S. HRG. 109–99

NOMINATION OF LESTER M. CRAWFORD

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS UNITED STATES SENATE

ONE HUNDRED NINTH CONGRESS

FIRST SESSION

ON

TO BE COMMISSIONER, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

MARCH 17, 2005

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STATEMENTS

MARCH 17, 2005

ADDITIONAL MATERIAL

NOMINATION OF LESTER M. CRAWFORD

THURSDAY, MARCH 17, 2005

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 9:34 a.m., in room 430, Dirksen Senate Office Building, Senator Enzi, chairman of the committee, presiding.

Present: Senators Enzi, Isakson, DeWine, Ensign, Hatch, Sessions, Roberts, Kennedy, Dodd, Harkin, Mikulski, Jeffords, Bingaman, Murray, and Clinton.

OPENING STATEMENT OF SENATOR ENZI

The CHAIRMAN. Good morning, and welcome to the confirmation hearing for Dr. Lester M. Crawford to be the Commissioner of the Food and Drug Administration.

Recently when we met, it became obvious our shared commitment to protect and advance America's health. Clearly, we have a lot of work to do together.

Dr. Crawford, the FDA is no stranger to you. In fact, over the last 30 years, you have been at the FDA four times, twice serving at the helm of the agency already. Next year will mark the 100th anniversary of the landmark legislation that ushered the FDA into the modern era. This is truly a historical milestone and a dramatic time for you to take up the reins of the agency.

Back then, 100 years ago, there was a controversy—similar to today's drug controversy—that spurred the FDA's dramatic growth from a chemist at the Department of Agriculture to the full-fledged agency it is today. Back then, it was a crisis in food safety. Today, it is a concern with drug safety. The FDA weathered the previous storm. It will handle this one, too, with the same kind of talent, diligence, and hard work that solved the previous one.

You will face some tough questions today, but I want to let you know that we will be asking these questions so that we can be sure the man chosen by President Bush to head the FDA at this critical juncture in its history is up to the task.

The FDA has a very broad and critical mission in protecting the public health. You will be in charge of an agency that regulates $1 trillion worth of products a year. The FDA ensures the safety and effectiveness of all drugs, biological products, such as vaccines, medical devices, and animal drugs and feed. It also oversees the safety of a vast variety of food products, as well as medical and consumer products, including cosmetics. As Commissioner of the FDA, you will be responsible for advancing the public health by

helping to speed innovations in its mission areas and by helping the public get accurate, science-based information on medicines and foods.

The FDA has been without a confirmed Commissioner for over a year. You have been picking up the reins during that time and pulling it through.

Earlier this year, 17 members of this committee sent a letter to the President urging him to nominate a Commissioner to provide the agency with greater clarity and certainty in its mission to protect our food and drug supplies. By having you before us today, it is clear that the President is committed to restoring the FDA to its fully mandated authority and we appreciate the promptness with which your nomination followed our letter.

One of Congress's most important responsibilities is oversight. As Chairman, I have already held bipartisan hearings on drug safety and drug importation and I plan to continue to focus on these and other important areas.

Dr. Crawford, you are as committed to government accountability and responsibility as I am, so I know you will welcome our participation in the process.

In recent months, the FDA and its system for approving drugs and ensuring their safety have been on the front pages of our newspapers—quite often lately. The role of pharmaceuticals in health care has never been as vital to our health as it is today. That is why people need to be reassured that they can trust the FDA. Our bipartisan hearings to review the FDA's drug approval and post-marketing surveillance system examined the recent controversies and reviewed some options for strengthening our drug safety system. I trust you share our concerns and that you will continue to work with us to evaluate and eventually implement the necessary reforms to the system.

We also need to look at last year's flu vaccine shortage and what steps we need to take to prevent this from happening again. Both the FDA and the Centers for Disease Control and Prevention have been criticized. I intend for this committee to review what happened and to determine how we, as legislators, should respond. One thing we must do, however, is attract companies back into the vaccine business. Relying on one or two companies to produce some of the most critical vaccines is a prescription for public health disaster. I would welcome your thoughts on how we can rebuild our domestic vaccine industry.

With respect to food safety, I represent a State that has substantial agricultural interests. Issues of food safety and food labeling are critically important to me and my constituents. The FDA is responsible for the safety of a variety of our food products and I look forward to hearing from you what the agency plans to do to continue protecting the American food supply from outside threats.

It will fall upon you to build on your record on behalf of President Bush, and I am confident that the President has chosen wisely in nominating you to be the Commissioner of the FDA. I look forward to working with you, with Senator Kennedy, and with the other members of the committee to protect and promote the public health and to maintain the FDA's status as one of the strongest regulatory agencies in the world.

We all know the FDA has a storied past that made it the gold standard of the world. In previous hearings, we heard from members of your staff who spoke with pride of that designation. Recent events have called into question that standard in the eyes of some of the people in the public. I have no doubt that with the right leadership in place, the FDA will again be the gold standard and our regulatory process the envy of the world.

I look forward to hearing your testimony today. I welcome your wife, Kathy, to the hearing, and I would turn the floor over to Senator Kennedy on this great Irish day.

Senator KENNEDY. You can keep going, St. Patrick's Day—[Laughter.]

Thank you very much, Mr. Chairman. I want to say how much we appreciate your calling the hearing this morning on the nomination of Lester Crawford to be the Commissioner of the Food and Drug Administration and I welcome Dr. Crawford and I look forward to hearing about his plans for leading the agency in the coming years and I join Senator Enzi in welcoming Mrs. Crawford, as well.

Effective leadership of FDA is essential to protect the health of all Americans, and friends and colleagues speak highly of Dr. Crawford's dedication and commitment to public service. But our committee has a special responsibility to make a careful evaluation of the qualifications of any nominee for this critical position.

As Acting Commissioner, Dr. Crawford has led FDA during troubled times. Serious side effects were belatedly discovered for several major drugs already on the market, raising alarming questions about the adequacy of FDA's review. And there have been significant failures by FDA to disclose and manage conflicts of interest on scientific advisory panels. Over half of the Nation's flu vaccine was lost to contamination. And disturbing allegations have been raised that FDA has prevented open scientific discussion of important drug safety issues, has disregarded science that conflicts with ideology, and has retaliated against whistleblowers. And just today, the New England Journal of Medicine published an article stating that at FDA, there is an atmosphere that stifles debate and discourages some employees from expressing scientific concerns about drugs.

It is essential to address these serious issues and for Dr. Crawford to present a clear plan to restore the Nation's trust in the ability of FDA to do its job. FDA, as our chairman has pointed out, oversees about a quarter of all products purchased by American consumers. Whether FDA does its job effectively can mean the difference between whether the infant formula you feed your child is safe or not, or whether the prescription drug you take does more harm than good.

Doubts have risen about the agency's effectiveness in the wake of Merck's withdrawal of its pain-killing drug Vioxx from the market because of estimates that tens of thousands of patients may have suffered heart attack or stroke because of it.

And last October, we learned that half of last year's flu vaccine was lost because of poor manufacturing conditions at a plant in Britain, and we were surprised to learn that FDA had not actively inspected the plant and then compounded the problem by doing too

little after it learned that some of the vaccine had been contaminated.

Last year, the agency declined to approve emergency contraception for over-the-counter use after a nearly unanimous advisory group recommended such approval, and the agency is now 2 months late in ruling on a revised request for such use.

The agency has also prohibited or discouraged some of its medical officials from presenting their studies at advisory committee hearings, at scientific meetings, or in respected journals. The agency also chose not to disclose in advance potential conflicts of interest by members of the advisory committee who reconsidered Vioxx and related drugs a few weeks ago and approved their continuation on the market.

As the President's nominee, Dr. Crawford owes this committee, the Senate, and the American people his assurance that if the committee confirms him as Commissioner, there will not be more of the same. The stakes could not be higher. No patient who takes a pill should have to worry whether the drug inside is safe or whether the decisions to approve the drug were based on politics or profits instead of science. It is a tragedy that the FDA's recent failures have caused millions of patients to ask those questions now. It would be far worse if we don't insist on clear answers.

We know that Dr. Crawford is here to answer these questions and other questions of the committee and I look forward to his response and I thank you very much, Mr. Chairman, for holding these hearings.

The CHAIRMAN. Thank you, Senator Kennedy.

I would mention that we are doing a little different seating arrangement on this side. Since we allow people to ask questions in the order in which they arrive after the gavel has sounded, we are just moving everybody up here in that order on this side.

This morning, we have the Senator from Alabama to do an introduction, Senator Sessions.

STATEMENT OF HON. JEFF SESSIONS, A U.S. SENATOR FROM THE STATE OF ALABAMA

Senator SESSIONS. Thank you, Mr. Chairman. It is an honor to be before you as chairman of this committee. We came to the Senate together and you have moved up more rapidly than most of us to chair this august body and I couldn't be more proud of you. You have the right instincts for public service, the professional commitment to doing things right, and the work ethic that is necessary to deal with the complex issues that come before us.

Mr. Chairman, it is my honor and privilege to introduce my fellow Alabamian, Dr. Lester Crawford, to this committee. I am addressing the committee today not only because Dr. Crawford hails from Demopolis, AL, which was the original vine and olive colony founded by a group of Napoleon losers who had to flee France and established on the river there in Alabama the vine and olive colony. I am not sure it succeeded as a vine and olive colony, but it has succeeded as a wonderful community that sets a good example in that whole region of the State.

He received his Doctorate of Veterinary Medicine at Auburn University, one of the Nation's great universities. But I am also here

because this nominee is a recognized scientist, scholar, and academic, a public servant of unassailable personal integrity who brings with him the perspective of personal experience in academia, government, private practice, and industry. Most importantly, he combines openness, good humor, and a commitment to the common good.

Dr. Crawford brings to the agency expertise in a remarkable range of relevant fields. We frequently forget that in addition to authority to regulate drugs, the FDA is charged with overseeing foods, biological products, medical devices, animal feed and drugs, among other responsibilities. I don't know that you could find another candidate with his degree of expertise, not only in pharmacology and issues related to drugs and biologics, but also food safety, and in the era of "mad cow" disease and avian flu, the fields of agriculture and veterinary medicines, which are proving ever more crucial to the public health. In fact, he has a particular expertise in mad cow disease.

At a time when rising to the substantial challenges will require innovation and interdisciplinary thinking, a man who brings this quintessentially interdisciplinary training and experience could not be more appropriate.

In addition to his substantial academic and professional achievements, Dr. Crawford has demonstrated a tremendous dedication to public service during more than 13 years at the Food and Drug Administration and the United States Department of Agriculture. Colleagues who have worked with Dr. Crawford over the years unfailingly note his exemplary personal qualities, as well. Integrity, dedication, and enthusiasm have been hallmarks throughout his training and career.

Dr. Timothy Boosinger, Dean of Auburn University's nationally recognized College of Veterinary Medicine, called yesterday to share his own and Auburn's unreserved endorsement of Dr. Crawford as a scientist and administrator, a leader, and a man. He is really one of our most distinguished alumni. Auburn is proud of the contribution he is making to all our lives, he said.

