

Testimony before the Congressional Agriculture-FDA Appropriations Subcommittee hearing on drug safety (HRG Publication #1835)

February 27, 2008

Sidney M. Wolfe M.D.
Public Citizen's Health Research Group

Chairwoman DeLauro and Members of the Subcommittee, thank you for the opportunity to discuss the dangerously deepening crisis at Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). Between the time I left the National Institutes of Health (NIH) in early 1972 to start the Health Research Group and now, two-thirds of our work has focused on the FDA, especially drugs. The situation at the FDA has never been worse than now and this can be attributed to a confluence of 3 factors:

- Terrible leadership at the FDA, including the Commissioner and most of the Center Directors
- Increasing reliance on industry to fund FDA activities, with almost 2/3 of the drug approval budget coming out of the \$400 million+ Prescription Drug User Fee Act (PDUFA) drug allocation for FY 2008
- Relative to the 1970's and 1980's, a perilously low level of Congressional oversight and oversight hearings by the same Congresses that have, since 1992, increasingly turned over FDA funding to the industry

I will discuss the CDER budget from the perspective of funding of activities up through approval and post-approval.

Pre-approval budget and function

I do not think that the size of CDER's budget for these activities is inadequate but the source is entirely wrong. The FDA's public health mission is too important to be left to funding by the drug industry with all of the concessions and negotiations that industry extracts for paying the majority of the bill for the FDA drug approval process. Instead, adequate funds need to be appropriated by the Congress, as they were for the first 86 years of FDA's existence (1906-1992) with structured, regular, mandatory oversight by appropriations and oversight committees.

An analysis of serious post-PDUFA mistakes made by CDER in approving a number of drugs that had evidence prior to approval of bright red warning signs illustrates the problem of CDER funding by industry:

- Duract (bromfenac): The FDA Medical Officer reviewing bromfenac sodium, the 20th nonsteroidal anti-inflammatory drug (NSAID) approved in the United States, unsuccessfully advocated a black box warning label as a condition of approval because, "The review of the 'liver' laboratory data from the submission shows that bromfenac sodium causes hepatocellular damage to a greater degree than other

NSAIDs".^[1] After at least 4 deaths and 8 liver transplants, bromfenac sodium was removed from the market.

- Posicor (mibefradil): Data from congestive heart failure trials presented at a FDA Advisory Committee meeting on whether or not to approve mibefradil suggested that more patients treated with the drug died of sudden deaths than those taking placebo. Several committee members voted against approval. The drug, the ninth calcium channel blocker approved in the United States, has since been removed from the market because of life-threatening arrhythmias from drug interactions.
- Rezulin (troglitazone): The 11th drug for diabetes in the United States, was approved even though 1.9% of patients in the pre-marketing trials, 54% of whom had taken the drug for at least 6 months, had liver function test results greater than 3 times the upper limit of normal, and 0.4% and 0.2% had 10-fold and 20-fold elevations, respectively. Well before it was removed from the market, troglitazone had already been associated with a minimum of 43 cases of liver failure, including 28 deaths.
- Trovan (trovafloxacin): Trovafloxacin was approved by the FDA in 1997. Like Duract, there was also clear evidence of liver damage caused by Trovan in animals and in humans before the drug was approved in December 1997. In one pre-approval study in which the drug was used to treat prostatitis, 10% of the men (14 out of 140) given the drug developed evidence of liver toxicity. With 8 other drugs in this fluoroquinolone antibiotic family available in the U.S., as well as dozens of other safer and equally or more effective drugs for infections, the removal of Trovan from the market by the FDA would not have deprived doctors or patients of a drug that could possibly be considered indispensable. Instead of banning Trovan in 1999, as was done everywhere else in the world, the FDA chose to "limit" its use in the United States to patients who were either hospitalized or in nursing homes. At the time of our petition in 1999 to ban the drug, there were 8 cases of liver failure, including 5 deaths and 3 liver transplants. There were, as of December 31, 2004, a total of 58 cases of liver failure, including 29 deaths and 9 people requiring liver transplants. This is especially alarming since for the past several years there were a total of only 350,000 prescriptions filled in the U.S. (from April 2002 through Feb 2005). As sales waned following the 1999 market withdrawal in Europe but more and more cases of liver failure and death occurred, Pfizer quietly discontinued making the drug in 2002. However, during the latest year for which U.S. sales data are available, there were still 18,000 prescriptions filled in the U.S. (March 2004 through February 2005), long after Pfizer quietly stopped manufacturing the drug.
- Lotronex (alosetron): Seven cases of life-threatening ischemic colitis occurred in clinical trials for this drug with marginal benefits in treating the diarrhea variety of irritable bowel syndrome. Within 6 months of marketing an additional 16 cases had occurred. We petitioned the FDA to remove it from the market but, after its removal, it was approved with very limited distribution.

