**Oral Testimony by Steven E. Nissen**
**Before the House Committee on Energy and Commerce**
**Subcommitte on Oversight and Investigations**
**February 13, 2007**

My name is Steven E. Nissen, M.D. I am Chairman of the Department of Cardiovascular Medicine at Cleveland Clinic and the President of the American College of Cardiology (ACC). My testimony does not reflect the views of either Cleveland Clinic or the ACC.

We face a crisis in public confidence in the FDA following an unprecedented series of revelations about drug and device safety. The American people no longer trust the FDA to protect their health. Unfortunately, patients are increasingly suspicious of new therapies and sometimes are reluctant to accept potentially life-saving medications or devices. Decisive legislative action is now essential to improve the safety of drugs and medical devices and restore public confidence in this critically important agency.

I have served on many FDA Advisory Panels and this experience has undermined my confidence in the ability of the agency to adequately protect the public health. In 2001, I participated as a guest member of the Arthritis Advisory Panel that recommended a warning label for cardiovascular risk for Vioxx™. Under current law, the Agency must "negotiate" with industry to make even simple changes in drug labels and FDA officials frequently make inappropriate concessions to pharmaceutical companies. Following the 2001 Advisory Board, it took 14 months before the FDA could secure agreement from the company to accept a weakly written warning. During this period, patients and physicians were not appropriately warned about the cardiovascular hazards of Vioxx™. When the label was eventually modified, the wording was so weak that it did not adequately inform physicians and patients of the potential for Vioxx to cause harm.

In 2005, another disturbing personal experience brought into sharp focus the inadequacies of the FDA in assessing new drug applications. On September 9, 2005, officials from the Endocrine and Metabolism Division presented a new diabetes drug known as muraglitazar to an Advisory Panel for consideration of approval. Because of a previous lawsuit by the advocacy group Public Citizen, the FDA is required to publicly disclose the "briefing materials" for Advisory Panels.

Because of my interest in this class of drugs, I reviewed the briefing documents posted on the Internet by the Agency on September 8, the day before the public hearings. I observed that this investigational drug seemed to lower blood sugar, but I also noted that there was a striking excess of heart attacks, strokes, and deaths in patients treated with muraglitazar compared with placebo or other diabetes drugs. Based upon this observation, I assumed that the Advisory Board would recommend that the Agency not approve muraglitazar.

Yet astonishingly, the following day, Agency reviewers presented the drug in a favorable manner, understating any concerns about cardiovascular risk. This Advisory Panel, that did not include any cardiologists, voted 8:1 to approve muraglitazar, ending the panel meeting at 2 pm. In Cleveland, I watched the news reports, complete with predictions from financial analysts that this drug would achieve annual sales exceeding $1 billion.

I felt compelled to act. My statistician and I rapidly downloaded the FDA material available from the Internet and performed our own independent analysis of the risks and benefits of this drug. We concluded that muraglitazar doubled the risk of death, heart attack stroke and congestive heart failure. I phoned the editors of the Journal of the American Medical Association, who treated our findings as a public health emergency. Peer reviews were secured in a matter of days, and JAMA posted the manuscript on their website October 20, just 7 weeks following the FDA advisory panel

meeting. Shortly prior to our publication, the FDA issued an "approvable" letter to the sponsor. Following this publication, the pharmaceutical company developing muraglitazar abruptly ceased all further development. Fortunately, this drug will never threaten the public health, but frankly, it was a close call.

We were able to independently analyze the risks of muraglitazar because the drug was presented to an advisory panel. For many new drugs, the agency approves them without public disclosure of the key findings in pivotal clinical trials. When drugs are presented to Advisory Panels, the agency frequently provides an uncritical presentation that fails to adequate inform the advisory panel members of any internal FDA concerns.

This phenomenon was very evident during a meeting of Drug Safety and Risk Management Advisory Board of the FDA, which met February 9, 2006, to review drugs used to treat Attention Deficit Hyperactivity Disorder or ADHD. I was asked to serve on this Advisory Panel to help evaluate the cardiovascular risks of these drugs, most of which are amphetamines or amphetamine-like agents. These drugs are closely related to methamphetamine or "speed", a major drug of abuse.

At nearly all Advisory panel meetings, the FDA provides a list of questions to the panel members designed to assist in discussions and to guide the formulation of an action plan. When the Advisory Board briefing materials arrived, I was rather surprised by the questions that the Agency intended to ask. In this case, the FDA did not request the committee to consider the risks of the ADHD drugs, nor did they ask us to comment on the need to change labeling. Instead, they asked the committee to discuss how the Agency might study the class of drugs.