I think that his own advice to a recent class of veterinary graduates is telling. He noted that he has always tried to let his own life be guided by the Latin phrase, I credo, I believe. The point is, he explained, when you have talent, you have to develop it and practice it. Develop your own credo and live by it. And Dr. Crawford has throughout his career demonstrated not only remarkable talent, but a consistent dedication to honing and applying that talent for the public good.

In summary, I believe that Dr. Lester Crawford is a man of great knowledge, talent, dedication, and integrity. As Commissioner, he will be even better able to bring these qualities to bear in the service of the safety and well-being of the American people. I urge you to join me in working to enable this superb nominee to get to his essential task as soon as possible.

Thank you, Mr. Chairman. I am honored to be with Dr. Crawford.

The CHAIRMAN. Thank you, Senator.

We welcome Dr. Crawford. I would mention that the committee has received over 100 letters and statements of support for Dr.

Crawford's nomination from individuals and organizations around the country. We received one letter with some concerns, that if they are not addressed at the hearing, we will ask that you address following the hearing. I would ask unanimous consent that all of those letters be entered into the record, without objection.

The CHAIRMAN. Dr. Crawford, we look forward to hearing your testimony.

STATEMENT OF LESTER M. CRAWFORD, D.V.M., PH.D., TO BE COMMISSIONER, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. CRAWFORD. Thank you very much, Mr. Chairman. First, I would like to introduce my wife, who is seated over here. This is my wife, Katherine, who is from Birmingham, Alabama, and is the mother of my two daughters and the grandmother of my four grandchildren.

The CHAIRMAN. Welcome.

Dr. CRAWFORD. I would like to thank the committee for inviting me here today. I am honored to be here and I appreciate the opportunity to tell you about myself and share ideas for how we can strengthen and advance the Nation's public health.

FDA is the Nation's principal consumer protection agency when it comes to food, drugs, and medical devices. The agency impacts the lives of all Americans every day. We ensure the safety and efficacy of the medicines they consume. We regulate 80 percent of the food Americans eat. FDA regulated products account for approximately 20 cents out of every dollar in the economy. American consumers rely on FDA to protect and advance the Nation's public health while people around the world share the view that the agency upholds the gold standard in terms of public health protection.

I have had the opportunity over the course of my career to serve four different tenures at FDA. This is the second time I have served as Acting Commissioner of the agency. I previously served as FDA Deputy Commissioner from 2002 to 2004, and as Director of FDA's Center for Veterinary Medicine from 1982 to 1985. Prior to that, I held several different positions, including Director in the former FDA Bureau of Veterinary Medicine in 1970s.

My career outside of FDA has likewise been dedicated to advancing public health. I served as Administrator of the Food Safety and Inspection Service, or FSIS, at the U.S. Department of Agriculture from 1987 to 1991. Prior to that, I was Chair of the Department of Physiology-Pharmacology at the University of Georgia and held the position of Associate Dean for several different offices at the University of Georgia's College of Veterinary Medicine.

More recently, from 1997 to 2002, I was Director of the Center for Food and Nutrition Policy at Georgetown University and at Virginia Tech, where it moved in 2001. I also served as the Executive Director of the Association of American Veterinary Medical Colleges.

I am a member of several professional and scientific societies. I am a member of the National Academy of Sciences Institute of Medicine, a Fellow of the Royal Society of Medicine in the United Kingdom, and a Fellow of the International Society of Food Science and Technology. In 1984, I was inducted into the French Academy

of Veterinary Medicine and I received the Wooldridge Award, the British Veterinary Association's highest award, in 1991. Additionally, I have been an advisor to the World Health Organization of the United Nations.

In terms of academic training, I received my Veterinary degree from Auburn, my Ph.D. in Pharmacology from the University of Georgia, and I have an Honorary Doctorate from Budapest University.

Throughout my diverse career, I have had the unique opportunity to contribute to a number of groundbreaking public health initiatives. For example, I played major roles in the development of mandatory nutrition labeling and the control of chemical and microbiological contaminants of food. In recent years at FDA, I have led efforts to combat the obesity epidemic, counterterrorist threats through new food security regulations, and revitalized the regulation of biomedical and food industries through the development of current good manufacturing practices. I also played a role in designing FDA's Critical Path Initiative, a new cutting-edge approach to advancing medical innovation that seeks to bridge the so-called gap between bench and bedside.

Going forward, as Commissioner of the Food and Drug Administration, if confirmed, I look forward to the opportunity to build on these initiatives to help America reach new levels of public health protection and innovation.

This is a critical time for the Nation's health. We face exciting opportunities from new cross-cutting science and biomedical innovation, but at the same time, we are confronted with profound challenges of every shape and size—emerging diseases, product safety concerns, the threat of bioterrorism, and much more.

Our success and the Nation's health are continually challenged by these emerging threats, changes in technology and global market forces. At the same time, FDA's responsibilities are growing in scope and complexity. To overcome these growing challenges and to truly capitalize on the boundless opportunities presented by modern science, we need a vision for the future, a vision for a 21st century FDA.

I would like to tell you briefly about my vision for the future of FDA. It is one of transformation. Internally at FDA, we are transforming from domestic-focused, paper-based processes employing yesterday's technologies to global, electronic data-driven decisions that apply the latest science. And we are transforming our culture to one of transparency, collaboration, and cutting-edge thinking.

We are going to tap into new technologies and new ways of thinking and build upon collaborations with a broad network of partners, public and private, U.S. and international. By capitalizing on 21st century innovation, information technology, and regulatory process innovation, we can leverage public investment in FDA to yield an even greater level of public health protection and a more efficient and predictable critical path to innovation. By adopting a quality systems approach in all our operations, we will increase productivity and promote better health outcomes.

In particular, I am committed to addressing existing concerns regarding postmarket safety of FDA-regulated products, both in medical products and food, respectively. I remain focused on bioterror-

ism and on minimizing the threat of terrorist attacks both through heightened food security and through the development of new medical countermeasures.

As we confront 21st century challenges, 21st century solutions are key. That is why innovation will be at the center of everything FDA does in the time ahead. I look forward to helping lead the way as we enter a new era of individualized medicine and electronic health.

Finally, we need to continue to do more to empower our citizens with better health information about the foods they eat, the medicines they use, and the other health products they consume. Under my leadership, I will see to it that FDA continues to provide all Americans with the tools they need to make informed choices about their health so that they can live longer, happier, and healthy lives.

These issues affect us all and I look forward to being part of the solution to these problems. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Dr. Crawford.

[The prepared statement of Dr. Crawford follows:]

PREPARED STATEMENT OF LESTER M. CRAWFORD, D.V.M., PH.D.

Mr. Chairman and members of the committee, I am Dr. Lester M. Crawford, D.V.M., Ph.D., Acting Commissioner of the Food and Drug Administration (FDA or the Agency). I would like to thank the Committee for inviting me here today. I am honored to be here, and I appreciate the opportunity to tell you about myself and share ideas for how we can strengthen and advance the Nation's public health.

FDA is the Nation's principal consumer protection agency when it comes to food, drugs and medical devices. The Agency impacts the lives of all Americans every day. We ensure the safety and efficacy of the medicines they consume. We regulate 80 percent of the food Americans eat. FDA-regulated products account for approximately 20 cents out of every dollar in the economy. American consumers rely on FDA to protect and advance the Nation's public health while people around the world share the view that the Agency upholds the gold standard in terms of public health protection.

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More recently, from 1997–2002, I was Director of the Center for Food and Nutrition Policy at Georgetown University and at Virginia Tech, where it moved in 2001. I also served as Executive Director of the Association of American Veterinary Medical Colleges from 1993 to 1997.

I am a member of various professional societies. I am a Member of the National Academy of Sciences Institute of Medicine, a Fellow of the Royal Society of Medicine (UK), and a Fellow of the International Society of Food Science and Technology. In 1984, I was inducted into the French Academy of Veterinary Medicine. In 1991, I received the Wooldridge Award, the British Veterinary Associations highest award. Additionally, I have been an advisor to the World Health Organization of the United Nations for much of my career.

In terms of academic training, I received my Doctor of Veterinary Medicine (D.V.M.) from Auburn University, my Ph.D. in pharmacology from the University of Georgia, and an Honorary Doctorate (M.D.V.) from Budapest University.

Throughout my diverse career, I have had the unique opportunity to contribute to a number of groundbreaking public health initiatives. For example, I played major roles in the development of mandatory nutrition labeling and the control of chemical and microbiological contaminants of food. In recent years at FDA, I have

led efforts to combat the obesity epidemic, counter terrorist threats through new food security regulations, and revitalize the regulation of biomedical and food industries through the development of current good manufacturing practices. I also played a key role in designing FDA's "Critical Path" initiative, a new cutting-edge approach to advancing medical innovation that seeks to bridge the so-called gap between bench and bedside.

Going forward, as Commissioner of the Food and Drug Administration, if confirmed, I look forward to the opportunity to build on these initiatives and help America reach new levels of public health protection and innovation.

This is a critical time for the Nation's health. We face exciting opportunities from new cross-cutting science and biomedical innovation, but at the same time we are confronted with profound challenges of every shape and size—emerging diseases, product safety concerns, the threat of bioterrorism, and much, much more.

Our success—and the Nation's health—are continually challenged by these emerging threats, changes in technology, and global market forces. At the same time, FDA's responsibilities are growing in scope and complexity. To overcome these growing challenges, and to truly capitalize on the boundless opportunities presented by modern science, we need a vision for the future—a vision for a 21st century FDA.

I would like to tell you briefly about my vision for FDA and my priorities for the time ahead. The FDA of today understands, perhaps better than ever, the need for both protecting and advancing the public health, and we are focusing on new and better ways to perform our core mission.

My vision for the future of FDA is one of transformation. Internally at FDA, we're transforming from domestic-focused, paper-based processes, employing yesterday's technologies, to global, electronic-data driven decisions that apply the latest science. And we're transforming our culture to one of transparency, collaboration, and cutting-edge thinking.

We're going to tap into new technologies and new ways of thinking, and build upon collaborations with a broad network of partners—public and private, U.S. and international. By capitalizing on 21st century information technology and regulatory process innovation, we can leverage public investment in FDA to yield an even greater level of public health protection, and a more efficient and predictable critical path to innovation. By adopting a quality systems approach in all of our operations, we will increase productivity and promote better health outcomes.

In particular, I am committed to addressing existing concerns regarding post-market safety of FDA-regulated products, both in medical products and food, respectively. I remain focused on bioterrorism and on minimizing the threat of terrorist attack both through heightened food security and through the development of new medical countermeasures. As we confront 21st century challenges, 21st century solutions are key; that is why "innovation" will be at the center of everything FDA does in the time ahead. I look forward to helping lead the way as we enter a new era of individualized medicine and e-health. Finally, we need to continue to do more to empower our citizens with better health information about the foods they eat, the medicines they use, and the other health products they consume. Under my leadership, I will see to it that FDA continues to provide all Americans with the tools they need to make informed choices about their health, so that they can live longer, healthier, and happier lives.

