advertising, there is little enforcement and defendants may not be obligated to pay if they claim insufficient funds. Two weeks earlier, the manufacturer of Sagee, an herbal supplement, was fined for claiming that it could repair damaged brain cells; improve memory or concentration; slow down the brain's aging process; and treat or alleviate conditions such as Alzheimer's, Parkinson's insomnia, migraine, or stroke due to cerebral embolism and hemorrhage. The order requires the defendant to pay \$10,000 in redress and also a \$1.38 million avalanche clause that would become due if the court finds they misrepresented their financial condition. Last December, the FDA seized a ginseng product because of pesticide residues as well as several Ayurvedic supplements that, when taken as directed, contained unsafe levels of lead, mercury and/or arsenic.

Promising That Cortislim Can Promote Weight Loss By Reducing Stress

As previously reported, CortiSlim is one of several dietary supplements whose makers claim will produce dramatic weight loss by reducing stress and blocking the production of cortisol that causes big bellies. While it is quite true that stress induced excess cortisol levels can lead to increased accumulation of abdominal fat and interfere with weight reduction efforts, there is no scientific evidence that any supplement or drug will block or reverse this process. Last July, a class action lawsuit on behalf of plaintiffs from almost 30 states was filed seeking a refund for anyone who purchased CortiSlim because of misleading and false advertising. It also asked for a ban on various promotional claims, including that it promptly and permanently causes weight loss of 10 to 50 pounds for everybody, that these pounds are specifically shed from the abdomen, stomach, and thighs and that the efficacy of CortiSlim and its ingredients have been confirmed by over 15 years of scientific research. No such studies have ever been published.

The estimated 60 to 90 million dollars in annual Cortislim sales are largely due to infomercials and TV ads featuring Dr. Greg Cynaumon, whose credentials appear to be as fraudulent as Cortislim. Although he does not claim to be a physician, some ads imply this and in others he is represented as a certified psychologist and marriage or family therapist, neither of which is true. Last October, Cynaumon was forced to admit that these were lies when the California Board of Psychology issued a citation and fined him \$1500 for continuing to impersonate a psychologist and the Board of Behavioral Sciences fined him \$1,000 for continuing to impersonate a marriage/family therapist. He was also forced to shut down his www.drgreg.org web site because of misleading falsehoods. Sensational testimonials from satisfied customers and alleged endorsements by celebrities and popular magazines have similarly been proven to be phony. Although the company recently received strict warning letters from both the FDA and FTC, these are nothing more than a slap on the wrist. New ads have been toned down a bit but they continue to be quite deceptive and to rake in big bucks from gullible consumers. It is not likely that any significant changes will be made unless stricter laws for nutritional supplement safety and efficacy claims are enacted, as has been proposed. However, many consumers have also reported significant side effects from Cortislim and attempts are being made to place it on the FDA MedWatch list for adverse reactions. For a real eye opener that documents all of the above as well as numerous other charges and complaints, see Dr. Gary Adams' web site www.edresearch.com. For over a year, Adams has offered to pay Cynaumon or Cortislim's manufacturer \$1 million if either can prove that any of his derogatory accusations are false. To date, there have been no takers.

The Codex Alimentarius Commission

A variety of efforts have been made to get supplement manufacturers to refrain from making unproven claims and to insure that supplements contain what is stated on the label and are free of harmful contaminants. As indicated in a previous Newsletter, The Codex Alimentarius Commission was created in 1963 by the Food and Agriculture and World Health Organizations

of the United Nations. Its prime purpose was to protect the health of consumers by insuring fair practices in the food trade and to promote international coordination of all food standards in its more than 160 member countries. The Commission accomplishes its work through Committees hosted by member nations, including the U.S., where the Codex office is located in the Food Safety and Inspection Service of the Department of Agriculture. All of its activities seemed quite benign and beneficial but in the early 1990's, Codex began to establish "harmonization standards" for nutritional supplements. Nobody here paid much attention to this until several years later, when a bill was voted on that would give Codex the following controls:

- Σ No vitamin, mineral, or herb, etc., could be sold for preventive or therapeutic use without prior approval of the Commission.
- Σ None of these could exceed potency or dosage levels that had not been approved by the Commission.
- Σ All new dietary supplements would automatically be banned unless they went through the Codex approval process.
- Σ All of these regulations would become binding under the current General Agreement on Tariffs and Trade and would not be subject to any escape clause that might allow a member nation to set its own standards.
- Σ While not binding, failure to comply with these new rulings could result in heavy fines and sanctions from other members of the World Trade Organization.