During the hearings, we learned that the ADHD drugs increase blood pressure and we heard reports indicating that approximately 25 children has suffered sudden cardiac death after taking these drugs, occasionally after he first dose. ADHD drugs are closely related to ephedra, a drug that the FDA has sought to ban from OTC products. We also learned that 4 million Americans take ADHD drugs, including 1.5 million adults, and up to 10% of 5$^{th}$ grade boys.

By mid-afternoon, I had heard enough. I departed from the FDA's carefully orchestrated agenda and introduced a motion proposing that the committee recommend a black box warning for the ADHD drugs. Surprisingly, the motion passed by an 8 to 7 vote. Agency officials looked horrified and quickly called a news conference, where they defended the safety of the drugs and sought to undermine the recommendations of the Advisory Committee.

Some months later, the FDA actually did write new warnings. But it took a rogue advisory committee to motivate the Agency to act.

It is important for the Congress to recognize that there are many fine and dedicated public servants working within the FDA. However, their concerns often fail to reach advisory committees because of the actions of their supervisors, who adopt a less courageous approach.

The Congress must now fully evaluate the deficiencies within the FDA. Your engagement to investigate the problem and take decisive action can improve this Agency. The 300 million American who rely upon drugs to stay healthy are counting on you to take action.

These measures need not slow drug development. If we improve drug safety oversight, the increased vigilance will inspire confidence and allow us to bring new medicines to patients more quickly, because we will have a better "safety net."

In my more extensive written testimony, I outline 10 critical initiatives needed to put the FDA back on course. I hope you will consider these ideas as you move forward and greatly appreciate the opportunity to appear before you.

**Written Testimony by Steven E. Nissen**
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My name is Steven E. Nissen, M.D. I am Chairman of the Department of Cardiovascular Medicine at Cleveland Clinic and the President of the American College of Cardiology (ACC). My testimony does not reflect the views of either Cleveland Clinic or the ACC.

We face a crisis in public confidence in the Food and Drug Administration (FDA) following an unprecedented series of revelations about drug and device safety. The American people no longer trust the FDA to protect their health. Unfortunately, patients are increasingly suspicious of new therapies and sometimes are reluctant to accept potentially life-saving medications or devices. Decisive legislative action is now essential to improve the safety of drugs and medical devices and restore public confidence in this critically important agency.

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What the solutions to improving the performance of the FDA?

The FDA operates in a "culture of secrecy." When studies reveal toxicity or lack of efficacy, the Agency does not release the results and the findings are often not published, thereby denying patients and physicians access to vitally important safety information.[1] This approach is antithetical to the public health and undermines good scientific practice. Free and open access to all relevant information is required to enable physicians to thoughtfully select therapies for their patients. The FDA withholds findings in deference to industry's claims that such information constitutes "trade secrets." In my view, this is misguided. When a patient volunteers to participate in a drug or device study, there is an implicit moral obligation that the patient's participation will benefit medical science and their fellow citizens.

Most relevant information on drug safety is readily available to the FDA through "study reports" routinely submitted by pharmaceutical and device companies. However, these reports are usually not widely circulated within the agency and invariably not released to the public or scientific community. It remains theoretically possible to access submitted study reports via a Freedom of Information Act (FOIA) request, but we are usually unaware of the existence of relevant studies. Accordingly, no one ever requests such information.

There are innumerable examples of drug safety information that took years to reach our attention despite reasonable knowledge of the problem within the Agency. Examples include Baycol™, Ketek™, Vioxx™, and antidepressants risks in children. During the months to years in which safety information was not publicly available, many patients suffer complications needlessly. Often, the FDA knew there was a problem. Those of us who prescribe drugs did not.

This lack of transparency dramatically worsened after passage of the Prescription Drug User Fee Act (PDUFA) legislation. Although a well-intentioned effort to speed drug development, PDUFA has seriously undermined the effectiveness and transparency of the Agency. PDUFA makes industry, not the American public, the FDA's primary stakeholder and creates a conflict in loyalty for FDA employees. The time pressure induced by PDUFA deadlines often forces the FDA to make hurried decisions under conditions of considerable uncertainty, resulting in poor outcomes. The premature Advisory Board hearings on muraglitazar represent an excellent example of this phenomenon.[2] Good regulatory decisions are not performed in an environment where a "rush to judgment" is forced by artificial legally-mandated deadlines.

We should fund the FDA from public funds, not fees paid by the regulated industry. Virtually, every American takes one or more medications, so drug safety affects all of us. Yet the annual expenditure for drug regulation approximates only about $2 per person. We cannot expect outstanding performance for an Agency operating on an inadequate budget. The Agency needs more staff to adequate supervise a huge and complex industry. Salary levels should be adequate to attract the most skilled professional staff. The current flight of talented staff from the Agency must be reversed.

It takes many years of experience to perform complex regulatory tasks in a skillful fashion. The individuals currently leaving the FDA are simply irreplaceable.