These issues impact us all. I know that the members of this committee are genuinely focused on doing all you can to address these public health challenges and capitalize on our public health opportunities. I am truly honored to have worked with you in the past to advance FDA's public health mission, and I look forward to continuing to work with each and every one of you to better protect and advance the public health in the time ahead. Thank you.

The CHAIRMAN. We will now have a series of 5-minute rounds to give everybody a chance to ask some questions. We appreciate your being here today. We appreciate the turnout of the members of the committee. This is the first round of the NCAA tournament, a great Irish day, and also the hearings on the House side on baseball steroids, which has some relationship to this. [Laughter.]

I have heard some people argue that the Prescription Drug User Fee Act was a bad idea because the fees co-opt the FDA and force the agency to make a hasty or unwise decision. I assume you disagree with this perspective, so would you please explain to the committee the importance of PDUFA and the way you will ensure,

as Commissioner, that there will continue to be no compromise on FDA's standards in reviewing products covered by user fees?

Dr. CRAWFORD. Yes. Thank you, sir. As you know, the Prescription Drug User Fee Act was enacted in the early 1990s and it is reenacted as it sunsets every 5 years. The two times that it has been up for review, changes have been made and so we anticipate that, based on experience, probably we will be entertaining some new proposals.

Virtually every country in the world has a user fee system. The question is how they utilize that user fee system.

We think the goal letter that we develop between the industry that we regulate and FDA gives us an indication of what is coming down the pike, what new kinds of drugs and drug classes are coming and what the load will be upon FDA. And so we are—and as you know, that goal letter is ratified by the Congress as we finish it.

The second part is is that because of the Prescription Drug User Fee Act, we get funding to increase our staff and to be more efficient in the drug approval process. That has worked well for FDA under the years of PDUFA. One particular year in the mid-1990s, we approved more drugs than any other year in history, and I think we are doing a better job of reviewing them. Some drugs are not approved. Some need more work. But what the companies pay for is the review itself, and I think on balance that it is working well.

The CHAIRMAN. Thank you. Most of the questions today will shift gears pretty fast so that we can cover a wide range of things.

The GAO report released earlier this week indicates serious breaches in the FDA's oversight of the 1997 ban on the feeding of meat and bone meal from livestock to other livestock. This ban is intended to guard against the spread of mad cow disease in the United States. This report follows up on a 2002 report that also found gaps in the FDA's enforcement of this regulation. GAO also noted that the FDA may not even have enough information to assess compliance rates. What are you planning to do to improve the enforcement and compliance with this and other food safety regulations?

Dr. CRAWFORD. We are in the process of analyzing the GAO report. As you know, we worked with them through the 2-year process that they employed to come up with the report. There are some suggestions in there that we think are very good and we intend to implement them.

The report does say that we made improvements since the last report, and we appreciate that. There are more improvements to be made. We now know that there are about a million people in the United States that feed one or more cattle. We have to adopt a program that both educates them about the use of the prohibited material in feed and also encourages them to be very careful about what they mix in their cattle feed. We now know that that is a menace FDA has to stay on top of, so we appreciate the report and we will adopt the recommendation.

The CHAIRMAN. Thank you. I do want to also discuss the FDA's action on the abortion drug RU-486. I don't believe that the FDA should spend time and resources reviewing products that are in-

tended solely to end life. I am also very concerned that a number of deaths have been linked to RU-486.

In August 2002, a number of organizations sent a citizen petition to the FDA asking that the FDA revoke its approval of RU-486. The petition argues that FDA violated drug law and its own regulations and standards in approving the RU-486 for medical abortion. Now, these are pretty serious allegations, and 18 months later, the FDA has yet to give a final response. Can you assure me that the FDA will respond to this petition sooner rather than later?

Dr. CRAWFORD. As you know, the issues raised in the petition are very complex, indeed. We are still working through those. We are in the final stages of that. I can assure you we will respond to the petition. I can't give an exact date, but we are in the final stages of it.

The CHAIRMAN. Thank you. My time has almost expired.

Senator Kennedy.

Senator KENNEDY. Thank you, Mr. Chairman.

As we all know, the FDA should be the gold standard for objective science and unwavering commitment to the public health. On Plan B, emergency contraception there are serious concerns the FDA was guided more by ideology than by sound science.

In your testimony on March 11, 2004, before the House Appropriations Committee, you said that the Scientific Advisory Committee on Plan B was all over the board, but that is not really the case, I don't think. Isn't it the reality that the Advisory Board voted 24 to three to approve OTC status for Plan B?

Dr. CRAWFORD. That is correct.

Senator KENNEDY. Yet the FDA rejected the recommendation?

Dr. CRAWFORD. Actually, what we did was we evaluated the then-application and we could not approve it. But the company has now submitted a second one. We also have, just in the last few weeks, been sued on the original decision, so we are evaluating what the impact of that is and we are also considering the application that is before the agency at the present time. We are continuing to evaluate both as we go forward.

Senator KENNEDY. Well, in response to the question from Representative Farr at the March 2004 hearing, you said the FDA's deadline for acting on the resubmitted application was January 22 of this year. Is it usual for FDA to miss the deadlines by months, and who is responsible for the hold-up?

Dr. CRAWFORD. We usually don't miss the deadlines. In this case, it is very complex. We have a kind of application that the company is seeking which we have never approved before, and so it is taking a little longer than it would have in the past.

Senator KENNEDY. Well, do we want to leave it there? The problems, as you indicated in your earlier answer were the difficulty in the application and then the review of the legal issues and the suit, and you are unable to indicate to us when you are going to act?

Dr. CRAWFORD. I can't give a date, but it won't be very much longer.

Senator KENNEDY. Well, are we talking days? Are we talking weeks?

Dr. CRAWFORD. I wouldn't want to say days, Senator. I would say weeks.

Senator KENNEDY. I want to move on. On the drug safety issue, we have talked about this and you have commented on it, so it is an old issue, but I want to get answers today. Last year, Merck withdrew Vioxx from the market because the drug doubled the risk of a heart attack or stroke, but that was more than 5 years after the FDA approved the drug and after 20 million Americans had used it. As a result, tens of thousands of Americans needlessly suffered heart attack or stroke and many died. It is the single largest drug safety failure the Nation has ever faced. It simply should not take that long, nor should so many people use a drug before such a significant safety risk is discovered.

If a similar disaster had happened through fire or flood or terrorism, we would be moving heaven and earth to make sure that such a catastrophe never happened again, yet the FDA has so far recommended only minimal adjustments to its procedures.

In our hearings on drug safety earlier this year, the FDA witness, Dr. Kweder, admitted that there had been lapses in how the FDA handled this tragedy. Do you agree that there were lapses, that mistakes were made?

Dr. CRAWFORD. When these drugs entered the marketplace, as you mentioned, in the late 1990s and early parts of this decade, they held great promise. As they were used over time, and particularly in two NIH trials at higher doses for longer durations of therapy, some problems did show up. They could not have been anticipated, we do not believe, until that time. We had ordered earlier warnings and we were monitoring the drug very carefully, but it was only the very large, very long, high-dosage trials at NIH that revealed the problem.

Senator KENNEDY. "They can't be anticipated" is rather an ominous response when you have put at risk so many people on a prescription drug. I want to know whether this is going to be business as usual out at FDA or whether you are setting up some kind of system that will be able to flag these issues. I mean, we have just gone through one of the great, great, lapses for whatever reasons. I am not sure the American people are going to be satisfied that there are a number of situations that can't be anticipated and, therefore, that is the way it is going to be. That is not the answer that the American people, or certainly I, would like to hear.

We heard Dr. Kweder indicate that there had been lapses, and I think most of us believe there had been, and the real issue is what the agency is going to do to deal with those lapses. I think, first of all, there has to be a recognition that there is a serious problem, and if there is, what are you going to do about the problem, is what I would like to direct your attention to.

Dr. CRAWFORD. To make sure there aren't lapses in the future, what we are going to do is like a multipronged approach. We are instituting a Drug Safety Board which will, when we get these signals, such as we did on Vioxx and some of those other kinds of drugs, we will put it in to the board. They will prescribe for us what we should do in order to find out whether or not this is a false signal, that is a false alarm, or whether it is something real. We will announce that at that point, not wait, and the Drug Safety Board's deliberations will be public, and we will also advise the Nation's physicians as well as consumers, that is patients, of what we

have found at that point and what we are doing in order to get to the bottom of the matter. Then we will establish a drug watch so that we will list that drug so that it is accessible on our websites and elsewhere to the American people and we will have a progress report as we go forward.

And then the other things we have asked the National Academy of Sciences Institute of Medicine to evaluate and affect the FDA culture. We want to figure out a system that is more transparent for decision making. We also want to effectuate a system so that minority opinions are involved. It is true that in the culture and milieu of FDA, there is a lot of give and take on these decisions based on the science, but we want to honor that and also to record what the minority opinions are.

Senator KENNEDY. My time is up, Mr. Chairman. I would just ask about that recent advisory board, you know, there were questions about the conflicts of interest. Are you committed when you publish the members of the board to also indicate the background of each?

Dr. CRAWFORD. We will. We are going to change those procedures. There is disclosure, but there should be easier disclosure for the press and others to get access to. We are going to change that entirely.

Senator KENNEDY. My time is up. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you. Senator Sessions.

Senator SESSIONS. Thank you, Chairman Enzi.

You have a difficult challenge. Delaying an effective drug from coming on the market because of concerns that prove to be insubstantial can cost hundreds, maybe thousands, of lives. And likewise, if a drug is approved too rapidly, it turns out to have side effects unexpected, it can also cost lives. So I know it is a very challenging position for you. Sometimes, the only way we can know for certain is to see a drug actually operate over a period of years and the costs then are weighed against the benefits and you can make the best decision insofar as possible.

But your challenge is to identify in advance what will work, what will not work, and make those decisions that are best. I think your integrity, experience, and background will lead you to make good decisions, and that is what we expect and that is all we can ask. We can't expect perfection.

Dr. Crawford, I have an interest in generics. I asked you about it as we talked yesterday, about let us not create a situation in which generics are delayed too long because that keeps the price higher for the public. A generic drug will come in at a lower cost, normally. You provided some information on that. I would like to get your philosophy about generics and what we can do to bring those on at the appropriate time.

Dr. CRAWFORD. Three years ago, when we began to address this problem, we found that generics were taking about 19 months to be approved or disapproved, that is, to be reviewed. We have now been able to shorten that down to 12 months, and what that has resulted in is the approval of a new generic drug in America every day. We are now trending toward somewhere between 400 and 500 generic drug approvals for this coming year.

Generic drugs cost less, and not only that, they cost less in America than they do in other countries around the world. The key thing, though, I think, in terms of our efforts with generics is that now, about half of all prescriptions are for generic drugs. Generic drugs, we are pledged to make sure are as safe and as effective and as potent as any other drug that is on the market, including the prescription counterparts in cases.

So we are very pleased with this. We continue to work with generic drugs in order to get them on the market and also to have them be an appreciable percentage of the prescription drugs that are used by the American people.

Senator SESSIONS. I think that is good progress, and I salute you for it. I think we ought not to have unnecessary delays in the time between an expiration of a drug manufacturer's patent and the approval of generic products. That just costs the purchasers of those drugs extra money, and I salute you for the progress that you made there.