The bill was passed by a 16-2 majority, one of the dissenters being the U. S., since this obviously had the potential for crippling large sectors of our economy. It was sponsored by Germany, whose Commission E established in 1978, had already reviewed some 360 herbal supplements and published some 462 detailed monographs that classified them as either acceptable, worthless or dangerous. Although most of those approved are sold over the counter, almost 10 percent of prescription drugs covered by German health insurance plans are for herbal preparations. In 2002, a European Union Directive finally set up guidelines for Codex standards that essentially called for supplements to be subjected to the same standards for approval as drugs. Australia, Norway, Denmark and Germany have already adopted these "foods as drugs" guidelines, Canada is close to doing so, and they will become effective for the entire European Union in August. Implementation here is scheduled for 2007 since, according to the Congressional Research Service: "As a member of the World Trade Organization, the United States does commit to act in accordance with the rules of the multilateral body. **The United States is legally obligated to ensure national laws do not conflict with World Trade Organization rules.**" However, it is doubtful that this will happen because of the tremendous power of the supplement industry. Critics claim that more than 5000 products will be banned and that the only non-prescription supplements will be vitamins containing worthless RDA dosages. On the other hand, larger amounts of these or other supplements that do pass standards would likely be covered under prescription plans. A major battle seems likely - so stay tuned to see what happens and for additional interesting updates on other topics.

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Paul J. Rosch, M.D., F.A.C.P.

Editor-in-Chief

www.stress.org

e-mail: stress124@optonline.net

Testimony of David J. Graham, MD, MPH, November 18, 2004

Mr. Chairman and members of the Committee,

Introduction. Good morning. My name is David Graham, and I am pleased to come before you today to speak about Vioxx, heart attacks and the FDA. By way of introduction, I graduated from the Johns Hopkins University School of Medicine, and trained in Internal Medicine at Yale and in adult Neurology at the University of Pennsylvania. After this, I completed a three-year fellowship in pharmacoepidemiology and a Masters in Public Health at Johns Hopkins, with a concentration in epidemiology and biostatistics. Over my 20 year career in the field, all of it at FDA, I have served in a variety of capacities. I am currently the Associate Director for Science and Medicine in FDA's Office of Drug Safety.

During my career, I believe I have made a real difference for the cause of patient safety. My research and efforts within FDA led to the withdrawal from the US market of Omniflox, an antibiotic that caused hemolytic anemia; Rezulin, a diabetes drug that caused acute liver failure; Fen-Phen and Redux, weight loss drugs that caused heart valve injury; and PPA (phenylpropanolamine), an over-the-counter decongestant and weight loss product that caused hemorrhagic stroke in young women. My research also led to the withdrawal from outpatient use of Trovan, an antibiotic that caused acute liver failure and death. I also contributed to the team effort that led to the withdrawal of Lotronex, a drug for irritable bowel syndrome that causes ischemic colitis; Baycol, a cholesterol-lowering drug that caused severe muscle injury, kidney failure and death; Seldane, an antihistamine that caused heart arrhythmias and death; and Propulsid, a drug for night-time heartburn that caused heart arrhythmias and death. I have done extensive work concerning the issue of pregnancy exposure to Accutane, a drug that is used to treat acne but can cause birth defects in some children who are exposed in-utero if their mothers take the drug during the first trimester. During my career, I have recommended the market withdrawal of 12 drugs. Only 2 of these remain on the market today-Accutane and Arava, a drug for the treatment of rheumatoid arthritis that I and a co-worker believe causes an unacceptably high risk of acute liver failure and death.

Vioxx and heart attacks. Let me begin by describing what we found in our study, what others have found, and what this means for the American people. Prior to approval of Vioxx, a study was performed by Merck named 090. This study found nearly a 7-fold increase in heart attack risk with low dose Vioxx. The labeling at approval said nothing about heart attack risks. In November 2000, another Merck clinical trial named VIGOR found a 5-fold increase in heart attack risk with high-dose Vioxx. The company said the drug was safe and that the comparison drug naproxen, was protective. In 2002, a large epidemiologic study reported a 2-fold increase in heart attack risk with high-dose Vioxx and another study reported that naproxen did not affect heart attack risk. About 18 months after the VIGOR results were published, FDA made a labeling change about heart attack risk with high-dose Vioxx, but did not place this in the "Warnings" section. Also, it did not ban the high-dose formulation and its use. I believe such a ban should have been implemented. Of note, FDA's label change had absolutely no effect on how often high-dose Vioxx was prescribed, so what good did it achieve?

