

**MEMO**

To: FDA Transition Team
From: Margaret Mellon, Director, Food and Environment Program
Date: December 4, 2008

Re: Recommendations to address the antibiotic resistance health crisis by reducing agricultural overuse of medically important antibiotics

Antibiotic resistance leads to more illnesses and greater severity of illnesses as antibiotics become less effective. As people with resistant infections stay in the hospital longer and require treatment with more expensive, invasive antibiotics, resistance contributes to ballooning healthcare costs. The Centers for Disease Control ranks antibiotic resistance as the nation's number one public health challenge.

Seventy percent of all antibiotics used in the United States are estimated to be used as feed additives for chickens, hogs, and beef cattle. Scientific evidence points to this massive agricultural use of antibiotics as a significant contributor to antibiotic resistance in the general human population. The Institute of Medicine has determined that to fight this scourge a decrease in the inappropriate use of drugs in human medicine alone is not enough. Substantial efforts must be made to decrease inappropriate overuse of drugs in animals and agriculture.

Accordingly, most major medical and public health organizations, including the American Medical Association, the American Academy of Pediatrics, the American Public Health Association, and the World Health Organization, have called for an end to non-essential uses of medically important antibiotics in farm animals. Antibiotics are typically added to feed (without a prescription) to help animals grow slightly faster – and to compensate for crowded, often unsanitary conditions on industrial-scale farms.

FDA's Center for Veterinary Medicine (CVM) should move aggressively to reduce feed additive uses in poultry and livestock of those antibiotics, like penicillin and tetracycline, that are important in human medicine.

CVM should:

- ***Review drugs currently used in both human and animal medicine for their resistance implications.*** Antibiotics need periodic scientific reviews for resistance effects, which increase over time. CVM should set a timetable to review all drugs currently used in both human and animal medicine for their resistance implications and, where the reviews indicate that drugs are no longer safe from a resistance standpoint, initiate cancellation proceedings for non-essential uses. CVM should publish a reasonable timetable for completing the reviews.





- **Reissue the ban on extra-label use of cephalosporins.** Early in December 2008 the CVM, under pressure from industry, withdrew a ban on the extra-label use of cephalosporins (drugs of extraordinary value in human medicine) before implementation. The agency should reissue that ban, which was based on solid scientific evidence. CVM should also encourage veterinary organizations and other stakeholders to develop clinical practice guidelines that provide alternative treatments for disease indications currently treated with extra-label cephalosporins.
- **Implement and strengthen requirements on veterinary drug use data collection and reporting.** Data on drug use are essential to crafting an effective response to antibiotic-resistant diseases. The first steps toward a comprehensive data collection system were required of CVM as part of drug user fee legislation signed into law in 2008. CVM should begin implementing this program immediately and strengthen it where possible.
- **Request increased funding for antimicrobial resistance surveillance through the National Antimicrobial Resistance Monitoring System (NARMS).** The public health infrastructure for surveillance and monitoring of antibiotic-resistant bacteria is chronically underfunded and unable to keep up with emerging threats like methicillin-resistant *Staphylococcus aureus* (MRSA). FDA should seek to substantially bolster the funds available through NARMS to develop a robust national surveillance system for resistant diseases, and especially to address the animal sources of MRSA.

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Scientific Integrity Recommendations for the Food and Drug Administration

Problem: For too long, top FDA officials have put politics and the priorities of commercial interests above public health and safety. This has harmed thousands of Americans, and shaken the public's faith. In 2006 nearly 1000 scientists responded to a survey conducted by UCS. 145 FDA scientists (18 percent) said they "have been asked, for non-scientific reasons, to inappropriately exclude or alter technical information or my conclusions in an FDA scientific document" and 378 FDA scientists (39 percent) disagree that the "FDA is acting effectively to protect public health." 311 scientists (32 percent) disagree that the "FDA routinely provides complete and accurate information to the public. (The full report is at www.ucsus.org/surveys.)

Solving these problems will require a concerted effort by the next FDA Commissioner, the new FDA chief scientist, and FDA managers. They must fully implement and build on reforms enacted by the 110th Congress. They must use their leadership to reduce the politicization of the regulatory process, make agency decision making more transparent, protect FDA scientists from reprisals, and reform FDA advisory committees.