Would you share with us any thoughts you may have concerning the problem that lawsuits, liability questions, have with regard to establishing effective vaccines' availability in this country? It is something that seems to me to be rather significant and we need to deal with it or we may never get the vaccine problem settled.

Dr. CRAWFORD. Well, as you know, we have had a number of hearings on the subject, starting back in 2002. The main focus of that hearing in Congress was to expose the fact that the vaccine industry was extremely fragile. We predicted then that we would have only one supplier by this past flu season, this flu season that we are in, and there was a great deal of discussion about how to incentivize and indemnify the industry. The result of that hearing was some extra funding in order to develop alternative vaccine production methods which would make for a more viable industry, but not much was done with respect to liability.

That is not an area that I testified on, not an area that I am expert in. It was, I believe, the report of that hearing and also two of these hearings that we have had recently did explore that, but I am not sure if conclusions were made.

Senator SESSIONS. I think it is a factor in the declining number of suppliers, and I think it is something we are going to have to deal with.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you. The next Senator is Senator Clinton.

Senator CLINTON. Thank you, Mr. Chairman. If I could, I would like to submit additional questions for the record.

The CHAIRMAN. Yes. The record will be held open so that people can submit questions.

Senator CLINTON. Thank you very much, and welcome, Dr. Crawford. There are a number of issues that are of concern to me, ranging from the flu vaccine, which was mentioned, the eventual decision on the COX-2 issue, and others which I will submit, but I want to zero in on this emergency contraception issue.

Back on July 8, I, along with six of my colleagues on this committee, sent a letter asking that you and Dr. Galson meet with us to discuss this matter. My staff followed up repeatedly, but we were never able to establish a meeting time.

So my first question, very simply, is can I have your assurance that in the future, you will make yourself available to meet with members of this committee to discuss matters that are of great importance to us?

Dr. CRAWFORD. Absolutely. I think that might have turned into a briefing, but I apologize for not meeting with you personally and that will not happen again.

Senator CLINTON. Thank you. Now, Dr. Crawford, I would like to ask a simple, straightforward question that may help to illuminate a great deal of the concern and confusion in the press and elsewhere about what exactly emergency contraception is and what it isn't.

The label for Plan B says the method is indicated, and I quote, "for the prevention of pregnancy after unprotected sex if a contraceptive fails or if no contraception was used," unquote. Would you clarify for the committee that emergency contraception is a method for prevention of pregnancy, not the termination of pregnancy?

Dr. CRAWFORD. I can certainly clarify. I may need to confer with the experts in the FDA about exactly what the physiology of it is, but the label will say prevention.

Senator CLINTON. Well, in fact, as the FDA's own questions and answers on Plan B released in May 2004 say, and I quote again, "Plan B works like other birth control pills to prevent pregnancy. Plan B acts primarily by stopping ovulation. It may prevent fertilization. If fertilization occurs, Plan B may prevent a fertilized egg from attaching to the womb."

So just to be clear, are you confirming that FDA, in its own printed information which I have a copy of here, in response to questions that people legitimately have from both the public and other points of view, that it says explicitly what is emergency contraception, and I quote, "emergency contraception is a method of preventing pregnancy." That is the FDA position, is that correct, Dr. Crawford?

Dr. CRAWFORD. We haven't finally finished the label, but that is what is before us at the present time and we have not at this present time finally decided. We have no real dispute with the label at this point. But as you know, the product is not approved and so I can't say how it will finally turn out.

If I may answer that for the record, I can give some of the scientific interpretations of what happens at conceptus and whether or not—the term of art here is called nidation, whether or not the conceptus attaches to the wall of the uterus. But I would like, if I may, to consult with the experts in the Center and——

Senator CLINTON. Well, in fact, though, Dr. Crawford, the experts at FDA have made their recommendation, that emergency contraception should be available and it should be available over the counter and that the studies on it and the assessment of it confirm that it is as described, emergency contraception, a method of preventing pregnancy.

And what has disturbed many of us is what appears to be political interference in a scientific process. For those of us who believe that prevention is the key for decreasing the number of abortions, it is somewhat disturbing to see the injection of political concerns. I think it is perfectly appropriate for citizens to petition, to send

letters, to ask questions, but there must be a scientific basis for these decisions.

And insofar as we are aware, the experts at the FDA and the outside experts have voted overwhelmingly in favor of making this drug available. More than 70 organizations, including the American Academy of Physicians, Family Physicians, Obstetricians and Gynecologists, the American Medical Association submitted testimony. If we are going to return the FDA to the gold standard, then it is perfectly appropriate for people to say, don't use this or that it is somehow inappropriate and to be in any way involved in the public debate over it, but not to politicize the science, and that is what I want your assurance of, Dr. Crawford.

It is deeply disturbing to me. We rely on the FDA for everything we take. I am hopeful that we will reverse what appears to be a dangerous slide into political opinion as opposed to scientific evidence.

Dr. CRAWFORD. Well, I can assure you that this decision will not be based on politics. It will be based on science. It is delayed, and I think that is the way to look at it, because it is a very complex approval process that the company has proposed. And so we are working through the legality of that. But I am not aware of political pressure to make the decision one way or the other.

You are absolutely correct about the Advisory Committee, so I think the science part is generally done. We are just now down to how the label will look. This is going to be a very unusual sort of approval and it is delayed and I apologize for that, but——

Senator CLINTON. When might we expect the approval to be forthcoming?

Dr. CRAWFORD. I can't say for sure because we—Mike could have predicted it, but the lawsuit has complicated it a little bit. We have to work through that. It is for the prior approval, and what effect it has on it, I can't really say at this time. But I don't think it is going to be a long delay.

Senator CLINTON. Thank you. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you. Senator DeWine.

Senator DEWINE. Thank you, Mr. Chairman.

Dr. Crawford, like drugs, for too long, we assumed that children were small adults and could just take reduced doses of adult products. We are finding that many essential medical devices used extensively by pediatricians are really not designed and sized for children's special needs.

According to pediatricians, the development of cutting-edge medical devices suitable for children's smaller and growing bodies can lag 5 to even 10 years behind those for adults. That is really not acceptable. Could you tell us, under your leadership, what the Food and Drug Administration will be able to do to ensure that devices used in children are designed and sized for their use?

Dr. CRAWFORD. Thank you for the question. When I came on as acting in 2002, we had just gotten the Best Pharmaceuticals for Children Act, as you know, and it was my privilege to implement that and it has gone forward. After that time, we had the codification of our regulation on labeling for pediatric uses of existing drugs. We had a regulation that was overturned in the courts. We

pursued that. The Congress codified the regulation, thereby making it legal.

And what has happened since that time is for those drugs that are on patent, the ones that have exclusivity, we have gotten a lot of activity and there have been multiple changes in the labeling, and also as the products go on the market, more and more, they do show pediatric indications. Not all drugs can be used in children, but many can and many more are as a result of these two pieces of legislation.

The other thing is those drugs that are off-patent, however, we haven't made as much progress with because we actually need the National Institutes of Health to do some work on those products in order to make sure they are okay for pediatric uses. As you may know, Secretary Thompson and the past administration did order some funding for this particular project and it has yielded some results, but not enough at this point.

Senator DEWINE. Doctor, my question—I appreciate that. My question was about devices, though, which is a new area. What can you do in that area?

Dr. CRAWFORD. We are going to have the same people who work in my office that have spearheaded this effort with the drugs do it also with the devices. They have essentially the same kind of scheme, the same authorities in order to get it done, and I expect—you have my assurance that I am fully committed to that project. I will make the resources available for it, and I expect the same kind of results, and we will hold them to that expectation.

Senator DEWINE. What is your timing on that?

Dr. CRAWFORD. The timing on setting up the office is within this fiscal year, so it should be done within a month or two.

Senator DEWINE. Setting up the office?

Dr. CRAWFORD. The office is already set up, basically. We have to recharge it——

Senator DEWINE. What will be done within a couple months?

Dr. CRAWFORD. The office will be fully charged to do devices evaluation, the same as it did in drugs.

Senator DEWINE. Let me go on to another question. Currently, few programs specifically target the treatment of children with HIV/AIDS in developing countries. A primary reason, of course, is the lack of appropriate pharmaceuticals for use in children. We all know that children do need special drugs. With 2.5 million children infected with HIV/AIDS around the world, it is essential that we have appropriate medications to treat them.

Let me ask you, Doctor, how do you plan to ensure that HIV/AIDS drugs, both generic and brand name, approved by the FDA expedited process also include pediatric formulations as well as important dosing information needed for treating the different age groups?

Dr. CRAWFORD. We are actually using these same authorities that I mentioned in the drug area. As you know, the President has made $15 billion available over a period of time for the use of these kinds of therapies in Africa and elsewhere. We have had to put in, with great dispatch, an FDA quick approval process for those kinds of products that will be used in Africa. We had many countries willing to enter that market once the amount of funding was made

available. However, we have insisted that they be FDA approved, and the fact that they go through an abbreviated approval process also means that the Best Pharmaceuticals for Children Act and so forth will be applicable. So we will try to use that mechanism to make sure it works.

Senator DEWINE. Doctor, you are looking at the—you have been looking at the issue of salt in what is called healthy food products. When could we expect those guidelines, or what are you doing in that area?

Dr. CRAWFORD. Essentially, what has happened there is that we gave the industry, that is the food industry, a grace period of 6 years to try to reformulate the products that they would be drastically reducing the salt content of so that they would be palatable and also that they would be at the same nutrition level.

The industry has had a hard time doing that, and yet we have some notable brands that have materially reduced the salt. We think that is good for public health. We don't want to in any sense invalidate those procedures, what they have done, and the progress that has been made, so we are considering now the finalization of a regulation which will enable them to label correctly and also to proceed with those efforts.

That will be done sometime this summer, but there has been some concern that we might take action against companies in the salt area. I assure you that we are working with them. If there is too much salt, we will also be working with them. But those that are genuinely trying to reduce the salt and maintain the nutrition level, we will have a place for them.

Senator DEWINE. But something will happen this summer?

Dr. CRAWFORD. Yes.

Senator DEWINE. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you. Senator Murray.

Senator MURRAY. Thank you, Mr. Chairman, and first, let me commend Senator DeWine for his work on pediatric labeling. I share his concern and agree with him that we need to really make sure we are moving forward on that.

Dr. Crawford, thank you for coming before this committee at a very troubling time for FDA, where across this country, we are seeing allegations of safety lapses, of political interference, conflict of interest. It is extremely important that FDA's reputation remain sterling and that the public can count on FDA to give us the best scientific information and approve drugs and let consumers make decisions for themselves, and we have heard that on this committee many times as we have had discussions about safety over the last several weeks, on the COX-2 drugs, for example, that patients need to know about the drug, but they need to have the right to make decisions about it themselves.

So within that context, I just want to follow up on a comment that was made earlier on this committee on RU-486. RU-486 is not about ending life, it is about protecting women's health, and, in fact, FDA has approved this drug as safe and effective, is that not correct?

Dr. CRAWFORD. That is correct.

Senator MURRAY. Thank you. I just want that for the record.