In March of 2004, another epidemiologic study reported that both high-dose and low-dose Vioxx increased the risk of heart attacks compared to Vioxx's leading competitor, Celebrex. Our study, first reported in late August of this year found that Vioxx increased the risk of heart attack and sudden death by 3.7 fold for high-dose and 1.5 fold for low-dose, compared to Celebrex. A study report describing this work was put on the FDA website on election day. Among many things, this report estimated that nearly 28,000 excess cases of heart attack or sudden cardiac death were caused by Vioxx. I emphasize to the Committee that this is an extremely conservative estimate. FDA always claims that randomized clinical trials provide the best data. If you apply the risk-levels seen in the 2 Merck trials, VIGOR and APPROVe, you obtain a more realistic and likely range of estimates for the number of excess cases in the US. This estimate ranges from 88,000 to 139,000 Americans. Of these, 30-40% probably died. For the survivors, their lives were changed forever. It's important to note that this range does not depend at all on

the data from our Kaiser-FDA study. Indeed, Dr. Eric Topol at the Cleveland Clinic recently estimated up to 160,000 cases of heart attacks and strokes due to Vioxx, in an article published in the New England Journal of Medicine. This article lays out clearly the public health significance of what we're talking about today.

So, how many people is 100,000? The attached Tables 1 and 2 show the estimated percentage of the population in your home State and in selected cities from your State that would have been affected had all 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx occurred only in your State or city. This is to help you understand how many lives we're talking about. We're not just talking numbers. For example, if we were talking about Florida or Pennsylvania, 1% of the entire State population would have been affected. For Iowa, it would be 5%, for Maine, 10% and for Wyoming, 27%. If we look at selected cities, I'm sorry to say, Senator Grassley, but 67% of the citizens of Des Moines would be affected, and what's worse, the entire population of every other city in the State of Iowa.

But there is another way to put this range of excess cases into perspective. Imagine that instead of a serious side-effect of a widely used prescription drug, we were talking about jetliners. Please ignore the obvious difference in fatality rates between a heart attack and a plane crash, and focus on the larger analogy I'm trying to draw. If there were an average of 150 to 200 people on an aircraft, this range of 88,000 to 138,000 would be the rough equivalent of 500 to 900 aircraft dropping from the sky. This translates to 2-4 aircraft every week, week in and week out, for the past 5 years. If you were confronted by this situation, what would be your reaction, what would you want to know and what would you do about it?

Brief history of drug disasters in the US. Another way to fully comprehend the enormity of the Vioxx debacle is to look briefly at recent US and FDA history. The attached figure shows a graph depicting 3 historical time-points of importance to the development of drug safety in the US. In 1938, Congress enacted the Food, Drug and Cosmetic Act, basically creating the FDA, in response to an unfortunate incident in which about 100 children were killed by elixir of sulfanilamide, a medication that was formulated using anti-freeze. This Act required that animal toxicity testing be performed and safety information be submitted to FDA prior to approval of a drug. In 1962, Congress enacted the Kefauver-Harris Amendments to the FD&C Act, in response to the thalidomide disaster in Europe. Overseas, between 1957 and 1961, an estimated 5,000 to 10,000 children were born with thalidomide-related birth defects. These Amendments increased the requirements for toxicity testing and safety information pre-approval, and added the requirement that "substantial evidence" of efficacy be submitted. Today, in 2004, you, we, are faced with what may be the single greatest drug safety catastrophe in the history of this country or the history of the world. We are talking about a catastrophe that I strongly believe could have, should have been largely or completely avoided. But it wasn't, and over 100,000 Americans have paid dearly for this failure. In my opinion, the FDA has let the American people down, and sadly, betrayed a public trust. I believe there are at least 3 broad categories of systemic problems that contributed to the Vioxx catastrophe and to a long line of other drug safety failures in the past 10 years. Briefly, these categories are 1) organizational/structural, 2) cultural, and 3) scientific. I will describe these in greater detail in a few moments.

