Testimony of Sidney M. Wolfe, M.D.
Director, Public Citizen's Health Research Group
before the
Committee on Appropriations, Subcommittee on Agriculture, Rural Development and Related Agencies
Hearing on FDA Appropriations
January 31, 1995

Chairman Skeen and Members of the Subcommittee, thank you for the opportunity to present testimony concerning this important public health agency. For more than 23 years, the Public Citizen's Health Research Group has been a major critic of the Food and Drug Administration (FDA). During this time, we have filed more than 50 petitions for warning labels or bans of prescription or over-the-counter drugs or medical devices in addition to a significant amount of additional research and petitions to the FDA concerning food safety issues. Thus, our criticism of the agency is usually that it is not doing enough to protect the public.

However, as far as we can determine, the FDA does a better job of protecting the public from unsafe food, drugs, medical devices or other products which it regulates than any other such agency in the world.

Despite this, or, possibly because of this, there has been an epidemic of recent criticism about the agency, particularly that it is being too cautious in its review of drugs and devices and that, as a consequence, Americans are being deprived of drugs or devices which are available earlier in other countries. In a full-page ad which has run twice in the *Wall Street Journal* and three weeks ago (January 12) in the *New York Times*, the Washington Legal Foundation (WLF) listed a number of unfounded examples in which Americans had been harmed as a result of FDA caution. Attached is a letter rebutting this criticism from the FDA which mentions, by way of example, that the WLF's claim in the ad that the American Heart Association (AHA) had said "that at least 1,000 lives were lost during the time an approved heart defibrillator was delayed" was false. AHA has, in fact, stated that the ad was "irresponsible and incorrect" and denied making such a claim.

Additional criticism of the FDA from the Competitive Enterprise Institute and Citizens for a Sound Economy (CFASE) was based on some of the same false and/or misleading examples used in the WLF ad. All three organizations call for major weakening of FDA's regulatory authority under the guise of protecting Americans by making miracle drugs and devices more readily available.

Recent Improvements in FDA Performance

Significant improvements in FDA's handling of New Drug Applications have already occurred during the past 15 years, most strikingly in the past four years. The critical combination of more funding and better management, neither of which would be sufficient alone, has resulted in a retention of the important legal standards for safety and efficacy while

rationally expediting the approval of new drugs, especially the relatively small number which are actually an important therapeutic advance over existing therapy. Thus, approval times and backlogs have been substantially reduced, in large part by the better management which Dr. Kessler has imposed on the agency and which the user fee system--enabling the hiring of more reviewers and imposing deadlines for review--has accomplished.

The fruits of this improved process have already become apparent. In 1994, for example, according to the major international publication on the pharmaceutical industry, the London-based *SCRIP*, there were 47 new chemical entity drugs (as opposed to new dosage forms or salts) approved in the world through December 8, 1994, when the January issue of *SCRIP* Magazine, which contains this analysis, went to press. Of these, only two were thought to be important therapeutic advances over existing therapy. One is dornase alfa (Pulmozyme, Genentech) for cystic fibrosis and the other, imiglucerase (Cerezyme, Genzyme) for Gaucher's Disease. Not only were both made by American companies but both were approved here before approval in any other country in the world.

Upset and inflamed by irresponsible ads and press conferences by the FDA-bashing groups mentioned above or articles on the editorial page of the *Wall Street Journal*, it is not surprising that a recent survey by CFASE found that 68 percent of those interviewed thought that FDA review time costs lives by forcing people to go without "potentially beneficial drugs." Presented with the evidence on 1994 drug approvals cited above or, for example, the fact that the first AIDS drug, AZT, was also approved here before being approved in any other country, the survey respondents might answer differently. Ironically, in parts of the survey which were not included in the organization's press release, a much more favorable view of the FDA was in evidence. Sixty-one percent, for example, thought that pharmaceutical and medical products in the U.S. are safer than in other nations such as Canada, Japan, France, or Germany. Seventy-two percent thought that U.S. food products were safer than those in other countries.

