PDUFA Reauthorization
The Need for Congressional Oversight
And Legislative Changes to Improve Drug Safety

February 12, 2002

Public Citizen believes that our nation's drug safety system has deteriorated since the authorization of the Prescription Drug User Fee Act (PDUFA) in 1992. The Act contributed to that deterioration by making the FDA subject to pressure from the industry it is supposed to regulate. In order to end the agency's dependence on the industry, the agency's activities ought to be fully funded through direct appropriations rather than through user fees. We also believe that the significant number of recent drug withdrawals because of safety concerns demonstrates that there is a need for aggressive congressional oversight of the agency's drug approval process. However, in light of the fact that Congress is not likely to abolish PDUFA, we believe that there are several changes that could be made to the law when it is reauthorized this year that, together with regular congressional oversight hearings, would improve drug safety. Of paramount concern to Public Citizen is that the agency be given more flexibility to set its own priorities.

Background

After years of criticism from the drug industry that the drug approval process was too slow, the U.S. Congress passed the Prescription Drug User Fee Act (PDUFA) in 1992. The Act created a system whereby drug companies pay user fees in exchange for the FDA achieving performance goals agreed to by Congress, the pharmaceutical industry and the agency. The agency uses the revenues it receives from user fees to increase its capacity to perform new drug reviews by funding salaries and support equipment for additional reviewers. The collection of user fees was reauthorized in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA) and will expire if not reauthorized before September 2002.

The Act has increased dramatically the speed of approval decisions. In the late 1980s, median times for the agency to approve a new drug were approaching 30 months. In the years after the passage of PDUFA, median approval time fell consistently until it reached 11.6 months in 1999. In 2000, median approval times increased to 15.6 months.[1] The recent reversal in the trend towards shorter approval times may be due to the high number of drugs withdrawn from the market recently for safety reasons, or it may be due to sloppy applications by manufacturers or applications for less safe and effective drugs.

Now it is also the case that drugs are more likely to be approved first in the United States. In the early 1980s, only 2% to 3% of new drugs introduced in the world were first introduced in the United States. By 1998 that number had jumped to over 60%.[2] There also has been an increase both in the absolute number of drugs approved and in the number of drugs approved as a proportion of those submitted for review to the agency. From 1986 to 1992 there were 163 new drugs approved. From 1993 to 1999 there were 232 approved, a 42% increase.[3] The proportion of drugs reviewed that are ultimately approved has increased from 60% at the beginning of the 1990s to 80% by the end of the decade.[4]

While the time to approve new drugs has decreased dramatically, as a result of PDUFA, there have also been a high number of drugs approved since the Act's passage that have later been withdrawn as a result of safety concerns. This has led Public Citizen to believe that there is an urgent need for Congressional oversight hearings to determine if pre-approval safety issues are receiving adequate attention in the agency's decisions. Another downside to PDUFA is that it has led to critical under funding of activities not defined as part of the drug approval process, such as the monitoring of adverse events and oversight of post-launch advertising campaigns, both of which are important in assuring consumers' safety. This is because PDUFA requires the agency to increase funding from non-user fee revenues for drug approval activities by an inflation adjusted amount every year. Given that the agency as a whole has seen limited funding increases, the only way it has been able to meet the requirement to increase funding for the drug approval process is to take resources away from other activities.

For fiscal year 2002, Congress passed and the President signed legislation significantly increasing direct appropriations to the agency, including increases for the monitoring of postmarket adverse events and the review of new drugs. However, given expected budget constraints in the years ahead it is unclear if Congress will be willing to continue to make available to the agency the appropriations it needs to conduct activities that do not benefit from user fees.