Now, on the emergency contraceptives, Plan B and emergency contraceptives, I heard you say that this is unusual. You have a panel that has recommended 24 to 3 to approve this. I know you said a court filing has been made, but what is unusual? Are there other times that it's 24 to 3 and it is not approved?

Dr. CRAWFORD. Yes. There have been times when we have overturned the Advisory Committee. I think it is important for me to state that we have a decision pending with respect to the product you asked about and we are moving forward. What is unusual is the kind of application that the company has filed with us——

Senator MURRAY. In what way?

Dr. CRAWFORD. I can't—I am really not supposed to discuss what they have filed, but it is complex and it has never been done before, so it is taking us a little longer. I am not saying we are going to deny it, but we are moving toward a decision. But it is a unique application.

Senator MURRAY. You may or may not know, but Washington State is one of the four States that currently have an over-the-counter agreement on emergency contraceptives. It is based on good science. It is based on good public health policy. It allows consumers to make their own decisions. And I, frankly, think that is part of what we need to do to make sure that FDA is something that all of us have confidence in, that it is not political decisions, it is based on good health, good public health, and good science.

So I just want to ask you, you said that a decision is coming, a decision is coming. Will this committee know by the time we vote on your confirmation—I believe it is April 13—either what that decision is or an exact time line of when that decision will be made?

Dr. CRAWFORD. I can't commit to that.

Senator MURRAY. Well, I find that troubling because this is an issue that is extremely important. I think many of us on this committee care deeply that FDA make decisions based on good science, good public health policy, and that troubles me greatly that we won't have that answer.

Senator MIKULSKI. Would the gentlelady yield? Perhaps, I wonder if Dr. Crawford could share—he can't say this at a hearing. Could he say this at a briefing, perhaps with you and I and Senator Clinton and the leadership of the committee?

Dr. CRAWFORD. Yes. I would be happy to meet with you.

Senator MURRAY. Then I would request that we have that time and that briefing before this committee votes on this nomination, if I could ask the chairman for his approval of that.

The CHAIRMAN. We will work on that.

Senator MURRAY. OK, and I think there are a number of us who would like to——

The CHAIRMAN. We will work on having that happen. We have a little bit of time to——

Senator MURRAY. I appreciate that.

The CHAIRMAN. We have a number of people to get together. I hope we are not counting on all of them being there all at the same time, if that is what presents the difficulty.

Senator MURRAY. I think we are asking for a specific briefing from Dr. Crawford before this committee votes on his nomination

to give us the reason why he believes that the request on the Plan B emergency contraceptives is unusual.

Senator MIKULSKI. And the relevant people will be Senator Clinton, you and I, the leadership of the committee if it wishes to participate, and, of course, your staff being present, Senator.

The CHAIRMAN. Certainly. The point that I am making, though, is that if we have to coordinate all of those people to be at the same place at the same time——

Senator MIKULSKI. We will be there.

Senator MURRAY. We will be there.

The CHAIRMAN. [continuing]. As opposed to setting up a time——

Senator MURRAY. You tell us the time.

The CHAIRMAN. OK.

Senator MURRAY. All right. We will work on that with you. I have other questions I will submit for the record, and I thank the chairman.

The CHAIRMAN. Thank you. Senator Hatch.

Senator HATCH. Dr. Crawford, welcome to the committee. Congratulations on this nomination. I have been around here a long time and watched all kinds of FDA Commissioners come through. I have to say, you are as qualified as anybody who has ever been nominated for this position. I know that you have done an excellent job during the time that you have been there as Acting Commissioner, but also in other capacities, as well. So I am grateful for your willingness to serve and expect you to be a great Chairman.

I look forward to working with you on a wide variety of issues, including drug safety, Hatch-Waxman reform, DSHEA, the White Oak facility, which, of course, I take a great interest in, as you know, and so many other issues. And I agree with those who have spoken for you and have mentioned your integrity, your capacity, the background, the education, and all the things that you have that would add, I think, a great deal to this position.

Let me just ask you this. Would you please take just a few minutes to talk about your plan to ensure the safety of our food supply against bioterrorist threats?

Dr. CRAWFORD. Thank you, Senator. We were blessed when I came on board in 2002 with the fact that the Bioterrorism Act, which I know you and other members worked on, was about to be passed. The President signed it into law in June of that year and we immediately went to the four regulations that implemented that law. They are now, I am happy to report, are all in place.

For the first time in its history, FDA has a thoroughly effective legislative authority to protect the food supply. We deployed a number of our inspectors in specific areas. At the time of the passage of the law, we were only at 35 ports of entry. We are now at basically half of them, which is well over 100. We are also able to order companies to tell us when they are having food come into the United States. We are also able to debar them, to prevent them from entering. We can condemn the food. We have a very strong food safety net both domestically and internally.

I think the proof of the pie is in the pudding. We have been able to prevent these kinds of attacks and we also are doing a better job at essential food safety, because each time there is a major outbreak of any kind, we ask ourselves first, could this be a terrorist

attack, and because of that, our people are in tune with looking very much more carefully at food safety events than they were in the past.

So I think the system is working very well and a lot of it has to do with that law.

Senator HATCH. Thank you so much. I would like to talk a little bit about your broad view of drug safety and basically how we should approach this issue so that consumers are better informed. Senator Kennedy referred to serious lapses on the FDA's part and specifically mentioned Vioxx, as you know. Dr. Crawford, how many serious lapses do you believe have taken place at the FDA on drug safety review and how do you feel about the creation of an independent Board on Drug Safety? Is that really a good solution?

Our HELP Committee hearings on drug safety heard from a lot of people who did not think that an independent board was a very good solution or approach. Instead, they supported keeping the drug safety review within the FDA so that those overseeing drug safety could directly communicate with those who reviewed the drug application. I would just like to have your thoughts on these areas.

Dr. CRAWFORD. Well, the Drug Safety Board will be within FDA. There was some interest in having it placed outside the agency. That is not something we are considering. We want to take advantage of the critical mass of personnel in the scientific and medical areas that we have in FDA when these problems come up. So the Drug Safety Board will be appointed by the Commissioner and will report within FDA. So I think that is the way to do it.

The other thing that we have to do in concert with that is be more open, to inform the public what we have under consideration, and also to have a better system of communicating with physicians.

Senator HATCH. Thank you. My time is just about up. Let me just ask one last question, but it is a very important one. As you know, I take a great interest, as does Senator Mikulski and others on this committee, in the White Oak facility that is being built pursuant to the bill that I passed a long time ago on this committee, the FDA Revitalization Act. I am watching its progress closely. Could you provide us with a progress report on the work done to date, your projected time table for the future, and the cost estimates of the remaining work? Is the necessary funding to complete work at White Oak contemplated in the President's budget?

Dr. CRAWFORD. Yes. We are now about halfway through at White Oak and we want to thank you, Senator Mikulski, and others for the FDA Revitalization Act. That was the stimulus that got us where we are today. FDA is in 55 different buildings in the Washington area. It is very difficult to manage the agency like it is. Once White Oak is open, which will be 2010, it will be a far more effective and efficient FDA.

We have about half of the funding that we need. We need just under a billion dollars total. We have already had committed by the Congress between—slightly over $500 million, and we do ask for the recommended amount in this upcoming budget. We haven't had the budget hearings yet, but we have made public the President's budget for 2006 and we do include the increment that we need to stay on course for occupying the building fully in 2010.

Senator HATCH. Thank you so much. I appreciate it, Mr. Chairman.

The CHAIRMAN. Thank you. Senator Jeffords.

Senator JEFFORDS. Before I go on to my questions, Dr. Crawford, I want to say that I share the same concerns as Senators Kennedy, Murray, and Clinton about the FDA's handling of Plan B.

Dr. Crawford, there have been concerns raised that having both the Office of Drug Safety and the Office of New Drugs in the same component of the FDA creates conflicts. What are your thoughts on taking ODS out of CDER and putting it elsewhere within the FDA?

Dr. CRAWFORD. Well, that is one of the suggestions that has been made. The Office of Drug Safety, we have over the past, actually, about 5 years, we have doubled the number of people and also doubled its budget and made it a separate unit. It does report to the same director as the people that are in the pre-approval process and we are still looking into that.

But the Drug Safety Board that I mentioned that will oversee all this will not include people that are primary reviewers, that is, those people that evaluate the drugs before they come on the market. We have heard it said, and we believe it could be true, that they may have an affinity with a drug that probably doesn't look good, at the very minimum, so we are going to make that separation of personnel. But we have not decided to move it outside of FDA, change its location, at the present time.

Senator JEFFORDS. Would you give us some ideas of the things that you would do to increase the FDA's commitment to drug safety?

Dr. CRAWFORD. Yes. I think we need to continue to build up the Office of Drug Safety. Ten years ago, it had very few personnel and virtually no funding. It now is—I would call it fully funded, and we are adding more funds this year in the President's budget, also more personnel—in fact, an appreciable increase in personnel if the budget is accepted. I think the strength of the Office of Drug Safety is very important and they need to be carefully monitored by me and the other leadership in FDA to make sure that they are truly experts in drug epidemiology, in other words, figuring out the early signals that would make us either bring about a labeling change or in some cases suspend marketing or take the drug off the market. They need to have that mentality and they also need to have the tools to do it. So that is what we are committed to doing.

Senator JEFFORDS. Relative to PDUFA, in the past, the Congress has authorized the FDA to accept user fees to augment its ability to review drug and medical device products. Some have urged that a portion of these fees should be directed toward ensuring the safety of these products. Thus far, the Congress has agreed with the industry's position that postmarket product safety review is the responsibility of the government and should be paid for through general revenues.

Dr. CRAWFORD. That is correct. That has been what the situation is now. I understand that there are people that think that some of these funds should come out of PDUFA, and as you know, we are reauthorizing that particular law—hopefully we are reauthorizing it in a year and a half, I think it is. So I suspect that will be under consideration.

Senator JEFFORDS. I would like to hear your thoughts on how you plan to provide funding for postmarket product safety. Failing the availability of appropriations, would some portion of user fees be a reasonable source of funding?

Dr. CRAWFORD. Right now, the law as constructed doesn't really provide for that. However, we have always generally been able to redirect funds, with the permission of the appropriate Appropriations Committees on Capitol Hill, to take care of these kinds of exigencies, and we will continue to—we will keep it funded. The funding profile of the Office of Drug Safety has been steadily improving.

Senator JEFFORDS. Dr. Crawford, clinical trials are an important part of the drug approval and use process. Information that comes out of clinical trials continues to be a vital concern to doctors, patients, manufacturers, and regulators. To that end, it seems like a good idea to expand the amount of information about trials that is available. What is the response to the idea of creating a mandatory clinical trials registry?

Dr. CRAWFORD. We have been working with the National Institutes of Health and other entities both in the government and outside to consider that. We have heard the unalloyed message from the public that they want to know about those clinical trials. They want to be able to read about them, air them if possible, and they think there ought to be a common source. So that is a charge to keep that we have and we will move forward with that as best we can.

It may take some funding, but I think that funding would probably come through NIH and not FDA because they maintain the database. Nonetheless, I think it is a good idea and it is one we are pursuing.