Since most new drugs which come on the market here or in any other country are not important therapeutic advances and since the few that are more important are as, or more, likely to be approved here first, the FDA seems to be doing a good job on that score. For medical devices, the approval process is much too lax since more than 90 percent of the devices which are on the market have avoided the pre-market testing requirements because of two huge loopholes in device regulation. Although there have been important gains in the backlog for devices, it is clear that this part of the FDA would benefit as much from a user fee system as the drug division already has and I hope that this subcommittee will seriously consider such legislation as soon as possible.

In summary, the American public is not likely to tolerate any weakening of FDA's regulatory authority or reduction in funding which, in either case, will reduce the safety of the food supply or worsen the safety of drugs or devices. The managerial and funding changes which have already improved the process for drugs without any apparent sacrifice in safety or efficacy standards need to be extended to devices.

Thank you.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

January 25, 1995

Mr. Daniel J. Popeo
Chairman and General Counsel
Washington Legal Foundation
2009 Massachusetts Avenue, N.W.
Washington, D.C. 20036

Dear Mr. Popeo:

Recent articles, public statements and advertisements of the Washington Legal Foundation and its representatives contain a number of factual errors and misleading representations about the Food and Drug Administration. Some of these errors and misrepresentations have then been repeated by others.

Contrary to your claims, the agency's reviews of Interleukin 2, Tacrine and TPA are examples of how lives were saved and risks minimized by answering important questions about appropriate doses and potentially fatal effects of these promising drugs. In a similar manner, the agency has acted in the cases of the Ambu CardioPump and Sensor Pad to ensure that these products provide people with the benefits claimed for them.

Moreover, your statements and ads fail to recognize the steps taken by the FDA in recent years to make promising drugs available before final approval. In addition, there have been and continue to be significant improvements by the FDA to reduce the time for drug reviews and approvals, as well as device reviews and approvals.

To help you correct the public record and to prevent others from being misled, please consider these facts in your future statements and advertisements:

Interleukin 2

Even before the company sought FDA approval in 1988, the FDA and the National Cancer Institute expanded access in 1987 to Interleukin 2, making it available at NCI-supported clinical and comprehensive cancer centers. The NCI scientist, Dr. Steven Rosenberg, who did pioneering work on this drug, said at the time: "These treatments are still in a developmental stage, and considerable refinement is necessary before their role in cancer therapy can be established."

In its review, the FDA found problems in the manufacturing and proposed administration of Interleukin 2 and found inadequacies in the clinical data which made it impossible to determine which patients were more likely to benefit than be harmed and which of the proposed dosing regimens had favorable outcomes. As a result

of the FDA review, the manufacturing, dosing and patient selection were substantially modified to maximize efficacy and decrease toxicity. It should be noted that Interleukin 2 is not a panacea, and the U.S. Pharmacopeia recommends "because of its potential life-threatening toxicities,...that this medication be used only after careful consideration of risk-benefit."

In fact, the clinical trial data showed a complete remission of the tumor in 4% of the patients. It is also important to note the serious side effects: nearly all the patients in the clinical trials experienced severe or life-threatening side effects, and the drug-related mortality rate was 4%, a significant risk even for patients with a life-threatening illness.

Moreover, a representative of the drug's manufacturer -- interviewed about your recent ad -- said the mortality rate was "not a trivial matter to be glossed over" and that the 1990 advisory committee that requested more data about the drug before considering approval was not asking "unreasonable questions."

Ambu CardioPump

The assertions of the WLF are contradicted by the published literature. A study reported in a May 11, 1994 Journal of the American Medical Association article showed no significant benefit from using this device compared to traditional CPR with regard to hospital discharge rates, return to baseline neurological function or return to baseline neurological function at hospital discharge. Two additional studies from California presented at a recent cardiology meeting also showed no significant benefit for this device over standard CPR.

The Washington Post recently interviewed one of the investigators for that study, Dr. Michael Callaham. The December 11, 1994 article reported: "One study in Minnesota showed that the device helped to resuscitate more patients, 'but it didn't change how many of them left the hospital alive,' Callaham said." Dr. Callaham went on to say the device needs more study.