The following are Public Citizen's major concerns about drug safety issues and recommendations for corrective action:

1) **Congress fails to vigorously oversee the agency.**
   Throughout the past decade, Congress has been focused on increasing the speed of drug approvals with seemingly little concern for the FDA's approval standards. Despite the unprecedented removal from the market for safety reasons of 9 drugs approved from 1993 through 2000, not one committee with jurisdiction over the FDA has held a single oversight hearing on the FDA's handling of the approval of these drugs. Aggressive oversight hearings of the FDA are not unprecedented. Indeed, Congress used to take a much more active oversight role with regard to the agency. In 1973 it was Congress that uncovered problems with the Dalkon Shield IUD. In the 1980s congressional investigations led to criminal prosecution of Lilly and Hoechst A.G for withholding information about death and adverse events among patients taking their drugs Oraflex and Merital.[5]

Recommendations:

- House and Senate committees of jurisdiction should hold aggressive and regular oversight hearings to assure that the FDA is upholding high standards for the approval of new drugs. (See page 10 for an outline of suggested hearings about recent drug safety failures)

- Congress should consider requiring that whenever a drug is withdrawn from the market for safety reasons, the Inspector General of the Department of Health and Human Services or the General Accounting Office should be directed to investigate the circumstances surrounding the original approval of the drug and its withdrawal.

2) FDA under pressure to approve drugs.

As part of PDUFA, the FDA agreed to a set of rigorous timeframes for its drug review process. Under the user fee program as reauthorized by FDAMA in 1997, the agency agreed to review 90% of priority applications in six months and that by 2001 it would review 70% of standard applications in 10 months and 90% in 12 months or less.[6] Although PDUFA only specifies timeframes for decisions, a *Los Angeles Times* investigative report in 2000 revealed that the leadership of the agency believed that what they were really being asked for was not simply timely review decisions but more speedy drug approvals.[7] Many of those interviewed by David Willman for his article echoed the sentiment of Kathleen Holcombe, a former legislative affairs staffer and congressional aide, now a drug industry lobbyist who said, "There has been a huge shift. FDA historically had an approach of, 'Regulate, be tough, enforce the law [and] don't let one thing go wrong.'" Now the FDA "sees itself much more in a cooperative role [with industry]."[8]

Public Citizen's late 1998 survey of FDA Medical Officers, who are in charge of reviewing new drugs, revealed that many feel they are under inappropriate pressure to approve new drugs. Fifty-three out of 172 Medical Officers contacted responded to Public Citizen's survey. Of these, 19 identified a total of 27 new drugs that they reviewed that they believed should not have been approved but were approved. In contrast, five Medical Officers identified only a total of six new drugs that they believed should have been approved but were not. One Medical Officer said, "We are told that approvability is our goal with 'problems to be addressed in labeling.'"[9]

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3) **Pressure to approve drugs may have led to the approval of a group of unnecessary and dangerous drugs ultimately withdrawn from the market.** Nine of the drugs (Baycol, Raplon, Lotronex, Propulsid, Rezulin, Raxar, Duract, Posicor, Redux) approved during the eight-year period from 1993 to 2000 have been withdrawn because of safety concerns. By comparison, only five of the drugs approved during the eight-year period from 1985 through 1992 later had to be withdrawn. The high number of recently approved drugs that have been withdrawn raises a red flag that the agency may have lowered its standards for drug approval as a result of the "sweatshop" environment created by PDUFA deadlines and greater cooperation with the industry fostered by the user fee regime. In the case of several of these drugs, their approval and the subsequent loss of life they are suspected to have caused was entirely needless. At least five of these nine drugs (Raplon, Raxar, Duract, Posicor, Redux) were approved despite known safety problems and the availability of multiple treatment options in other, older (and safer) drugs approved for the same medical uses.

Recommendations:

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- Raise the bar on efficacy standards in the Food, Drug, and Cosmetic Act so that in order to be approved a drug must be therapeutically superior to drugs already on the market and approved for the same indication. If Congress is unwilling to raise the standards for approval, at a minimum drug manufacturers should be required, as part of their application to the FDA to market a new drug, to submit the results of tests comparing the safety and efficacy of their drug to others already on the market used to treat the same indication. If this comparative information were required, companies may be more hesitant to introduce redundant drugs, because insurers may be less likely to cover them. Since all new drugs present the risk that they may carry with them unexpected dangers, by reducing the number of new and redundant drugs on the market the drug supply would become more safe.