Senator JEFFORDS. Dr. Crawford, you will likely be the third Commissioner of the FDA since the Congress first passed legislation allowing for the reimportation of prescription drugs. The FDA helped draft that bill almost 6 years ago, but since then, the agency has opposed any efforts to allow reimportation. I would like you to tell me that you are ready to change that situation.

Dr. CRAWFORD. Well, that has a history, as you know, within FDA. When the Prescription Drug Marketing Act of 1987 was passed, it basically made reimportation illegal. But then after that, you are absolutely correct, another bill was passed which called on first Secretary Shalala and then Secretary Thompson to affirm that this process would be safe. Neither of them were able to affirm that it would be safe, so as Acting Commissioner, I was guided by the determination that these products were not safe.

Our concern is safety. FDA has been into the cost debate. That is not something that we have authority over. As far as the drugs being safe, that worries me a lot. We have to be very concerned about it. I am not trying to stonewall the situation, but we are not at this time able to tell you that the government is changing its position.

Senator JEFFORDS. Well, are you willing to work with us?

Dr. CRAWFORD. I am certainly willing to work with you, and as a matter of fact, as we have gone around prior to this hearing, a number of Senators have said that they have bills pending or they are thinking about it and we offered FDA's expertise in evaluating

that in terms of safety and those responsibilities that we have. So yes, we are open to that.

Senator JEFFORDS. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you. Senator Isakson.

Senator ISAKSON. Thank you, Mr. Chairman. First of all, Mr. Chairman, I would like the record to reflect that Dr. Crawford has his Ph.D. in Pharmacology from the University of Georgia, and further, serves as the head of the Department of Physiology and Pharmacology, which in and of itself should certify his complete competence to serve in this capacity. [Laughter.]

I say that as a Senator from Georgia who is very proud of your nomination.

Dr. CRAWFORD. Thank you, sir.

Senator ISAKSON. Following up a little bit on some of the questions, the Office of Drug Safety is a postapproval office, is that correct?

Dr. CRAWFORD. That is correct.

Senator ISAKSON. And it collects data from drugs that have been approved from various sources to determine whether there is a safety problem.

Dr. CRAWFORD. That is right.

Senator ISAKSON. How do you collect that data?

Dr. CRAWFORD. What we do is there are about three major sources. There are databases. For example, the Veterans' Administration has a very complex and very useful database where they keep records on adverse reactions and so forth. So do some of the HMOs, Kaiser Permanente, the National Institutes of Health, and we tap into those databases.

The second thing is that there are scientific reports that appear in the scientific literature around the world. We comb through that.

And then we receive adverse event reports each and every day of the year and we compile all of that.

So those are the three main sources of information, and then once we get one of those signals that something may be wrong, it is up to the Office of Drug Safety to evaluate whether it is a false alarm or the real thing.

Senator ISAKSON. Is that collection system institutionalized within the agency or does someone just have the responsibility of going to these three sources and asking if they have information?

Dr. CRAWFORD. No, it is institutionalized in the agency. There is an Office of Drug Safety. I would say that prior to 10 years ago, prior to 1995, it was not institutionalized, but it was at that point, and gradually over the years the funding and the number of people in that office have improved both in terms of what they do and what their expertise is, and we are asking this year in the President's budget for more personnel. I think this is the biggest increase we have asked for. We are also asking for more funding for the office. I am taking a personal interest in it, as is the rest of FDA's leadership.

Senator ISAKSON. Is any of that collection electronic?

Dr. CRAWFORD. Not as much of it as it should be. What we are working with—I met with the Secretary of Veterans' Affairs just recently and what we are hoping to do is get online with their med-

ical databases. We also want to do that with NIH. And I think we are very close. But right now, it is a little bit of both.

Senator ISAKSON. The reason I asked the question is that life experiences are the best teachers. My sister's life was saved through a field trial where she was a volunteer and she had a very serious, complex case of cancer. And so I am fully an advocate of getting drugs to the marketplace and technologies as expeditiously as possible for the benefit of those who suffer from terribly crippling diseases or other effects.

I am equally committed to ensuring that we have good safety, and it seems to me like two things. One, drug safety ought to remain within the agency. If you get into sending it outside, that doesn't seem to make any sense at all except to maybe be symbolic of something that I don't think needs to be symbolized.

But second, it would appear to me that the timely collection from all sources of adverse effects or some commonality of reoccurrences of those on different drugs or taking different treatments post-approval would serve to be a great second certification of what a field trial in itself does from the beginning.

And I guess my comment is—I am not really asking you a question, but after the two hearings I have attended on this and conversations I have had and my personal experience, it would seem like to me if the Department—and it may be doing this—could initiate or institutionalize electronic collection from all sources—Veterans' Administration is a great source and you have great reliability in the information, but once you go beyond that, like Kaiser Permanente or an HMO or maybe this drug program or that drug program, it seems to me like it is probably as comprehensive as you can get given what you have but not as comprehensive as we probably ought to have.

And so I would hope you all would look toward initiating whatever you can to expedite the collection of all that data from its various sources, and I think then the post safety process will be that much better and certainly that much more timely. Spoken as one who has no degree in any chemistry or pharmacology, but just based on what I have heard.

The CHAIRMAN. Thank you. Senator Mikulski?

Senator MIKULSKI. Thank you very much, Mr. Chairman, and good morning to you, Dr. Crawford.

First, I want to associate myself with Senators Clinton and Murray on the issues raised by Plan B and look forward to a briefing with you and discussing it in an appropriate forum, recognizing your legal and regulatory constraints.

I am really proud that FDA is a Maryland agency. Nine thousand people work there, and what a great cornucopia, to have NIH down Route 270 and you up there in FDA, and hopefully with the move to White Oak, then to have these surrounded by the great academic centers that do research, like Hopkins and Maryland and Georgetown. So we are really very, very, very proud of it.

And we worked on a nonpartisan basis here on FDA reform. Some of the greatest advocates for making sure that the employees who work so hard and are so diligent have the best facilities, the move to White Oak has been jointly with myself, Senator Hatch, and Senator Frist. So you see where we are.

Looking at where we are, though, with FDA, there is a crisis of confidence over drug safety in the public's mind and even with some clinicians. Looking at page three of your testimony, you talk about transformation, which I think we would want to support, but I was puzzled why the number one issue wouldn't be to restore in the public's mind the integrity of FDA. So I am going to come back to that and ask for your elaboration about the drug safety issue so that patients, doctors who don't want to get their advice from a drug salesperson need to know FDA is there.

You talked about this independent agency, a separate group. Would you give us your views on whether or not, in all candor, you think that within the agency itself, no matter how diligent, there can be that independent review, because it is not a change of buildings. Your own staff, Dr. Graham, has recommended an independent agency, a watchdog agency separate from FDA and almost a devil's advocate approach to watching this to ensure ongoing safety.

Could you share with us, do you think that FDA can truly be a watchdog of itself, recognizing the professionalism of the people who work there, but do you think we need not a watchdog system in a different building or a different block on an organizational chart, but a truly independent agency with its own staff and no ties to the industry?

Dr. CRAWFORD. Well, thank you for the question. It is up, I think, to me to make sure that they act independently, that they are not intimidated, that the conclusions of the Office of Drug Safety are given the kind of emphasis that they should be. FDA, as you mentioned, is a large organization, about 10,000 people all told, so I think it is possible, and I think it is being done, to have the Office of Drug Safety serve in a place in the organizational chart and also physically so that they are not subsumed by the primary drug reviewers and the other parts of the Center for Drugs.

I believe they are operating independently. I believe we need to do more work, though, on what you referred to earlier, which essentially is the culture of FDA. I think that decision making is not understood by the public. I think it is basically, like most scientific—when scientists get together, they sort of shout each other down. We need to have it very different, because we are talking about something other than scientific debate. We are talking about the safety of the drugs that are on the market, and so we need to work on making that transparent. The National Academy of Sciences Institute of Medicine is advising us on how to make that sea change in how we do business.

Senator MIKULSKI. Doctor, I am going to ask you to walk me through it. First of all, the public wants two things. No. 1, they want those dazzling cures available as quickly as we can, that our colleague, Senator Isakson's, sister would be able to be cured of cancer, but anyone else facing it—my dear father with Alzheimer's, though he has since passed away, my mother, who had a chronic condition like diabetes, to be able to find either a cure or even more drugs to help people not develop all the complications of it. So the public wants it and so do the clinicians and the practitioners, and we want them in America.

The other, though, is they want to be safe when they take it. So there is the dual pressure. It is a dual pressure, and FDA has

served us well. That is why they are the gold standard. Emerging democracies that could never afford to have an FDA look to us.

So, again, how mechanically would that be? Are you going to have a separate office? Is it going to have a separate staff? Who is that person responsible to? How will they be held accountable, and yet then not get entwined with the other administrative or bureaucratic assets? How do you envision that?

Dr. CRAWFORD. Well, the Office of Drug Safety, as it is being changed, will be a separate entity entirely with its own director. We are about ready to announce the appointment of the director——

Senator MIKULSKI. Is that person—will that person only be responsible to you?

Dr. CRAWFORD. The person will be responsible to me, but through the Center Director for Drugs. So he will go through that person to me.

Senator MIKULSKI. Can I ask you why? First of all, I know that you are busy. I mean, an FDA Commissioner's job is really, between food safety and drug safety, it is really three jobs. But why not to you directly, because doesn't that again give them one more layer of bureaucracy, one more justification when we want intellectual rigor, scientific scrutiny, transparency?

Dr. CRAWFORD. Well, I think it is up to me to make sure that I am intimately involved in what they do. If the person reported to me, which is always something that we can consider and we are open to, I would essentially have to be the person who did their job evaluations, take care of their budget amendments——

Senator MIKULSKI. But that is the crux of it.

Dr. CRAWFORD. Yes, I know.

Senator MIKULSKI. That is the crux of it.

Dr. CRAWFORD. Well, I am not closed to that——

Senator MIKULSKI. Who is going to evaluate it—the chicken, the egg, do you see?

Dr. CRAWFORD. Mm-hmm.

Senator MIKULSKI. That is the point. I am not saying, let us create a whole new independent agency. Senator, I know my time is up, but that is the crux of it. Who evaluates them? Who decides whether they get the promotion? Who decides whether they keep the job?

Dr. Crawford, I know you are a professional person. You stood in twice now as acting. We need a permanent Commissioner of FDA. We are proud of FDA. And I am not saying that person in between you and the drugs, the watchdog department, would not be faithful as you intend to be. But I am telling you, I really strongly recommend that if it is going to be independent, it has got to be independent of the entire bureaucracy, responsible to the Commissioner to whom we then hold responsible.

Dr. CRAWFORD. Maybe we could talk further about that.

Senator MIKULSKI. Thank you very much.

Mr. Chairman, you have been very indulgent. I appreciate it.

The CHAIRMAN. Thank you. Senator Harkin.

Senator HARKIN. Thank you very much, Mr. Chairman, and welcome, Dr. Crawford. I would ask that my statement be made a part of the record, Mr. Chairman.

The CHAIRMAN. Without objection.