Tacrine

In fact, the FDA worked hard to encourage and speed the development of this drug. When an academic investigator reported dramatic results in a very small study, FDA encouraged and worked with the National Institute of Aging and a drug company to carry out a large, multi-center study that would, if it confirmed the early finding, lead to prompt marketing of the drug. The FDA continued this encouragement even when it was determined that the investigator's original study was seriously flawed.

The results of the first large trial were disappointing: at most, there was a small improvement in memory but no detectable difference in the overall condition of persons receiving the drug. Moreover, clinical testing showed the drug causes liver toxicity in a significant proportion of patients.

FDA encouraged the study of the drug at higher doses and in a way to protect patients from the risk of liver injury. Those studies showed that the higher doses were necessary to achieve effects both on a test of memory and attention and on the patient's overall condition. The study also showed that patients could receive the drug safely if the dose was carefully escalated with frequent blood tests to identify patients sensitive to the drug's liver toxicity.

As part of the agency's efforts to make drugs for life-threatening diseases available even before final approval, tacrine was granted "treatment IND" status in February 1992. More than 7,200 patients were allowed to receive the drug while the final studies were completed.

Finally, it should be noted that contrary to the implication in the WLF ad -- "Nobody knows how many died" -- there is no evidence that this drug prevents patients from dying from Alzheimer's or prevents progression of the mental deterioration caused by the disease.

Defibrillators

The American Heart Association, in a letter published in The New York Times on January 21, 1994, has repudiated your use of its name in your advertisements and has called your ad "irresponsible and incorrect." The AHA denies making the claim you attributed to the organization.

It appears from your October 28, 1994 Legal Backgrounder that you based your claim on the statements of an individual who was identified on a television program as chairing an AHA committee. This same individual was a paid expert witness for the defibrillator company in a recent lawsuit between the FDA and the manufacturer. The company was ordered by a federal court to comply with the Medical Devices Reporting (MDR) regulations and, under court order, has promised to improve its MDR practices; the court also ruled that the company had improved its good manufacturing practices and there was no longer a basis for enjoining the company on that issue. At no time during this court case was the company prohibited from shipping its devices as your ad states.

Sensor Pad

The manufacturer has not provided to the FDA any data to show that

the device does what your ad claims: the magnification of the sensation of lumps in a woman's breast. In fact, expert examiners on an advisory committee to the FDA raised the question of whether the device actually decreases the ability to detect lumps. And the manufacturer has failed to provide the FDA -- despite repeated requests -- with data that this device will not make it more difficult for women to detect breast lumps than the conventional breast self-examination. Given the seriousness of the breast cancer problem in this country, the reason to require this information is simple and compelling: The FDA wants to be sure that using the device will not cause women to delay seeking medical attention.

Most of the data presented so far to the agency by the manufacturers comes from women using the device on foam models of breasts. The advisory committee said the manufacturer should:

- o Do tests with women using the device on their own or other's breasts to determine if it enhances their sense of touch.
- o Do tests -- with and without the pads -- with physicians examining women about to undergo biopsies.

TPA

A proven safe and effective drug, with the information necessary for doctors to use it safely, was the result of the FDA review of this drug. TPA is intended to dissolve the blood clot blocking a coronary artery during a heart attack. Studies of TPA used a dose of 150 mg and showed that it led to a high rate (about 1.5%) of bleeding in the brain that was usually fatal or badly disabling. The manufacturer proposed a lower dose that would still dissolve the clots and was expected to lessen the risk of intra-cranial bleeding. The approval for this drug came in November 1987, only seven weeks after the manufacturer submitted the last critical data that had been requested during a May 1987 advisory committee meeting. During that meeting, the committee requested data on whether TPA provides a beneficial effect on survival or heart function and a detailed analysis of the intra-cranial bleeding rate at the recommended dose in a large study. The final questions resolved included the issue of dosage and intra-cranial bleeding and an accurate assessment of TPA's benefits despite its risk of stroke.