My Vioxx experience at FDA. To begin, after publication of the VIGOR study in November 2000, I became concerned about the potential public health risk that might exist with Vioxx. VIGOR suggested that the risk of heart attack was increased 5-fold in patients who used the high-dose strength of this drug. Why was the Vioxx safety question important? 1) Vioxx would undoubtedly be used by millions of patients. That's a very large number to expose to a serious drug risk. 2) heart attack is a fairly common event, and 3) given the above, even a relatively small increase in heart attack risk due to Vioxx could mean that tens of thousands of Americans might be seriously harmed or killed by use of this drug. If these three factors were present, I knew that we would have all the ingredients necessary to guarantee a national disaster. The first two factors were established realities. It came down to the third factor, that is, what was the level of risk with Vioxx at low- and high-dose.

To get answers to this urgent issue, I worked with Kaiser Permanente in California to perform a large epidemiologic study. This study was carefully done and took nearly 3 years to complete. In early August of this year, we completed our main analyses and assembled a poster presentation describing some of our more important findings. We had planned to present these data at the International Conference on Pharmacoepidemiology, in Bordeaux, France. We concluded that high-dose Vioxx significantly increased the risk of heart attacks and sudden death and that the high doses of the drug should not be prescribed or used by patients. This conclusion triggered an explosive response from the Office of New Drugs, which approved Vioxx in the first place and was responsible for regulating its post-marketing. The response from senior management in my Office, the Office of Drug Safety, was equally stressful. I was pressured to change my conclusions and recommendations, and basically threatened that if I did not change them, I would not be permitted to present the paper at the conference. One Drug Safety manager recommended that I should be barred from presenting the poster at the meeting, and also noted that Merck needed to know our study results.

An email from the Director for the entire Office of New Drugs, was revealing. He suggested that since FDA was “not contemplating” a warning against the use of high-dose Vioxx, my conclusions should be changed. CDER and the Office of New Drugs have repeatedly expressed the view that ODS should not reach any conclusions or make any recommendations that would contradict what the Office of New Drugs wants to do or is doing. Even more revealing, a mere 6 weeks before Merck pulled Vioxx from the market, CDER, OND and ODS management did not believe there was an outstanding safety concern with Vioxx. At the same time, 2-4 jumbo jetliners were dropping from the sky every week and no one else at FDA was concerned.

There were 2 other revelatory milestones. In mid-August, despite our study results showing an increased risk of heart attack with Vioxx, and despite the results of other studies published in the literature, FDA announced it had approved Vioxx for use in children with rheumatoid arthritis. Also, on September 22, at a meeting attended by the director of the reviewing office that approved Vioxx, the director and deputy director of the reviewing division within that office and senior managers from the Office of Drug Safety, no one thought there was a Vioxx safety issue to be dealt with. At this meeting, the reviewing office director asked why had I even thought to study Vioxx and heart attacks because FDA had made its labeling change and nothing more needed to be done. At this meeting a senior manager from ODS labeled our Vioxx study “a scientific rumor.” Eight days later, Merck pulled Vioxx from the market, and jetliners stopped dropping from the sky.

Finally, we wrote a manuscript for publication in a peer-reviewed medical journal. Senior managers in the Office of Drug Safety have not granted clearance for its publication, even though it was accepted for publication in a very prestigious journal after rigorous peer review by that journal. Until it is cleared, our data and conclusions will not see the light of day in the scientific forum they deserve and have earned, and serious students of drug safety and drug regulation will be denied the opportunity to consider and openly debate the issues we raise in that paper.

Past experiences. My experience with Vioxx is typical of how CDER responds to serious drug safety issues in general. This is similar to what Dr. Mosholder went through earlier this year when he reached his conclusion that most SSRIs should not be used by children. I could bore you with a long list of prominent and not-so-prominent safety issues where CDER and its Office of New Drugs proved to be extremely resistant to full and open disclosure of safety information, especially when it called into question an existing regulatory position. In these situations, the new drug reviewing division that approved the drug in the first place and that regards it as its own child, typically proves to be the single greatest obstacle to effectively dealing with serious drug safety issues. The second greatest obstacle is often the senior management within the Office of Drug Safety, who either actively or tacitly go along with what the Office of New Drugs wants. Examples are numerous so I’ll mention just a few.