4) **Drugs inappropriately given expedited review.**
PDUFA-FDAMA codified a system by which certain drugs are supposed to receive quicker review by the agency. The priority review system was originally intended as a way of expediting the approval of drugs the FDA and industry believe will represent a therapeutic advance. However, drug sponsors have abused the system by seeking and receiving fast approval for drugs that do not represent a therapeutic advance but may only work in some new way. In Public Citizen's survey of FDA Medical Officers, nine identified 19 new drugs

that they reviewed from 1996 to 1998 that they believed had been inappropriately shifted to the accelerated approval track.[10] The drug for type-2 diabetes, Rezulin, the flu drug Relenza, and Lotronex, approved for the treatment of irritable bowel syndrome in women, are all examples of drugs that fall into this category. Rezulin and Lotronex had to be withdrawn because of safety concerns. Relenza, which was originally approved despite a study finding that it was not effective among the U.S. population, had to undergo significant changes to its labeling because of safety concerns after it was on the market. While we are not certain that the speed of the FDA's review, or pressure on the agency to approve drugs, caused the mistakes that were made in each of these cases, expedited review certainly may have contributed to these dangerous drugs being put on the market.

Public Citizen believes that drugs that represent a significant therapeutic advance for the treatment of a serious or life threatening illness should be reviewed by the agency in a quick and thorough manner, a task it should be noted the agency was accomplishing before PDUFA. There is no reason to expedite the approval of drugs that are not urgently needed for the public's health.

Recommendations:

- House and the Senate committees of jurisdiction should hold aggressive and regular oversight hearings to assure that the FDA is upholding high standards for the approval of new drugs. (See page 10 for an outline of suggested hearings about recent drug safety failures.)

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5) Short review timeframes and foot dragging by companies lead to inadequate time for thorough review of drugs.

The law has created a situation where companies can game the approval system by procrastinating in responding to information requests from FDA reviewers who they know must meet PDUFA-FDAMA's tight review deadlines. By delaying the submission of important documents companies are able to force FDA to make a decision on drugs without the opportunity to thoroughly review all relevant material. The Director of the FDA's Center for Drug Evaluation and Research, Dr. Janet Woodcock, herself has commented that PDUFA-FDAMA's tight timeframes have created a "sweatshop environment" in the agency.[11]

One example of a company taking advantage of the tight deadlines in PDUFA-FDAMA can be seen in the priority review of Nolvadex to reduce the incidence of breast cancer among women at high risk for the disease. The application was submitted on April 30, 1998, creating a PDUFA deadline of October 31, 1998. The Medical Officer had 3.5 months to complete his draft review so that it could be distributed to the advisory committee by August 18, 1998. FDA records reveal that the company did not complete its data submission until

August 4, 1998, one and a half weeks before the deadline for review submission. During the review process the company took from two weeks to one month to respond to FDA requests for additional information.[12]

This example demonstrates how PDUFA's highly compressed timeframes can make it difficult for the FDA to adequately review applications.

Recommendation: Require that FDA review deadlines be stayed until the FDA receives requested information from the manufacturer needed to make a decision about approval.

6) Inadequate Post-Market Surveillance.

Public Citizen strongly believes that prevention of drug-induced injury or death through high approval standards is the best way to address the problem of adverse drug reactions. However, because of the small numbers of patients in the clinical trials required by the FDA to approve a drug and the fact that these patients are not generally representative of the population that will ultimately take a drug, pre-market trials cannot detect all of the dangers a new drug presents. For a few drugs dangers will only be discovered once they are on the market and being taken by a much larger and more diverse population.[13] This is why, even if there was no reason to be concerned that the FDA had lowered its standards for drug approval, an adequate post-marketing surveillance system that can quickly detect and take appropriate action in response to dangerous drugs is critical to assuring the public's health. Unfortunately, our existing post-marketing surveillance system for prescription drugs is both under funded and in need of improvements.