"Scientific discourse is strongly discouraged when it may jeopardize an approval... Whenever safety or efficacy concerns are raised on scientific grounds... these concerns are not taken seriously."
—A scientist from the Food and Drug Administration

Solutions:

Agency Regulatory Reform

The FDA was slow to recognize serious side effects of popular drugs such as the diabetes drug, Avandia, the painkiller Vioxx, and the antibiotic Ketek. As a result, thousands of Americans lost their lives or were seriously harmed. These incidents prompted the passage of the Food and Drug Administration Amendments Act of 2007. The act requires that the FDA make a drug approval "action package" publicly accessible on its web site. That package must include drug review documents, and a summary that describes the views of all reviewing disciplines about the drug. Disclosure must also include a description of any disagreements among the drug review team, and how they were resolved. In addition, the new law stipulates that a scientific review of a drug application is considered the work of the reviewer, and shall not be altered. To fully implement this law and go beyond its modest reforms FDA must:

- **Publish a summary statement discussing the scientific basis for any regulatory decisions informed by science.** The statement should be available in a timely fashion, and clarify how officials made the final decision given the evidence. The statement should include: (1) the rationale for the decision, including all scientific documents and data used to make it, (2) a minority report including any dissenting opinions and how the agency resolved such differences of opinion, and (3) identification by name of each official and employee who participated in the decision.





- **Make it easy for the public to access and understand the drug approval package.**
- **Disclose more** information about how it regulates. All scientific studies in the FDA's possession related to a proposed regulation, regardless of whether the study was directly cited or whether it directly informed the final decision.
- **Make clear that the agency's first priority is public safety**, and that its "clients" are American families, not drug companies.
- **Redefine a strengthened FDA chief scientist** to be a champion for scientific integrity at the agency.

Greater Transparency at the FDA

After facing years of attempts to censor, alter or suppress their work, FDA scientists must receive a clear message from the next FDA Commissioner, chief scientist, and senior managers that the culture has changed. FDA leadership must:

- **Permit FDA scientists to present their findings before FDA advisory committees.** Exceptions should be rare and part of the public record.
- **Issue a memo to all FDA employees declaring that the FDA will strive to be as transparent as possible and conduct its operations in "a fishbowl."** Such a memo follows in the footsteps of former EPA Administrator William Ruckelshaus who issued such a memo to restore the credibility of the agency, which had been recently rocked by multiple scandals.
- **Institute a transparency policy for official meetings with outside entities.** This policy should require that the agency post on its website in real time a complete record of all meetings with outside entities including for-profit and not-for-profit organizations, other agencies, and individuals.
- **Implement an FDA-wide policy that seeks to ensure free and open communication between scientists and researchers, and the media, policy makers, and the public.** This policy should explicitly state that (1) FDA scientists may freely express their personal views provided they make it clear they are not speaking on behalf of the agency, and (2) FDA scientists have the right to review, amend and comment publicly on the final version of any document that significantly relies on their research, identifies them as an author or contributor, or purports to represent their scientific opinion.
- **Provide training on the provisions of the FDAAA** and its rules concerning publication in peer-reviewed journals. The new law permits scientists who have asked for permission to publish their work in peer-reviewed journals, and who have not heard back from the FDA after 30 days, to publish with a disclaimer that they are not speaking for the agency.

Protecting FDA Scientists

Over the past five years, FDA scientists who have questioned the safety of the drugs such as diabetes drug Avandia, the painkiller Vioxx, and the antibiotic Ketek not only were ignored, they were intimidated and censored. In each case, concerns were ultimately proven right, but only after thousands of patients died or were seriously harmed.



- **The FDA Commissioner should instruct his management staff to refrain from retaliating against whistle-blowers through reassignments, demotions or terminations.**
- **The FDA Commissioner should issue a statement that encourages staff to speak out internally about concerns and communicate that the agency values their input.**
- **FDA staff members should feel empowered to report not just waste, fraud and abuse, but also instances where science has been manipulated, suppressed or distorted.**
- **FDA shall proactively educate its scientists and researchers regarding their rights and protections.** These efforts shall include mandatory briefings for new hires, requirements for posting educational information in workplaces, and in-service trainings.

Reforming FDA Advisory Committees

The FDA's drug and device advisory committees often include participants who have significant financial ties to special interests that will benefit from the committee's decisions. The FDAAA law makes very modest changes to the FDA advisory system. It directs the agency to increase its efforts to recruit non-conflicted experts and establishes some limits on the aggregate use of waivers for members with conflicts. Nevertheless, the current FDA advisory committee process continues to permit those with financial ties to a drug or device that will benefit from an advisory panel's review to have an unacceptable influence on the findings of advisory committees.