1998 Public Citizen Survey of FDA Medical Officers

In 1998, after 2 years (1996-7) of record numbers of FDA new drug approvals and the increasing numbers of these drugs that were rather promptly being taken off the market after post-approval deaths and serious injuries confirmed pre-approval concerns, Dr. Peter Lurie and I conducted a written survey of FDA Medical Officers to find out their views on the changes that had occurred post-PDUFA.[\[2\]](#) This was to be the first of several studies by others concerning this problem.

Of the 53 Medical Officers who responded there were the following findings:

- Nineteen Medical Officers identified a total of 27 new drugs in the past 3 years that they reviewed that they thought should not have been approved but were approved.
- Asked how they would compare the current standards of FDA review for safety and efficacy to those in existence prior to 1995, 17 Medical Officers described the current standards as "lower" or "much lower," 13 described them as "about the same" and 6 described them as "higher." None described the standards as "much higher."
- One Medical Officer stated: "My feeling after more than 20 years at FDA is that unless drugs can not be shown to 'kill patients' outright then they will be approved with revised labeling and box warning."
- Twelve Medical Officers identified 25 new drugs that they reviewed in the past 3 years that in their opinion had been approved too fast.
- Thirty-four Medical Officers stated that the pressure on them to approve new drugs was "somewhat greater" or "much greater" compared to the period prior to 1995.
- One Medical Officer stated: "We are in the midst now to approve everything but to describe drug weaknesses in the label. As one high ranking official said 'Everything is approvable. We can use the labeling creatively to lower the problems.'"
- Eight Medical Officers reported 14 instances in the past 3 years in which they had been instructed, usually by the Office Director, not to present their own opinion or data to an FDA Advisory Committee when to do so might have reduced the likelihood that a drug would be approved.
- Nine Medical Officers identified 19 new drugs that they had reviewed in the past 3 years that had been inappropriately shifted to the accelerated approval track.
- Thirteen Medical Officers identified 18 occasions in the past 3 years when a supervisor, usually their Division Director, had asked the Medical Officer to change his or her opinion to agree with the supervisor's, usually in a direction favoring approval.
- One Medical Officer reported: "In the last 2 years, I recommended that 2 drugs not be approved. They were both approved without consulting me. This never happened before. In one case, the drug did not meet the standards set up by the division, so they nullified the standards."

2001 FDA Survey of CDER Personnel

One of the reasons the morale in CDER is as low as at any time in the past 35 years was aptly summed up by a statement of CDER Director Dr. Woodcock that “the intense [user fee mandated] schedules create a sweatshop environment that's causing high staffing turnover.”[\[3\]](#)

In a survey by the FDA of CDER personnel in 2001, intended to discover the reasons for the high rate of staff turnover, the problems found included the following:

About 1/3 of respondents did not feel comfortable expressing their differing scientific opinions...over 1/3 felt that decisions such as holds, refuse-to-file actions, and non-approvals are stigmatized in the agency. Over 1/3 felt that their work has more impact on a product's labeling and marketability than it does on public health. A number of reviewers added comments stating that decisions should be based more on science and less on corporate wishes.