- **Existing system can be improved.**

A. Very limited data on adverse events assembled from spontaneous reports by health care professionals. For a variety of reasons, including fears that they will be blamed for these events, it is estimated that the current system, which relies heavily on reports from health care professionals and consumers, detects only 1% to 10% of all adverse events associated with prescription drug use.[14] Also, because physicians and consumers tend to report certain kinds of adverse events associated with the use of prescription drugs more than others, there are limitations to the conclusions we can draw from this data about the level of danger that a given drug presents. Although we cannot be precise about the magnitude of the problem, adverse events associated with prescription drug use clearly are a significant problem. One study estimated that adverse drug reactions account for over 100,000 deaths annually (this is in addition to the deaths caused by inappropriate prescribing by doctors).[15]

Recommendations:

- Charge the Centers for Education and Research on Therapeutics with examining the feasibility of implementing a patient self-monitoring system for signaling possible adverse drug reactions as suggested by Seymour Fisher and Stephen G. Bryant of the University of Texas Medical Branch in Galveston.[16] Under this system patients would be given information about how to report adverse drug reactions by their

pharmacist. This system would make it possible to compare the rates of adverse drug reactions from a new drug with drugs already on the market for the same indication.

- Create drug registries that will make it possible to follow patients who may be at risk of rare but serious drug reactions.

- Enhance current requirements for the reporting of adverse drug and device experiences to include the public disclosure of litigation documents after a certain number of adverse experiences have led to settlements of lawsuits. At present, many product liability settlements are contingent upon entry of protective orders that seal all information uncovered during litigation. These secrecy orders should be voided and the documents made available to the public following a threshold number of settlements.

- Give FDA inspectors/investigators subpoena power to compel the production of company documents. According to a 1990 Congressional Research study almost every other health and safety regulatory agency has subpoena power. Without the ability to subpoena company records the FDA's efforts to assure drug safety are hamstrung. The case of the FDA's post-approval investigation of the drug Halcion demonstrates the problems the agency faces. In that case the agency could not subpoena the company's records even though it had suspicions of criminal wrongdoing. At one point in that investigation the agency even went so far as to ask for the intervention of a federal judge to modify a gag order in a tort action against the maker of Halcion so that the agency could have access to crucial documents.

- Amend section 506B of the FDCA relating to "Reports of Postmarketing Studies" to expand the scope of information made available to the public about postmarketing studies to include information such as study protocols, patient accrual rates, reports of unexpected (i.e., unlabeled) suspected adverse drug reactions, and study results.

B. Companies fail to perform post-marketing studies. According to Public Citizen's analysis of FDA data, of the 88 new drugs that were approved between 1990 and 1994 with the understanding that the sponsor would complete at least one post-marketing study, only 13 percent (11 of 88) had completed all of the studies they had agreed to do as of December 1999.[17] Because companies are failing to do post-marketing studies, even though they have agreed to do them as a condition of a drug's approval, we are not learning about the dangers of drugs on the market in a timely manner. This means that drugs that should be withdrawn may be left on the market longer than they otherwise would be, and drugs that ought to have better information about their dangers go without it, leading to needless loss of life and injury. The FDA has the authority to revoke approval of some drugs for which commitments for post-marketing studies have not been honored. However, this is a rather blunt instrument that the FDA is unlikely to ever use to enforce companies' post-market study commitments.

Recommendation: Give the FDA authority to issue civil monetary penalties if companies fail to conduct Phase IV studies they have committed to do.