[The prepared statement of Senator Harkin follows:]

PREPARED STATEMENT OF SENATOR HARKIN

Thank you, Mr. Chairman. And I also thank Dr. Crawford for appearing before us today. Dr. Crawford and I have a long, positive history of working together on issues at the Food and Drug Administration. And I am pleased to see him here.

I'd like to take this opportunity to bring up two issues.

First, as you know, Dr. Crawford, Congress passed the Dietary Supplement Health and Education Act (DSHEA) to ensure the availability and safety of dietary supplements that millions of Americans rely on. Under the leadership of Dr. McClellan as Commissioner and you as Acting Commissioner, the FDA has made significant progress in implementing and enforcing DSHEA. I look forward to continuing to work with FDA to fully implement DSHEA, and to make sure that U.S. consumers have access to safe, effective, and affordable dietary supplements.

Second, as you know, Dr. Crawford, our Nation is confronting a major obesity epidemic, among both adults and children. While obesity is a complex condidtion with many contributing factors, that fact is that we need a comprehensive approach to combating it—with an active role by government, parents, communities, and also the food and restaurant industries. Last year HHS/FDA released a report titled, "Counting Calories: Report of the Working Group on Obesity." It notes that food consumed away from home—mostly food from restaurants—has increased dramatically over the last 3 decades. In 1970, this accounted for 33 percent of the average consumer's food budget. By 2002, it accounted for 47 percent. But while people are eating out more and more, they have little or no information available to make informed food choices in restaurants. I am sponsoring legislation, the Healthy Lifestyles and Prevention Act, which would require mandatory nutritional labeling on menues and menu boards in chain resyaurants.

I have questions on both these issues, and several additional questions for the record.

Senator HARKIN. First of all, Dr. Crawford, I would like to commend you on your work as Acting Commissioner in an area in which I have a great deal of interest and have since I was one of the authors of the Dietary Health and Supplement Education Act, but your work on vitamins, minerals, and dietary supplements. The FDA has made significant strides in the past couple of years in implementing and enforcing what is known as DSHEA and I look forward to working with you to ensure that we continue to make this progress.

Some people have been critical of DSHEA, saying that it does not give FDA the tools it needs to ensure the safety of dietary supplements. Do you believe that the Dietary Supplement and Health Education Act gives the FDA sufficient authority to regulate dietary supplements, vitamins, and minerals?

Dr. CRAWFORD. Yes. We need to go ahead and make solid this—the GMP part of it. It has not been finalized, and I know that is your next question. Until we do that, it is not really possible to

thoroughly answer that question, but it is my belief that once we get that done, we will have the authority we need.

Senator HARKIN. Let me ask a follow-up on that question, then. Do you believe that the Dietary Health and Supplement Education Act gives the FDA the authority to remove harmful items from the shelves?

Dr. CRAWFORD. Yes. As you know, we have done that with ephedra and also with andro and some other products, and so obviously we do have the authority.

Senator HARKIN. So looking back to the first question, then, you said that as soon as the GMPs, the Good Manufacturing Practices, are promulgated, you will have sufficient authority then. Your predecessors have answered that question by saying that they thought they had sufficient authority. But then again, we have waited 10 years—10 years, the FDA has drug its feet on getting the Good Manufacturing Practices out. Can you inform the committee, or provide us with a more definitive date as to when the final Good Manufacturing Practices regulations will be published in the Federal Register?

Dr. CRAWFORD. I hope to be able to do that within—to tell you the exact date within a few days. I cannot at this point, but if I can follow up in writing, I will do what I can do.

Senator HARKIN. I would appreciate it, because your predecessors going back to 1995, when the law was passed, and I have sat here and asked every one of them, they have said, oh, yes, we are going to get the GMPs out. Then they get confirmed and that is the end of it. And so I really want to try to pin you down as much as I can.

Dr. CRAWFORD. Well, you can pin me down and I will agree that 10 years is too long to wait for it.

Senator HARKIN. Right.

Dr. CRAWFORD. So I am on track to try to get it out as quickly as I can.

Senator HARKIN. I appreciate that. And you will let us know——

Dr. CRAWFORD. Absolutely.

Senator HARKIN. [continuing]. Sometime, when, the next couple of months? Sixty days?

Dr. CRAWFORD. I can't really say, but it is sooner rather than later, for sure. You have heard that before, too, Senator, and I really can't answer that. I just don't have a publication date.

Senator HARKIN. Before the end of the year?

Dr. CRAWFORD. Yes.

Senator HARKIN. Thank you. That is great. I finally got it before the end of the year. [Laughter.]

My second question, Dr. Crawford, last year, the FDA released a report on obesity, and I certainly again appreciate your work on this issue. You have been in the forefront on this. But I am concerned by the fact that many of the recommendations that pertain to the food industry, especially restaurant foods, are voluntary rather than mandatory. The FDA report notes that food consumed away from home, mostly from restaurants, increased significantly from 33 percent of consumers' food budget in 1970 to 47 percent in 2002. Over the same period, total calories consumed from food purchased outside the home increased from 18 percent to 32 per-

cent. So we know that consumers eat more when they are out and they are less aware of nutritional information.

The report that came out of FDA had specific recommendations for the industry, and specifically, the FDA urged the restaurant industry to launch, quote, "a nationwide voluntary and point-of-sale nutrition information campaign for customers," end quote. Can you tell me about the progress the restaurant industry has made toward that recommendation?

Dr. CRAWFORD. Yes. I think certain segments, and like fast food corporations and also chain restaurants that have an identifiable name, have made progress with it. When we unveiled the Obesity Working Group Report, which was called "Calories Count," you recall that Secretary Thompson did say that we were going to try the voluntary approach for a while. If it didn't work, we were going to have to do something else.

So I think some progress has been made. It has been uneven. Not every chain restaurant you go into and not every fast food restaurant has the material available, and it is voluntary. As you remember, the NLEA was silent on that subject, so we don't have the authority to require it. I have been encouraged by comments from restaurants, though, that seem to think that it is working and that it is good for them.

Senator HARKIN. Of course, as you know, NLEA was mandatory, and I don't know that we want to go back and say that all of the information that shoppers, now they go into a food store and you look at all the nutritional—and by the way, the FDA is doing some good work there in standardizing that, too, so that is good. But we know that consumers are using those labels now and they are reading them. But they don't have that kind of information when they go to a restaurant. And now that we know there is an obesity epidemic—there was just a new study that was just published today again.

And if you have voluntary guidelines, I am all for voluntary if they will do it. But then that leads to one chain having one sort of set of guidelines and another one having another set of guidelines and who do you know? At least with NLEA, we have got some basic standards by which you can measure different items in packages or cans or bottles and stuff like that. But how do you know when you go in a restaurant? You really don't.

So voluntary is fine, but it seems to me the FDA really has got to step in here and design an information system that will be helpful to consumers when they go out to eat.

Dr. CRAWFORD. You mean try to standardize it? Yes, I think you are right.

Senator HARKIN. Something like that so that it is across the board so they know what they are getting, something like that. I don't know how much longer we are going to go with the voluntary. Again, a few of the chains have done a pretty darn good job, but then the others haven't, so what do you wind up with here? There is kind of a mishmash of stuff out there.

And again, because of the obesity epidemic, because of the onset of diabetes earlier and earlier, we just may have to have the FDA come up with standardization guidelines and with some mandatory

provisions for these restaurants to all at least put it out there in understandable form for people to read and understand.

Thank you very much, Dr. Crawford.

The CHAIRMAN. Thank you. Senator Dodd.

Senator DODD. Thank you very much, Mr. Chairman, and Dr. Crawford, welcome to the committee. I appreciate your willingness to take on this job.

Let me, before our colleague from Iowa leaves, on his last point of questioning, the obesity issue, I think the papers this morning indicate that we may be looking at the first generation of Americans who will live shorter lifespans than their parents because of this issue, and I think too often in the past, it has been sort of ridiculed a bit.

I know when Senator Frist and I, along with Jeff Bingaman, introduced legislation a year or so ago dealing with improved nutrition and physical activity, really sort of a harmless piece of legislation that passed the Senate, we weren't able to get it out of the House, there was some sense of sort of ridiculing, here is the Federal Government sort of telling people whether they can go to fast food restaurants or not, which is obviously not the case of what we were trying to do.

But I would hope the FDA would take this issue seriously. Too often, I think there is a negative association with this issue. There have been a lot of studies and a lot of news reports and so forth indicating the seriousness of this issue, and particularly when you consider some of these food producing companies that are getting exclusive rights in schools by offering poor schools significant money if they can put their vending machines in those schools for use during the day. It is dangerous and it is a serious problem. It really deserves someone like yourself to really champion this issue and make something of it, so I would hope you would do that. Senator Harkin raised a very good point.

Second, I just want to raise—I know Mike DeWine was here earlier, but he and I have worked a long time on the pediatric testing issues, as you know, and the Better and Best Pharmaceutical Acts for Children, which were adopted a number of years ago. I just want to, again, I want to comment quickly and go ahead, but we would like you to continue to work on expanding pediatric testing. The SSRI issue certainly highlights the importance, and I know there were tests done on those—many of them were inconclusive with younger children and adolescents particularly. But pediatric testing is something that is very, very important, and I presume you agree with that, as well.

Dr. CRAWFORD. I do agree completely.

Senator DODD. And we will talk about expanding the opportunities for pediatric testing.

Dr. CRAWFORD. We are, and we are going to make sure that both on the exclusive side, where there is a patent, and off-patent that we get the same kind of penetration with those firms as they move forward with labeling.

Senator DODD. Let me come back, I know Senator Mikulski, and she had to leave, and I believe Senator Kennedy, certainly Senator Jeffords in the time I was sitting here, talked about the Office of Drug Safety issue. I am going to be a little bit repetitive here, but

I think it is an important issue, and maybe because I am going back over some of this ground again you get some sense of the importance of this issue.

Senator Grassley and I are planning to introduce as I think you are aware—you and I talked on the phone about this——

Dr. CRAWFORD. We did, yes.

Senator DODD. Legislation to create an independent office within FDA to deal with this issue, and you have expressed your views on this a bit already, but I want to continue to make the point to you here.

Let me, as a backdrop, underscore the point that I am sure all of my colleagues have made here. There is nothing like, when you travel around the world and you go out to buy a product someplace in a store in some foreign country and you see on the shelves, "product approved by the FDA." It is the gold standard, still all over the world. That Good Housekeeping Seal of Approval, that this is a product approved by the Food and Drug Administration of the United States, is incredibly important. And obviously, the issues of Vioxx and the SSRI issues and so forth have raised some serious questions.

So as a backdrop to all of this, and I know you feel this way, as well, but I think it is important to be stated here. We really need to make sure that the reputation of this incredible agency that has done so much to put products in the marketplace that have changed people's lives, extended lives, the quality of lives, as well as protecting people from adverse effects of those products that either are approved or those that shouldn't be approved. So there is a tremendously important critical moment we are at here and I am worried that if we don't get this right in the next couple of years, we could see this gold standard be diminished, and then I think we all suffer terribly as a result of that.