One of the 13 recommendations in the report is to “Encourage freedom of expression of scientific opinion.”[\[4\]](#)

We believe that unless this occurs, along with healthy debates, the FDA will not be able to attract and keep its best staff. Debate, attention to dissident views, and freedom of expression are not only the hallmarks of good science; they are also the essence of democratic governance.

HHS Inspector General Study of FDA: 2003

The IG study confirmed that decisions concerning drug safety and effectiveness were being overturned. Eighteen percent of surveyed FDA physicians and scientists felt pressure to recommend that drugs be approved for sale despite their reservations about the drug's safety, efficacy or quality. The report concluded: "Overall, these findings present a significant warning signal."

Post-approval budget and function

The 2 topics I will discuss here are post-approval safety reviews of drugs, often precipitated by a series of well-documented adverse reactions to drugs, and post approval compliance activities including inspections of pharmaceutical companies.

The concept of generating a signal from adverse drug reactions is useful only if the signal is taken seriously and the action taken is prompt and proportional to the strength of the signal. This is especially important when the signal confirms earlier pre-approval evidence of dangers seen in randomized controlled trials, as in 4 drugs cited above. There has been an historic split and an imbalance of power between FDA drug review divisions and the postmarked surveillance (offices of drug safety) divisions. In too many instances, serious post-marketing safety problems identified by the offices of drug safety have not

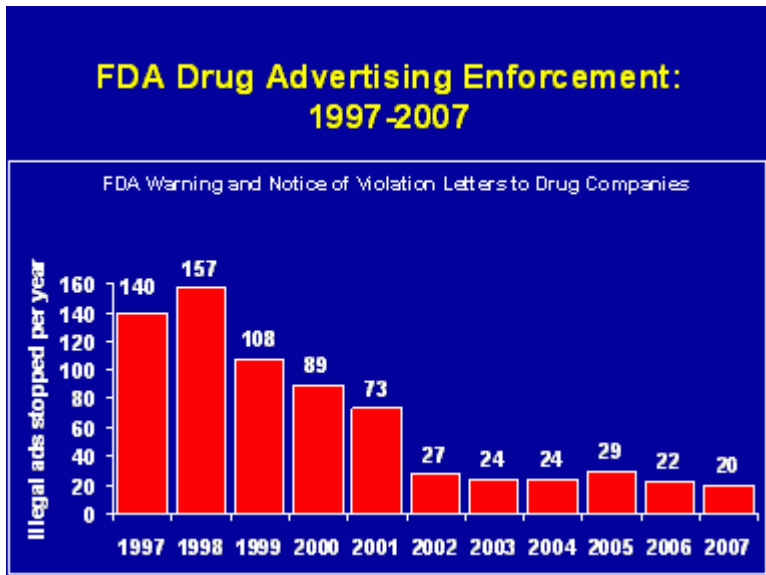
been acted upon because of resistance from FDA management and from the review division that originally approved the drug and now gets the majority of its funding from industry.

Increased funding, especially with much of it coming from PDUFA, in the absence of the increased independence that would occur if the offices of drug safety were made independent of CDER is not likely to solve this historic imbalance of power. The funds must be directly appropriated from the government.

Enforcement of Laws and Regulations Concerning Prescription Drug Advertising

Although we have always supported more funds for DDMAC (CDER's Division of Drug Marketing Advertising and Communications), starting in 1999, there has been an enormous reduction in enforcement actions (warning letters and notice of violation letters) each demanding that an illegal ad be stopped. From a maximum number of such illegal ads that were stopped in 1998 (157 ads), the number has fallen drastically and dangerously to 20 last year in the face of an actual increase in the amount of money spent on prescription drug advertising.