Studies of the FDA advisory committee system have revealed a flawed process. Between January 1, 2001 and December 31, 2004, an analysis of 221 FDA advisory committees found that conflicted experts were the norm, not the exception. In more than 20 percent of meetings, half the membership of an FDA advisory committee had a conflict of interest.ⁱ And in more than eight out of ten meetings reviewing a specific drug product there was at least one member with a conflict of interest.ⁱⁱ

The votes of conflicted experts can make a difference in the final outcomes of advisory committee recommendations. In 2005, for example, 10 of the 32 advisors on FDA panels considering whether painkillers Bextra, Vioxx and Celebrex should be permitted to continue to be marketed had financial ties to the makers of the drugs. The vote to continue the marketing of Bextra was 17 to 13; nine of the conflicted experts voted yes. The vote to continue marketing Vioxx was 17 to 15, with nine conflicted experts voting yes.ⁱⁱⁱ

The FDA must vigorously commit itself to reforming its advisory committee process, and to ultimately eliminating conflicted experts on its panels. FDA leadership must:

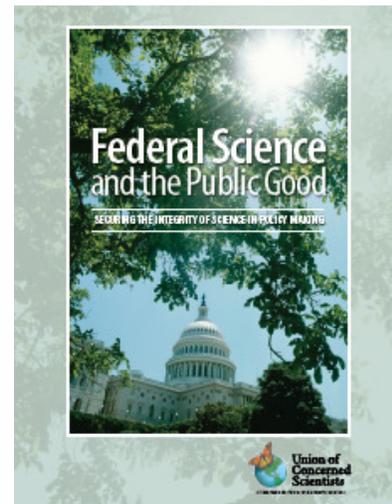
- **Aggressively recruit new committee members** by looking to universities and medical schools. The FDA has 30 advisory committees and 18 device panels, requiring the services of 463 members. The pool of non-conflicted qualified physician-scientists and other experts is well over 120,000^{iv} (The FDAAA directs the FDA to do more recruitment, and gradually limits the use of conflicted experts over several years.)
- **Adopt strict conflict of interest rules** that phase out significant financial conflicts of interest, with a lower threshold than current FDA policies that permit waivers for advisors with cumulative financial ties of up to \$50,000 to all companies whose products may be affected by a panel review.



- **Permit experts with conflicts to present** at advisory panels, and to answer questions, but do not allow them to participate in panel discussions or votes.
- **Take concrete steps to ensure that inappropriate criteria such as party affiliation and political opinions are never a part of the process for selecting members of scientific committees.** The FDA should select advisory committees members based solely on their experience and technical qualifications in the topic the committees will address.
- **Specify which advisory committees are expressly scientific and which are designed to gather stakeholder input.**
- **For committees whose mission is purely to provide objective scientific advice (as opposed to committees designed to gather input from stakeholders), committee members should be appointed as “special government employees”. Over time they should be entirely free of financial conflicts of interest.** Scientists and researchers with conflicts of interest may provide their expertise to scientific advisory committees, but agencies should take steps to ensure that they do not have decision-making roles on those committees, and that their participation is limited to making presentations and responding to questions.
- **Scientists who have taken public positions on issues should not be excluded from an advisory committee because of concerns about bias.** Having a point of view does not preclude an objective assessment of the information presented to a committee. A scientist’s membership in a scientific association should not be considered evidence of bias, even if that association has a stated policy agenda.

For more recommendations from the Scientific Integrity Program, please see our report, *Federal Science and the Public Good*, available at:

www.ucsusa.org/federalscience



ⁱ Peter Lurie, et. al., “Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings,” *Journal of the American Medical Association*, 26 Apr. 2006.

ⁱⁱ Ibid.

ⁱⁱⁱ Gardiner Harris and Alex Berenson, “10 Voters on Panel Baking Pills Had Industry Ties,” *The New York Times*, 25 Feb. 2005.

^{iv} Data provided by Susan F. Wood Ph.D., the former Assistant Commissioner for Women’s Health at the Food and Drug Administration.



Voices of Scientists at FDA: Protecting Public Health Depends on Independent Science

The U.S. Food and Drug Administration (FDA), now in its hundredth year, is responsible for protecting and advancing public health through the regulation of drugs, food, medical devices, cosmetics, and the blood supply—products that according to the FDA account for 25 cents of every American consumer dollar spent. The FDA mission statement calls for “helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.” Unfortunately, scientists at the agency are concerned that science no longer plays this crucial role in the FDA’s regulatory decisions.