The Agency has suffered from instability in leadership extending to the highest levels. Regardless of which party holds the White House, the FDA needs a passionate and committed leader who will resist pressure to make regulatory decisions based upon political expediency, rather than scientific evidence. The successful efforts by political forces to prevent or delay approval of over-the counter sales of "Plan B", an emergency contraceptive for women, seriously undermined morale at the Agency and must not be repeated. This Agency is too important to allow political expediency to influence decisions.

We need new laws to strengthen the authority of the FDA. Currently, the Agency must "negotiate" with industry to make even simple changes in drug labels. Companies routinely make commitments to perform Phase IV studies, but never actually launch the promised clinical trials and the agency is powerless to act. The requirement for the consent of the regulated industry to change drug labels is simply bad regulatory practice. Professional staff at the Agency should decide the content of labels, not pharmaceutical and device companies.

Some industry practices have seriously undermined drug safety. This problem of "negative publication bias" – the practice of suppressing and never publishing unfavorable studies has a catastrophic effect on the drug development system.[3,4] When drugs show serious toxicity in patients, the results are rarely published. Accordingly, other companies expose patients to closely related drugs without knowing that study of a similar agent showed significant harm. I am aware of a class of drugs where more than a dozen compounds showed serious toxicity, resulting in termination of development, but without a single publication of results. When studies are not published, we learn nothing from the experiment and make the same mistakes over and over again. This practice also significantly increases the costs of drug development (and ultimately drug prices), because companies continue to follow non-productive routes to drug development.

The post-marketing surveillance system for drugs and devices functions poorly. Adverse event reporting is voluntary and studies show that only 1 to 10% of serious adverse events are ever reported to the Agency. Accordingly, the actual incidence of serious or life-threatened complications cannot be calculated accurately. There are many examples where the failure of the FDA's Averse Event Reporting System (AERS) resulted in serious harm to our citizens. Baycol™ caused serious muscle toxicity at rate nearly 100 times greater than other cholesterol lowering drugs in this class.[5] Yet it was marketed for years before this hazard became known and the drug withdrawn.

I believe that Direct to Consumer (DTC) Advertising requires decisive legislative action. The standard for acceptable DTC advertising should require demonstration of a compelling public health advantage for this type of communication. Drugs with an addiction potential, such as sleeping medications, should be specifically prohibited from consumer advertising.

We must address another critical drug safety problem not addressed in this bill – the nutraceutical industry, currently not subject to regulatory scrutiny. This multi-billion dollar industry sells so-called "dietary supplements" that are often worthless and

sometimes harmful.[6] Patients take such drugs instead of effective medications with catastrophic implications for their health. I recently saw a patient who suffered a heart attack after switching from prescription niacin, a drug that raises HDL, the good cholesterol, to "no flush" niacin, a fraudulent therapy with no favorable effects. His cholesterol levels rapidly became abnormal after switching, resulting a very bad outcome.

We need to amend or repeal the Dietary Supplement Health and Education Act (DSHEA) of 1994. By moving dietary supplement out of the regulatory scrutiny of the FDA, we are inviting a public health catastrophe.

It is important for the Congress to recognize that there are many fine and dedicated public servants working within the FDA. However, their concerns fail to reach advisory committees because of the actions of their supervisors, who adopt a less courageous approach.

The Congress must now fully evaluate the deficiencies within the FDA. Your engagement to investigate the problem and take decisive action can improve this Agency. The 300 million American who rely upon drugs to stay healthy are counting on you to take action.

My recommendations for a 10-point program to fix this vitally important agency:

1) Insulate the FDA from political influence. Let scientific data determine the outcome of regulatory decisions, not politics.

2) Install FDA leadership with a passion to properly balance the vital need for speedy drug approval with appropriate vigilance on safety.

3) Create an "open access" system that allows the public and the scientific community access to study reports to enable full discussion of risks and benefits of therapies.

4) Require all trials involving human subject to be registered and either published or publicly disclosed.

5) Repeal PDUFA and increase public FDA funding to enable a more thorough, rapid and accurate review of new drug applications and the safety of existing drugs.

6) Strengthen the laws to allow the FDA to unilaterally re-label drugs when issues of safety of efficacy arise.

7) Consider stiff civil monetary penalties, and in extreme cases, criminal penalties for withholding vital safety findings from the Agency.

8) Restructure the post-marketing surveillance system to enable better identification of emerging safety issues.

9) Restrict DTC advertising to messages that offer a compelling public health benefit.

10) Enable the FDA to regulate dietary supplements and nutraceuticals.

These measures need not slow drug development. If we improve drug safety oversight, the increased vigilance will inspire confidence and allow us to bring new medicines to patients more quickly, because we will have a better "safety net."

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