- **System is under funded.**

Under PDUFA, user fee revenues are made available to the agency with a number of strings. The most significant conditions are that user fees can only be used to support the drug approval process and that the FDA can only collect user fees if it increases the amount it spends on new drug approvals from non-user fee appropriations by an inflation adjusted amount each year. In FY 2000, PDUFA made it possible for the agency to hire 1,009 more full time equivalent personnel for the drug approval process than it had in 1992. However, the FDA has indicated that limited increases in overall funding for the agency, combined with PDUFA's required increased funding for the drug approval process, and mandatory across the board pay increases for all agency staff have left the agency with inadequate resources to closely monitor adverse reactions from drugs in the first few years they are on the market. The agency has stated that increased funding for "More rigorous safety monitoring of newly approved drugs in the first few years after a product is on the market could help to detect unanticipated problems earlier."[18] As discussed above, the agency did receive an increase in appropriations for post-market review for fiscal year 2002. However, given current budget realities it is unclear if the agency will continue to receive the resources it needs to adequately monitor the safety of drugs in the post-marketing period.

Recommendations:

- Oppose the expansion of user fees to post-marketing surveillance. The demands the drug industry would inevitably make on the agency in exchange for increased fees would undermine the integrity of the post-marketing surveillance system.

- Increase direct appropriations to the agency.

- Alternatively, Congress could institute a relicensing fee based on yearly gross sales that would be assessed on all drugs on the market with remaining patent protection or additional market exclusivity. The funds gathered would go to support those agency activities not funded by PDUFA, because they are not connected with the approval of new drugs, such as post-marketing surveillance and review of post-launch advertising.

7) **Lack of adequate resources and enforcement tools to prevent misleading direct-to-consumer (DTC) advertisements and direct-to-professional advertisement is hazardous for consumers.** It is especially important for the public's safety that advertising that would stimulate inappropriate demand for a drug in the first few years it is on the market, when some of a drug's dangers may be unknown, be stopped. Unfortunately, the FDA does not

have adequate enforcement tools or resources to regulate an ever growing volume of DTC and direct-to-professional advertising.

The FDA has specifically pointed to the monitoring of drug advertisements as another activity that is inadequately funded as a result of PDUFA and limited increases in funding for the agency.[19] From 1996 to 2000 DTC advertising increased from $791 million to $2.5 billion. However, the resources the FDA has available to oversee such advertising have not kept pace with the increase. The number of FDA staff assigned to review all prescription drug advertising (both DTC and advertising aimed at medical professionals) has only increased from 11 in 1996 to 14 in 2001.[20]

Also, the FDA does not have adequate tools to enforce laws against misleading direct-to-consumer advertising. Presently the agency is limited to issuing a Notice of Violation or a Warning Letter when companies violate laws or regulations the FDA uses to govern DTC advertising. Theoretically, the FDA could seek criminal prosecution of a company that repeatedly broadcast misleading advertisements, but there are no known cases where the agency has pursued that course in response to violative DTC advertising, despite 11 illegal ads for Claritin (8 DTC) and 14 illegal ads for Flonase/Flovent (8 DTC) since 1997.[21].

Recommendations:

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- Alternatively, Congress could institute a relicensing fee based on yearly gross sales that would be assessed on all drugs on the market with remaining patent protection or additional market exclusivity. The funds gathered would go to support those agency activities not funded by PDUFA, because they are not connected with the approval of new drugs, such as post-marketing surveillance and review of post-launch advertising.

- Give the FDA the ability to impose significant civil monetary penalties on companies that repeatedly air misleading advertising. This might serve as a deterrent to repeat offenders.

- Require the distribution of Medication Guides for all drugs at the time they are purchased that meet the quality standards FDA outlined in its 1995 proposed Medication Guide rule.[22] Reliable, unbiased information about the risks and benefits of drugs would serve as an antidote to the misinformation by the industry. Currently drug packaging includes detailed information that is directed at professionals. Moreover, there is no mechanism for consumers to be notified directly when new safety concerns about a drug emerge that require a change in a drug's FDA approved labeling. Medication Guides would provide the public with accurate, understandable, and up-to-date information in order to make decisions about drug treatment and how to prevent drug induced injury. This information should also be available online.