In 2006, the Union of Concerned Scientists and Public Employees for Environmental Responsibility distributed a 38-question survey to 5,918 FDA scientists in order to

examine the state of science at the FDA. The results paint a picture of a troubled agency: hundreds of scientists reported significant interference with the FDA’s scientific work, compromising the agency’s ability to fulfill its mission of protecting public health and safety.

Independent science must be the driving force for decisions made by the FDA. Based on the survey responses from FDA scientists, it is clear that the agency needs to demonstrate a greater respect for independent science and improve both the transparency and accountability of its decisions. For this to occur, both the FDA leadership and Congress must act swiftly to pursue reforms. Without real leadership to defend impartial science, the FDA cannot do its job—with consequences for public health and safety.





Interference with Scientific Determinations at the FDA

Large numbers of agency scientists reported interference with their scientific work:

- Almost one in five (18 percent) responded, “I have been asked, for non-scientific reasons, to inappropriately exclude or alter technical information or my conclusions in an FDA scientific document.”
- More than three in five (61 percent) knew of cases in which “Department of Health and Human Services or FDA political appointees have inappropriately injected themselves into FDA determinations or actions.”
- Three in five (60 percent) also knew of cases “where commercial interests have inappropriately induced or attempted to induce the reversal, withdrawal or modification of FDA determinations or actions.” Fifty percent also felt that non-governmental interests (such as advocacy groups) had induced or attempted to induce such changes.

Negative Effect on Public Health

FDA scientists’ responses suggest that the agency’s ability to fulfill its mission—protecting public health—is being put at risk:

- Only half (51 percent) feel the “FDA is acting effectively to protect public health.”
- Less than half (47 percent) think that the “FDA routinely provides complete and accurate information to the public.”

- Less than half (49 percent) agree that “FDA leadership is as committed to product safety as it is to bringing products to the market.”

Chilling Effect on Scientific Candor

Agency scientists report being afraid to speak frankly about safety concerns and feel constrained in their roles as scientists:

- One-fifth (20 percent) say they “have been asked explicitly by FDA decision makers to provide incomplete, inaccurate or misleading information to the public, regulated industry, media, or elected/senior government officials.” In addition, more than a quarter (26 percent) feel that FDA decision makers implicitly expect them to “provide incomplete, inaccurate, or misleading information.”
- Two in five (40 percent) said they could not publicly express “concerns about public health without fear of retaliation.” More than a third (36 percent) did not feel they could do so even inside the confines of the agency.

FDA Scientists Face Immense Pressures

FDA scientists reported that they have inadequate resources to perform even the basic work of the agency. The lack of resources and other pressures have strained scientists’ morale:

- Nearly 70 percent do not believe the FDA has sufficient resources to effectively perform its mission of “protecting public health...and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.”



“Scientific discourse is strongly discouraged when it may jeopardize an approval... Whenever safety or efficacy concerns are raised on scientific grounds...these concerns are not taken seriously.”

A scientist from the Center for Drug Evaluation and Research

“The integrity of the scientific work produced by the FDA could best be improved by fostering a stronger scientific culture. Funds for research have dramatically declined in recent years...First class scientists are leaving the FDA, and recruiting new ones will be very difficult.”

“Most distressingly, there is no remaining support for or interest in SCIENCE.”

Scientists from the Center for Biologics Evaluation and Research

- Less than half (44 percent) say they “respect the integrity and professionalism of FDA leadership.”
- Two in five (40 percent) describe their morale as poor to extremely poor, while a mere four percent rate their morale as excellent.
- More than half (52 percent) say their personal job satisfaction has decreased over the past few years, while only 18 percent say their job satisfaction has increased.
- Less than a third (32 percent) think the agency “is moving in the right direction.”

Scientists Recommend Changes at the Agency

FDA scientists had strong opinions about reforms that would address some of their concerns:

- Nearly two in three (63 percent) said that the “laws and regulations that govern FDA, including the agency’s structure, need change for the agency to better serve the public.”
- More than four in five (81 percent) agreed that the “public would be better served if the independence and authority of FDA post-market safety systems were strengthened.”