The figure below shows that by the end of the Clinton administration there had already been a decrease to 89 such actions (a 43% decrease) and that has fallen to 20 last year (an 87% decrease), having bottomed out for the past 6 years. This is inexcusable and is not proportionate to any decrease in DDMAC staff nor any evidence of a law-abiding epiphany by the drug industry. This means prescribing decisions are too often based on perceptions that drugs are safer and/or more effective than they actually are because of the misleading ads, misleading doctors as well as patients.



(data compiled from FDA web site)

Sharp Decrease in Warning Letters for all of FDA to Regulated Companies

As seen in the chart below, there has been a similar FDA-wide decrease in warning letters to all regulated companies. Unlike DDMAC activities that are accomplished centrally, much of the other compliance activities in FDA depend on inspectors, most of whom are in the field. The number of warning letters decreased from a maximum of 1154 in 2000 to 538 in FY 2006 (a 53% decrease), the last year for which data were available.



Foreign Drug Company Inspections: Sharp Decrease in Funding

Although more funding could be used for domestic inspections which make up the bulk of the companies receiving warning letters and other enforcement actions, the situation with respect to inspections of foreign drug facilities is desperate and the consequences are increasingly being brought to attention in the form of dangerous products being produced in these inadequately inspected plants.

From FY 02, when the FDA foreign drug company pre-market inspection budget was \$ 8.274 million to FY 07 when it was \$5.836 million, there was a decrease of 30% in funds for foreign inspection. Similarly, the post-approval inspection budget decreased from \$ 5.256 billion in FY 02 to \$4.345 in FY 07, a 17% decrease. Overall, the foreign inspection budget had a total decrease, during this recent 5-year interval, of 25%. This unfortunately, for the health of American consumers of drugs, comes at a time when the number of foreign plants manufacturing drugs for import into the U.S., especially countries such as India and China, was rapidly increasing.

China: More Drug Disasters Waiting to Happen

From [table 2 of the recent GAO analysis of FDA data on foreign inspections](#),^[5] there is further cause for alarm about products coming from China.

Several inescapable conclusions from this table demand immediate action to remedy the seemingly unending series of dangerous drugs, often contaminated, coming from this country with an extremely low level of FDA inspections:

1. Of the 10 foreign countries with the most FDA inspections in FY 02 through FY 07, China was the one with the largest number of drug-producing establishments, 714 establishments.
2. Although India, with 410 establishments, had the second largest number, the odds of an FDA inspection in FY 07 in that country were much, much higher than in China.
3. India, whose 410 establishment comprised 12.65% of all foreign establishments, was the subject of 65 inspections in FY 07, or 22% of all foreign FDA inspections.
4. China, whose 714 establishments comprised 22% of all foreign establishments, was the subject of only 13 FDA inspections in FY 07, or only 4% of FDA inspections in foreign countries.

In summary, the FDA pre-approval budget is increasingly coming from industry, a trend which must be reversed as soon as possible. The post-approval budget for inspections was not only grossly inadequate in FY 02 but has decreased a further 25% by FY 07.

There is an enormous amount of tough policing of the relatively toothless FDA and its budget needed by your appropriations committee. We will help you in whatever way we can.

[1] Widmark RM, unpublished data; FDA Medical Officer review memo, bromfenac sodium, December 22, 1995.

[2] Lurie P, Wolfe SM. FDA Medical Officers Report Lower Standards Permit Dangerous Drug Approvals. 1998. Available at: <http://www.citizen.org/publications/release.cfm?ID=7104>.

[3] User Fees for Faster Drug Reviews: Are They Helping or Hurting the Public Health? FDA Consumer magazine September-October 2000.

[4] Quality Assurance Program. Recruitment and Retention of CDER Reviewers: Final Report (FDA). 2001.

[5] Crosse, M. Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers. November 1, 2007. Available at: <http://www.gao.gov/new.items/d08224t.pdf>.