8) **Need for clarification of Over the Counter uniformity provisions in the Food and Drug Administration Modernization Act (FDAMA).** Today the Over the Counter Uniformity provisions in FDAMA preempt all state requirements different from or in addition to the federal requirements, but also include a savings clause that says that "product liability" claims are not preempted. However, some defendants argue that certain claims, such as breach of warranty claims, are not "product liability" claims. We believe that reading is incorrect. However, at least one court has adopted that reading.

Recommendation

- As part of reauthorizing PDUFA, clarify language in the Over the Counter (OTC) uniformity provisions of FDAMA to preserve the right to pursue private legal action both to force drug companies to be more conscious of safety concerns and to seek compensation for injuries caused by OTC products. This can be done by Congress re-wording the savings clause to make clear that it included all state-law damages claims.

Aggressive Oversight Hearings

Holding meaningful FDA oversight hearings is perhaps the single most important thing Congress could do to assure that the FDA is able to adequately protect the public's health against the threat presented by exposure to dangerous drugs. Aggressive oversight hearings would send a signal to the leaders of the agency that patient safety, which may conflict with the desire of the drug industry for speedy approvals, must be the agency's top priority. Congressional hearings should focus on the following:

- Approval process of several of the drugs that have recently been withdrawn as a result of safety concerns.

- What the agency is doing to address the potential conflict of interest created by the existing structure at the agency in which the same personnel responsible for approving drugs have a central role in deciding if a drug should be withdrawn or undergo significant labeling changes as a result of safety concerns. Hearings should examine whether the current reorganization in the agency that will take the Office of Post Marketing Drug Risk Assessment out of the jurisdiction of the Office of Review Management will improve drug safety by giving personnel in the post-market safety office a greater ability to voice their concerns about the safety of a drug without interference from the drug review divisions, which have a vested interest in defending their original decision to approve a drug and its labeling.

Hearings conducted on the approval process of the following drugs would be most revealing of underlying problems in the agency's review process:

1. Rezulin

This drug for type-2 diabetes caused an estimated 43 deaths, including Japanese and American cases, due to liver failure from the time it was approved in January 1997 until February of 1999. There were also approximately 60 cases of patients with liver damage associated with the use of Rezulin.[23]

Issues:

a. Why was this redundant drug given expedited review and approved despite known safety problems?

b. What role did pressure from the drug's sponsor, Warner-Lambert, have in the FDA's decision to reassign the first Medical Officer to review the drug, John L. Gueriguian, who recommended against approval of the drug?

c. According to the *Los Angeles Times*, Gueriguian's negative medical review was purged from agency files and withheld from an FDA advisory committee. How did this happen?

d. Why was there no discussion of evidence, known to the sponsor, of Rezulin's liver toxicity at

the FDA's December 1996 advisory committee meeting when a vote to unanimously approve the drug was taken?

e. Why did the FDA require only a series of labeling changes for this drug instead of removing it from the market sooner, as the British did?

Witnesses:

a. Dr. John L. Gueriguian -- First Medical Officer assigned to review Rezulin.

b. Dr. Robert Misbin -- FDA Medical Officer involved with the approval of diabetes drugs at the FDA who published a letter in the *Washington Post* protesting the lowering of drug approval standards at the FDA.

c. Dr. David Graham -- Senior FDA epidemiologist who warned about Rezulin's dangers.

d. Dr. G. Alexander Fleming-- Dr. Gueriguian's supervisor at the FDA who, according to the *Los Angeles Times*, told Warner-Lambert that Dr. Gueriguian would be "eased out" of the review process if the company became dissatisfied with the positions he took.[24]

e. Dr. Janet Woodcock -- Director of FDA's Center for Drug Evaluation and Research at the time of Rezulin's approval.