“In my experience, it is never the ‘low level’ reviewers in the FDA who breach the integrity of our work. It is usually at much higher levels, such as center directors and above. Those higher levels are so far removed from the scientific work we do that politics has even more sway over their decisions....The people I work with are truly dedicated to serving the American public and doing whatever is in their power to ensure their safety.”

A scientist from the Center for Devices and Radiological Health

“The focus should truly be on protecting public health instead of catering to the interest of industry...FDA leadership should let FDA scientists do the jobs they were hired to do.”

A scientist from the Center for Veterinary Medicine

“We need more of a commitment by FDA management and the political establishment towards reversing the decline in the FDA science base...Morale is at the lowest point I’ve seen in 2+ years at the FDA. I am glad I will be eligible for retirement soon.”

A scientist from the National Center for Toxicological Research



FDA Survey Demographics

Surveys were sent to 5,918 scientists at all FDA centers, regional offices, and headquarters. Responses came from 997 scientists (17 percent), and 503 provided narrative responses. A significant majority (62 percent) were senior scientists at the General Schedule (GS) 13-15 level. Almost one-third of the scientists who responded had been with the FDA for more than 15 years, and nearly half had been with the agency for more than 11 years.

About the Survey

This survey is one in a series of surveys designed to explore the level of political interference in science at federal agencies. View full survey results, more detailed survey methodology, and excerpts from the survey essays at www.ucsusa.org/surveys.

Other Recent Reports on the FDA

Department of Health and Human Services, Office of the Inspector General, 2005. *OIG Oversight of FDA Activities; A Summary Report*.

Department of Health and Human Services, Office of the Inspector General, 2006. *FDA's Monitoring of Postmarketing Study Commitments*.

Institute of Medicine of the National Academies, in press (due out in 2006). *Assessment of the U.S. Drug Safety System*.

United States Government Accountability Office, 2006. *Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*.

United States House of Representatives Committee on Government Reform, Minority Staff, 2006. *Prescription for Harm: The Decline in FDA Enforcement Activity*.

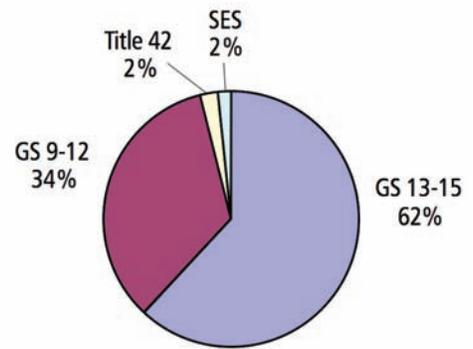
The Union of Concerned Scientists

The Union of Concerned Scientists (UCS) is a nonprofit partnership of scientists and citizens combining rigorous scientific analysis, innovative policy development, and effective citizen advocacy to achieve practical environmental and global security solutions.

The UCS Scientific Integrity Program

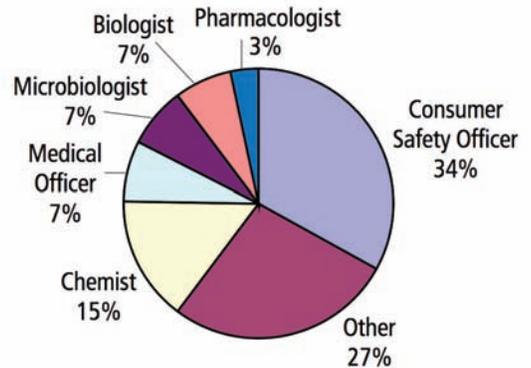
Policy makers depend on the results of independent research in order to make the informed decisions that keep us and our environment safe and healthy. The UCS Scientific Integrity Program mobilizes scientists and citizens alike to defend science from political interference and restore scientific integrity in federal policy making. To learn more, visit www.ucsusa.org/scientific_integrity.