With Lotronex, even though there was strong evidence in the pre-approval clinical trials of a problem with ischemic colitis, OND approved it. When cases of severe constipation and ischemic colitis began pouring into FDA’s MedWatch program, the reaction was one of denial. When CDER decided to

bring Lotronex back on the market, ODS safety reviewers were instructed to help make this happen. Later, when CDER held an advisory committee meeting to get support for bringing Lotronex back on the market, the presentation on ways to manage its reintroduction was carefully shaped and controlled by OND. When it came to presenting the range of possible options for how Lotronex could be made available, the list of options was censored by OND. The day before the advisory meeting, I was told by the ODS reviewer who gave this presentation that the director of the reviewing office within OND that approved Lotronex in the first place came to her office and removed material from her talk. An OND manager was “managing” an ODS employee. When informed of this, ODS senior management ignored it. I guess they knew who was calling the shots.

Rezulin was a drug used to treat diabetes. It also caused acute liver failure, which was usually fatal unless a liver transplant was performed. The pre-approval clinical trials showed strong evidence of liver toxicity. The drug was withdrawn from the market in the United Kingdom in December 1997. With CDER and the Office of New Drugs, withdrawal didn’t occur until March 2000. Between these dates, CDER relied on risk management strategies that were utterly ineffective and it persisted in relying on these strategies long after the evidence was clear that they didn’t work. The continued marketing of Rezulin probably led to thousands of Americans being severely injured or killed by the drug. And note, there were many other safer diabetes drugs available. During this time, I understand that Rezulin’s manufacturer continued to make about \$2 million per day in sales.

The big picture. The problem you are confronting today is immense in scope. Vioxx is a terrible tragedy and a profound regulatory failure. I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless.

It is important that this Committee and the American people understand that what has happened with Vioxx is really a symptom of something far more dangerous to the safety of the American people. Simply put, FDA and its Center for Drug Evaluation and Research are broken. Now, I’m sure you have read the recent proposal to have the Institute of Medicine perform a review of CDER and its drug safety program and make recommendations for fixing things up. Don’t expect anything meaningful or effective from this exercise. Over the history of CDER’s drug safety program, a number of similar reviews have been done. In the late 1970’s, I believe that a blue ribbon panel recommended that there be an entirely separate drug safety operation in FDA with full regulatory authority. It wasn’t implemented. During the 1980’s and early 1990’s, CDER organized its own “program reviews” of drug safety. The basic premise underlying each of these reviews was that the “problem” was with the drug safety group; it didn’t fit into the Center. So, the charge given to the review panel members was always framed as “figure out what’s wrong with drug safety, and tell us what to do to get it to fit in.” There was and is an implicit expectation that the status quo will remain unaltered.

The organizational structure within CDER is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division approves a new drug, it is also saying the drug is “safe and effective.” When a serious safety issue arises post-marketing, their immediate reaction is almost always one of denial, rejection and heat. They approved the drug so there can’t possibly be anything wrong with it. The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest. At the same time, the Office of Drug Safety has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs.

The corporate culture within CDER is also a barrier to effectively protecting the American people from unnecessary harm due to prescription and OTC drugs. The culture is dominated by a world-view that believes only randomized clinical trials provide useful and actionable information and that post-marketing safety is an afterthought. This culture also views the pharmaceutical industry it is supposed to

regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety.

Finally, the scientific standards CDER applies to drug safety guarantee that unsafe and deadly drugs will remain on the US market. When an OND reviewing division reviews a drug to decide whether to approve it, great reliance is placed on statistical tests. Usually, a drug is only approved if there is a 95% or greater probability that the drug actually works. From a safety perspective, this is also a very protective standard because it protects patients against drugs that don't work. The real problem is how CDER applies statistics to post-marketing safety. We see from the structural and cultural problems in CDER, that everything revolves around OND and the drug approval process.

When it comes to safety, the OND paradigm of 95% certainty prevails. Under this paradigm, a drug is safe until you can show with 95% or greater certainty that it is not safe. This is an incredibly high, almost insurmountable barrier to overcome. It's the equivalent of "beyond a shadow of a doubt." And here's an added kicker. In order to demonstrate a safety problem with 95% certainty, extremely large studies are often needed. And guess what. Those large studies can't be done.