f. Dr. Janet B. McGill – a St. Louis endocrinologist who helped lead 2 pre-clinical trials of Rezulin. Dr. McGill's claims that Warner-Lambert misrepresented the results of her tests to the FDA and that they were misrepresented in the drug's labeling as well, led to an FDA investigation.[25]

g. Representative of Warner-Lambert Co -- Sponsor of Rezulin.
Mary E. Taylor -- Warner-Lambert Senior Manager who, according to the *Los Angeles Times*, exerted pressure on the FDA that contributed to Dr. Gueriguian being removed from the team working on the approval of Rezulin.

2. Relenza

This flu drug, which is still on the market, was approved by the FDA despite the fact that it was not shown to be effective in the United States. The FDA has received reports linking Relenza to respiratory distress leading to hospitalization and, according to the *Los Angeles Times*, at least 22 deaths.[26]

Issues:

a. Why was this drug approved despite a 13 to 4 vote against its approval by the FDA's Antiviral Drugs Advisory Committee?

b. Why was the drug approved despite evidence pointing to its limited efficacy in the North American population?

c. According to the *Los Angeles Times*, Dr. Michael Elashoff, a biostatistician with the FDA, was asked to delete anti-Relenza recommendations from his review of the drug and told that he would no longer be asked to make presentations to the drug advisory committee after he wrote a negative review of Relenza. What are the circumstances surrounding these events?

d. Why is this drug still on the market when a *Los Angeles Times* analyses of FDA data shows it to be a suspect in 22 deaths through June of 2000 and there is only limited evidence of its effectiveness?

Witnesses:

a. Dr. Michael Elashoff – Former FDA biostatistician strongly criticized by FDA management for his opposition to approval of Relenza.

b. Dr. Barbara Styrt – FDA Medical Officer first assigned to review Relenza. Although she was ambivalent at first, according to the *Los Angeles Times*, she ultimately recommended approval.

c. Dr. Janet Woodcock – Director of FDA's Center for Drug Evaluation and Research at the time of Relenza's approval.

d. Representative of GlaxoSmithKline – Makers of Relenza.

3. Lotronex

This drug for women with irritable bowel syndrome was approved in February of 2000. By October of 2000 there had been 49 reported cases of ischemic colitis, including five deaths among patients taking Lotronex.[27]

Issues:

a. Why did the FDA approve this drug despite evidence of severe side effects and limited effectiveness in clinical trials?

b. Why did the FDA fail to require a "black box" warning about the drug's potentially serious side effects as some in the agency, according to the *Los Angeles Times*, suggested?

c. Why was Lotronex not immediately withdrawn from the market when the earliest signs of serious complications associated with taking the drug emerged?

d. What was the nature of the discussions between the agency and the company about the reapproval of Lotronex after the drug was withdrawn? Did these communications violate

requirements for transparency of the drug review process? Did the agency collaborate, as a commentary in the *Lancet*[28] infers, with the company in an inappropriate way about the agenda for an advisory committee meeting?

Witnesses:

a. Dr. John R. Senior – FDA Medical Officer and gastrointestinal specialist, who warned the agency about the dangers of Lotronex prior to its approval.

b. Dr. Janet Woodcock – Director of FDA's Center for Drug Evaluation and Research at the time of Lotronex's approval.

c. Representative of Glaxo Wellcome – sponsor of Lotronex.
Dr. Richard Kent -- Chief Medical Officer and Vice President with Glaxo Wellcome who was vocal in his opposition to the addition of a black box to the drug's labeling.[29]

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[1] FDA, "Approval Times for NDAs and NMEs Approved Calendar Years 1986-2000," www.fda.gov/cder/rdmt/CY00NDAAP.HTM

[2] Michael A. Friedman, Janet Woodcock et al, "The Safety of Newly Approved Medicines," *Journal of the American Medical Association*, May 12, 1999.