It should also be noted that while TPA was being reviewed, another drug -- streptokinase -- was already on the market and available for heart attack patients if physicians chose to administer it on the basis of their review of the literature.

This is not a comprehensive reply to recent WLF statements and advertisements. It should indicate, however, your need to be more accurate and factual in the future. If discussions and debates in

the coming months on drug and device regulation are to be of value, they will need to be conducted with rigorous intellectual honesty and scrupulous attention to the facts.

If FDA can assist you in that regard, please feel free to contact my office and we will attempt to provide you with appropriate information and references.

Sincerely,

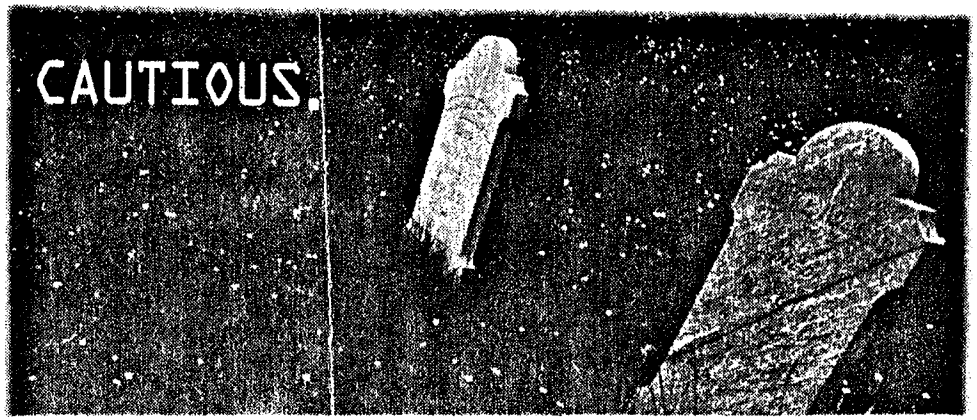
James A. O'Hara III
Associate Commissioner
for Public Affairs

IF A **MURDERER** KILLS YOU, IT'S HOMICIDE.

IF A **DRUNK DRIVER** KILLS YOU, IT'S MANSLAUGHTER.

IF THE **F D A** KILLS YOU,

IT'S JUST BEING CAUTIOUS.



Horror stories abound. Not just from accidents and crime—but from the paralyzed hallways of our own federal government's bureaucratic and apparently unaccountable Food and Drug Administration.

Right now, delays on approving lifesaving drugs, treatments, and devices are obstructing Americans from getting the best available medical treatment—forcing many to search instead for newer drugs and technologies abroad. For the majority who can't afford worldwide travel, the delays mean needless deaths. Some recent examples:

- 3,500 kidney cancer patients died during the 3½ years it took the FDA to approve the drug *Interleukin 2*. It had already been approved in nine European countries.
- 14,000 heart-attack victims so far have died who could have been saved by the cardio-pump during the two years the FDA has delayed approval.
- During the seven years it took to approve *tacrine*, thousands of Alzheimer's patients gradually lost their memories. Nobody knows how many died.
- The American Heart Association estimates that at least 1,000 lives were lost during the time an approved heart defibrillator was delayed. Why was it delayed? The FDA prohibited shipments because of paperwork problems.
- In spite of criticism in the *Wall Street Journal* and ABC's *20/20*, and in the face of 46,000 deaths per year from breast cancer, the FDA has obstructed approval—for nine years—of the Sensor Pad, a device that magnifies the sensation of lumps in women's breasts. In Canada, the product was approved in less than 60 days.
- The lives of more than 150,000 heart attack victims may have been saved had the FDA not delayed approval of the emergency blood-clotting drug *TPA* by a year and a half.

We all want safe and carefully tested medicines and treatments. But let's have them in our lifetime... not long after we've died in agony from a disease other nations have controlled for years.

For more information, contact: WLF Health Care Project, Washington Legal Foundation, 2009 Massachusetts Ave., NW, Washington, DC 20036. And of course, please feel free to reprint this message without permission.

THE PROBLEM WITH HEALTH CARE IN AMERICA IS THE FDA