There are 2 analogies I want to leave you with to illustrate the unreasonableness of CDER's standard of evidence as applied to safety, both pre- and post-approval. If the weather-man says there is an 80% chance of rain, most people would bring an umbrella. Using CDER's standard, you wouldn't bring an umbrella until there was a 95% or greater chance of rain. The second analogy is more graphic, but I think it brings home the point more clearly. Imagine for a moment that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets into those chambers. The gun represents a drug and the bullets represent a serious safety problem. Using CDER's standard, only when you have 95 bullets or more in the gun will you agree that the gun is loaded and a safety problem exists. Let's remove 5 bullets at random. We now have 90 bullets distributed across 100 chambers. Because there is only a 90% chance that a bullet will fire when I pull the trigger, CDER would conclude that the gun is not loaded and that the drug is safe.

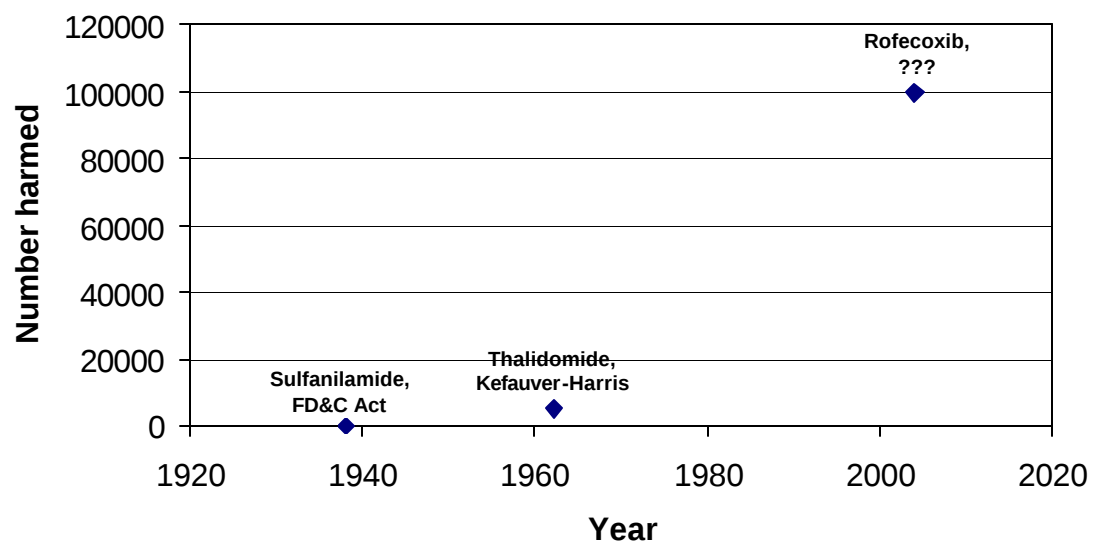
Table 1. The percentage of each State's population age 18 years or older that would be affected if an estimated 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx had all occurred in that State. The States are presented alphabetically. These are the States represented by members of the Senate Finance Committee.

State	Estimated % of population age 18 years or older
Arizona	2
Arkansas	5
Florida	1
Iowa	5
Kentucky	3
Louisiana	3
Maine	10
Massachusetts	2
Mississippi	5
Montana	14
New Mexico	7
North Dakota	21
Oklahoma	4
Oregon	4
Pennsylvania	1
South Dakota	18
Tennessee	2
Utah	6
Vermont	22
West Virginia	7
Wyoming	27

Table 2. The percentage of the population age 18 years or older from selected cities in the US that would be affected if an estimated 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx had all occurred in that city. The cities chosen were from the more highly populated States shown in Table 1. These cities are in States represented by members of the Senate Finance Committee.

State and city	Estimated % of population age 18 years or older
Arkansas	
Little Rock	73
Arizona	
Scottsdale	66
Tuscon	27
Florida	
Orlando	72
Tallahassee	89
Tampa	44
Iowa	
Des Moines	67
All other cities	100
Kentucky	
Louisville	52
Louisiana	
New Orleans	27
Oklahoma	
Oklahoma City	26
Oregon	
Portland	25
Pennsylvania	
Pittsburgh	40
Lancaster	100
Tennessee	
Nashville	23
Utah	
Salt Lake City	73

Figure. A brief history of drug safety disasters in the US.



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