[3] Public Citizen calculation based on FDA data, "Approval Times for NDAs and NMEs Approved Calendar Years 1986-2000," www.fda.gov/cder/rdmt/CY00NDAAP.HTM. Figures represent the total number of new molecular entities approved by the agency in these years.

[4] FDA, "The Prescription Drug User Fee Act; Notice of Public Meeting," *Federal Register* August 4, 2000, p. 47994.

[5] Dan Sigelman, "Unsafe Drugs: Congressional Silence Is Deadly," Public Citizen Health Research Group Health Letter, October 2001.

[6] FDA website, www.fda.gov/cder/pdufa/default.htm.

[7] David Willman, "How a New Policy Led to 7 Deadly Drugs," *Los Angeles Times* December 20, 2000, p. A 1.

[8] *LAT*

[9] Peter Lurie, Sidney Wolfe, "FDA Medical Officers Report Lower Standards Permit Dangerous Drug Approvals," Public Citizen, Health Research Group, www.citizen.org/hrg, December 2, 1998.

[10] Peter Lurie, Sidney Wolfe, "FDA Medical Officers Report Lower Standards Permit Dangerous Drug Approvals," Public Citizen, www.citizen.org/hrg, December 2, 1998.

[11] L. Thompson, *FDA Consumer*, September/October 2000.

[12] Larry Sasich, Public Citizen's Health Research Group, "Comments before the FDA's Public Meeting on the Prescription Drug User Fee Act," September 15, 2000.

[13] General Accounting Office, "Adverse Drug Events: The Magnitude of Health Risk is Uncertain Because of Limited Incidence Data," GAO/HEHS-00-21, January 2000, p. 9.

[14] General Accounting Office, "Adverse Drug Events," January 2000, p. 10.

[15] J Lazarou, BH Pomeranz, PN Corey, "Incidence of adverse drug reactions in hospitalized patients," *Journal of the American Medical Association* 1998; 279:1200-1205.

[16] S. Fisher., S.G. Bryant, "Postmarketing surveillance of adverse drugs reactions: patient self-monitoring," *Journal of the American Board of Family Practice*, 1992; 5:17-25.

[17] Public Citizen Health Research Group, "The Drug Industry's Performance in Finishing Postmarketing Research (Phase IV) Studies," April 2000.

[18] FDA, "Prescription Drug User Fee Act; Public Meeting," *Federal Register*, November 19, 2001, p. 57969. FDA, "Prescription Drug User Fee Act; Public Meeting," *Federal Register*, August 4, 2000, p. 47994.

[19] FDA, "Prescription Drug User Fee Act; Public Meeting," *Federal Register*, November 19, 2001, p. 57969.

[20] Testimony of Sidney Wolfe, Director of Public Citizen's Health Research Group before the Senate Commerce Committee, Subcommittee on Consumer Affairs, Hearing on Direct-to-Consumer Advertising, July 24, 2001.

[21] Public Citizen compilation of FDA data available at www.fda.gov/cder/warn.

[22] Department of Health and Human Services, FDA. "Prescription Drug Product Labeling; Medication Guide Requirements," *Federal Register* 1995; Vol. 60, 164, August 24, 1995, pp. 44182-44252.
[23] Sidney M. Wolfe, Director Public Citizen's Health Research Group, Statement before the FDA Endocrine and Metabolic Drugs Advisory Committee Meeting on Troglitazone, March 26, 1999.
[24] David Willman, "Risk Was Known As FDA Okd Fatal Drug Study," *Los Angeles Times* March 11, 2001, p. A 1
[25] David Willman, "FDA Investigating Rezulin Clinical Trials," *Los Angeles Times* March 15, 2000, p. A 15
[26] *Los Angeles Times* Analysis of FDA data.
[27] *Los Angeles Times* Analysis of FDA data.
[28] Richard Horton, "Lotronex and the FDA: a fatal erosion of integrity," *The Lancet* May 19, 2001.
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