Respondents' GS Grade Level

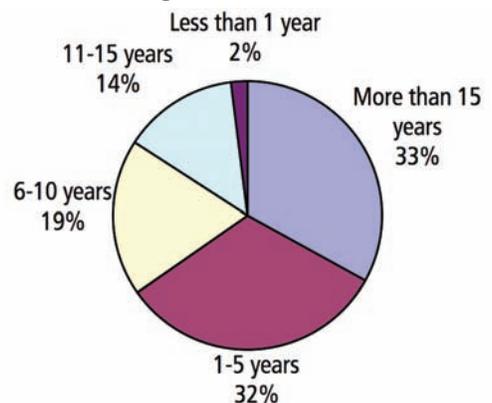


SES (Senior Executive Service): Scientists who serve in key positions just below the top presidential appointees
Title 42: Public health scientists
GS 13-15: Top-level federal employees
GS 9-12: Mid-level federal employees

Job Titles (Mailed Surveys)



Respondents' Length of FDA Service





Union of Concerned Scientists
Citizens and Scientists for Environmental Solutions

UCS Food and Drug Administration Scientists' Survey Centers for Drugs, Food Safety, Biologics and Devices

The 2006 Union of Concerned Scientists (UCS) and Public Employees for Environmental Responsibility (PEER) sent a survey of 38 questions to 5,918 scientists at the Food and Drug Administration (FDA). In addition, scientists at four FDA Centers received additional questions specific to their mission.

Center for Drug Evaluation and Research (CDER)

CDER oversees the development, marketing, and monitoring of prescription and over-the-counter drugs as well as some products such as fluoride toothpaste and sunscreens.

- Almost one in five (19 percent) CDER scientists reported that they have “been pressured to approve or recommend approval” for a New Drug Application “despite reservations about the safety, efficacy, or quality of the drug.”
- Close to half (43 percent) were not at all or only somewhat confident that “CDER’s final decisions adequately assess the safety of a drug.”
- About two thirds (66 percent) were not at all or only somewhat confident that the “FDA adequately monitors the safety of prescription drugs once they are on the market.”

Center for Food Safety and Applied Nutrition (CFSAN)

CFSAN oversees the safety of the nation’s food supply and cosmetic products.

- Nearly three quarters (72 percent) of CFSAN scientists were not at all confident that the “FDA adequately protects the public from risks due to herbal and other dietary supplements.”
- Nearly half (49 percent) were not at all or only somewhat confident that “FDA adequately protects the public from diets high on saturated/trans fat, cholesterol, and sodium, which contribute to disease.”
- More than half (58 percent) were not at all or only somewhat confident that “FDA adequately protects the public from deceptive food labeling.”

Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH)

CBER is responsible for assuring the safety and effectiveness of products such as the blood supply and vaccines. CDRH regulates medical and radiological devices and certifies mammography facilities.

- More than one quarter (28 percent) say they have been pressured to approve a product “despite reservations about the safety, efficacy, or quality of the product.”
- Two in five (40 percent) were not at all or only somewhat confident that their “Center’s final decisions adequately assess the safety of a product.”
- Nearly three quarters (74 percent) were not at all or only somewhat confident that “FDA adequately monitors the safety of products once they are on the market.”



Union of Concerned Scientists
Citizens and Scientists for Environmental Solutions

UCS 2006 Food and Drug Administration Survey Compared to the 2002 Health and Human Services Inspector General Survey

In 2002, the Department of Health and Human Service's Office of the Inspector General (IG) asked 846 Food and Drug Administration (FDA) scientists from the Center for Drug Evaluation and Research (CDER) a 52 question survey. The IG received responses from approximately 396 scientists.

In 2006, the Union of Concerned Scientists (UCS) and Public Employees for Environmental Responsibility (PEER) distributed a 38-question survey to 5,918 scientists at the Food and Drug Administration, including 1,303 in CDER. These additional questions were answered by 219 scientists. Below are the three questions that were asked on both the 2002 IG Survey and the 2006 UCS survey, along with the responses to both surveys.

The responses to both surveys are similar, demonstrating consistency between UCS' survey and the officially sanctioned IG survey. However, where the responses deviate, they demonstrate an increase in the level of concern and lack of confidence in the science based work of the FDA from 2002 to 2006.

A. Have you ever been pressured to approve or recommend approval for an NDA [New Drug Application] despite reservations about the safety, efficacy, or quality of the drug?

<u>IG</u>		<u>UCS</u>
18%	YES	19%
82%	NO	81%

B. How confident are you that CDER's final decisions adequately assess the safety of a drug?

<u>IG</u>		<u>UCS</u>
13%	completely confident	11%
52%	mostly confident	46%
31%	somewhat confident	30%
5%	not at all confident	12%
	not applicable	1%

C. Are you confident that FDA adequately monitors the safety of prescription drugs once they are on the market?

<u>IG</u>		<u>UCS</u>
6%	completely confident	4%
28%	mostly confident	28%
47%	somewhat confident	37%
19%	not at all confident	29%
	not applicable	3%