So this Office of Drug Safety idea, the idea of making it more independent so that you don't have to go through a 2-year period with Vioxx where literally tens of thousands of people have lost their lives—and I don't blame the FDA for this, but the ability to have someone that can say, outside of the group that has approved the product in the first instance, to make the decision to take it off the shelf, we think is very, very important.

I wonder if you would share just sort of your general thoughts about this. Is there a sense, and let me just give you an opportunity, I presume there is, but a sense of this FDA standard approval being tarnished a bit by all of this, and what steps do you envision, maybe going a little bit further, to make the point that we are not going to allow this to happen, particularly on your watch?

Dr. CRAWFORD. We are not going to allow it to happen. I don't think we have been tarnished. Checking with our international colleagues and also checking with various polls that are done, it looks like the American people have full confidence in the FDA.

I don't want to see it happen, though, and you are absolutely correct. That specter has been raised over the past few months and I pledge to you that I will do everything in my power to stem the tide by doing the right thing and I look forward to working with

you, Senator Grassley, and whoever else has some legislation in this regard.

I am open to solutions. I don't want on my watch FDA to be tarnished in any sense. I want us to move forward strongly and better than ever. We have some special challenges with the 500 percent increase in food trade and now a great increase in drug trade that is occurring. However, an independent Office of Drug Safety is something I am certainly open to discuss and I look forward to spending time with you on that.

Senator DODD. Obviously, we are talking to people, and Senator Enzi and Senator Kennedy and others are interested, as well, on the subject matter.

There was an internal study, as you know, conducted by the Health and Human Services Office of the Inspector General in 2002—I know you are aware of this—that revealed that approximately one-fifth of drug reviewers had been pressured to approve a drug despite concerns about safety, efficacy, or quality. In addition, more than one-third said, and I am quoting, "they were not at all or only somewhat confident that initial decisions of the Center for Drug Evaluation and Research adequately assessed the safety."

That seems to have been the case with Dr. Mosholder, if I am pronouncing his name correctly, when he had data to suggest that certain anti-depressants might increase the risk of suicide in children and adolescents. And as with Dr. David Graham when he had data to suggest that Vioxx was connected with cardiovascular problems.

I wonder if you might just, whether or not you would agree that mistakes were made in the handling of both of these two cases or not.

Dr. CRAWFORD. Well, I came on board when that report came out that you mentioned from the Office of the Inspector General and it was my responsibility to try to make sure that that part was fixed and remedied, and what we did was we put more funding in the Office of Drug Safety, gave them a bit more authority, and we continue to do that.

I think that the key to it is my own personal involvement. I mean, I have got—nothing is more important at FDA right now than this drug safety issue and I will continue to monitor it and we will also continue to enhance not only the number of personnel and the resources in the Office of Drug Safety, but the kinds of people. We need these epidemiologists that I mentioned earlier and we are building them up. I am going to monitor it very closely myself because if there is one thing that we are vulnerable in right now in terms of our reputation worldwide, that is it.

Senator DODD. Yes, you have hit it on the head. The transparency issue is related to this, obviously, and I would love at some point to be able to talk with you about that.

Mr. Chairman, I appreciate this and we will look forward to working with you on this, because obviously, doing it right is going to be tremendously important. The point that Senator Mikulski raised, and again, you are overburdened as it is, but that transparency issue, that sense of competence is going to be tremendously important, that whatever the entity is that we create, that

there is going to be a sense they can act and act intelligently when these matters arise. So I look forward to working with you.

I should mention, as well, Senator Grassley and I also introduced legislation dealing with clinical trials, which I know you have an interest in and we want to work with you on that, as well.

Dr. CRAWFORD. Absolutely.

Senator DODD. Thank you, Mr. Chairman, very much. I appreciate it very much.

The CHAIRMAN. Thank you, and since I allowed an average of two-and-a-half extra minutes per person on this side for questioning, is there one last quick question from either of you?

Senator HATCH. I won't ask a question, because I know the questioning is over for now, but I want to tell you how strongly I support you for this position.

Dr. CRAWFORD. Thank you, sir.

Senator HATCH. I know you will do a good job, but one last thing: Congress has appropriated funds to support a national inventory of high-quality cord blood units, an especially important resource for ethnic minority patients. It is my understanding the FDA has been collecting data on the therapeutic use of cord blood for some time, yet it has not issued regulations that would address the need for a set of standards or licensing to assure that cord blood units collected for therapeutic use are meeting the high quality expected of a biological product.

So what I would like you to think about under your leadership is to a way of assuring the quality and safety of cord blood and issuing regulations as soon as you can. Cord blood looks to me as though it may have remarkable stem cell advantages over adult stem cells and maybe help us resolve some of the conflicts and problems with regard to the whole embryonic stem cell area, as well.

So I hope you will give some real thought to that. It is important. I think it is important for you to make that a major part of your work. I won't ask you any questions on it, but I just wanted to ask you to really get into that, because what I am studying and what I am reviewing shows some tremendous promise.

Senator DODD. Would my colleague yield on this point?

Senator HATCH. I am happy to.

Senator DODD. I want to totally support Senator Hatch's point on this. Being the father of a 2-week-old, with my first child and second child, we took the cord blood. It is complicated to do this. There are private operators that do it, but a lot of them don't last very long.

Senator HATCH. That is right.

Senator DODD. The ones that do, we used the one out in Berkeley, California, which is a university-associated one, to send the child's cord blood, to go through it so you are part of the test, everything has to be done exactly right. I had to have a person on the phone making sure the packaging was all done properly.

But Senator Hatch is absolutely correct in this. There are some tremendous opportunities, I think, with the cord blood issue, much more so than people even thought a few years ago. I would like to support you in every effort you make along those lines.

Senator HATCH. Thank you, and I appreciate you jumping on that, because——

Senator DODD. It is a great point. Thanks.

Senator HATCH. Well, thanks. Thank you. We support you strongly.

The CHAIRMAN. Senator Isakson.

Senator ISAKSON. I will be quick, Mr. Chairman, but I want to go back to the obesity and the labeling thing. What percentage of that flier that I get when I get a prescription filled, the thing with the real small print, what percentage of all that information is dictated by the FDA after the approval of a drug?

Dr. CRAWFORD. You mean what is on the——

Senator ISAKSON. Just as a guess.

Dr. CRAWFORD. [continuing]. On the bottle itself?

Senator ISAKSON. Well, not just the bottle, but the inside stuff.

Dr. CRAWFORD. A hundred percent.

Senator ISAKSON. A hundred percent?

Dr. CRAWFORD. Mm-hmm.

Senator ISAKSON. OK. My comment is this, and I mean this very sincerely. I respect what Senator Harkin said about labeling on prepared foods and about the issue of obesity, but our first responsibility is to instill more personal responsibility in people than self-satisfy ourselves that we can label them into better health habits, particularly in something like the food issue.

CDC in Atlanta is doing a marvelous job, I think, on the obesity issue and you all are working in concert with them, but before we succumb to making ourselves feel good that we get into the mandatory labeling of menus as addressing the problem of obesity, let us do more to inform people so they make good decisions for themselves as advocates in the public sector, and that is the only thing I wanted to say, Mr. Chairman.

The CHAIRMAN. Thank you very much.

I appreciate Dr. Crawford's testimony. Unless there is objection, we will end the rounds of oral questions, but we leave it open for written questions.

I would mention that in regard—there was a lot of emphasis on an independent safety panel, a lot on the independence, and we covered that in one of the FDA hearings that we held. There was a lot of concern by a wide variety of panelists that if it is really independent, people watch ads on television and there are always some things that they ought to watch out for. And if you are in an office where your only job is safety, those may all sound like really bad things, and so you could end the drug if you have total independence. There are a lot of people relying on some of those drugs, even though they know the side effects, even though they know that it has affected people in their own family previously. For pain, they think that it is essential even though they know they will have heart problems from it.

So I am hoping there is some balance, as there always has been in FDA, of realizing that some people actually rely on these things even knowing the consequences. We even talked a little bit about how that affects the clinical trials and at what point ethically you can have people that were not in the actual test group begin to get the medicine.

So I hope everybody will review the results of that hearing and it will provide a little bit of a balance that I think you covered well in your testimony, but we will have some follow-up questions to do that.

Members of the committee may submit questions in writing. Per an agreement between myself and Senator Kennedy, we will be submitting our written requests to Dr. Crawford by Friday, March 18. That is tomorrow. Members will be notified of this, and we ask them to respectfully submit their written questions by that same date. And then, accordingly, it is my understanding that Dr. Crawford will answer the questions before we return from recess.

We will schedule the briefing that was talked about this morning so that to the degree that you can talk about an application prior to action on the application, you can brief us on what the status is and what the complications are.

I want to compliment the staff for, since this is St. Patrick's Day, for using the green tablecloth—which we always use—[Laughter.]

Thank you all very much for your participation and attendance. The hearing is now adjourned.

[Additional material follows:]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF SENATOR CLINTON

Thank you, Chairman Enzi and Senator Kennedy. And thank you to Dr. Crawford for appearing before the HELP Committee this morning.

I know that two of your colleagues—Dr. Sandra Kweder and Dr. Janet Woodcock—have recently appeared before this committee to testify about issues of drug safety, primarily in response to the controversies surrounding Cox-2 drugs and pediatric use of antidepressants. These drug safety controversies occurred during your tenure as Acting Commissioner of the FDA, and, quite frankly, I was disappointed by your response to them. I think that the American public lost a great deal of confidence in the ability of the agency to ensure the safety of their medications.

As someone who has worked to give the FDA the authority to increase the safety of drugs, particularly pediatric drugs, I would like additional assurances that you will use such authority to guarantee the safety and effectiveness of our drug supply.

Today, I will be looking for assurances that you will seek to strengthen the FDA's commitment to drug safety and increase the use of already-existing enforcement tools like the Pediatric Rule.

In addition to drug safety issues, I am concerned about the way that the FDA is letting political considerations interfere with scientific treatment decisions. During your tenure at FDA, you denied an application to make emergency contraception (EC) available for sale over the counter, despite the fact that the FDA's own advisory committees and career professionals at the agency had made such a recommendation.

The *New York Times* reported that several former FDA officials said they had never seen the recommendations of both staff and an advisory committee overruled in such a manner prior to the rejection of this EC application. The notion that politics might have entered into any decision about a drug approval is deeply disturbing and alarming.

During your tenure, the Nation also experienced its third influenza vaccine shortage since 2000, after the British government's drug safety agency closed down a contaminated vaccine manufacturing plant in Liverpool. While the FDA was aware of the problems that existed at this plant prior to the shutdown, it failed to alert the rest of the government about the possibility of a shortage.

Dr. Crawford, the FDA is a demoralized agency. It needs a strong leader with a clear vision of ways to restore its reputation. Today, you have the opportunity to present us with your ideas as to how to improve the FDA. More importantly, you have the opportunity to demonstrate what you have learned from the mistakes that have occurred during your tenure at the FDA, and what actions you will take to keep such mistakes from happening in the future. Our citizens look to the FDA to give its good housekeeping seal of approval. They need to trust that the Agency is looking out for their well being. I'm afraid that the gold standard which FDA has held for so long is in jeopardy. We need real leadership to ensure that our citizens can have faith that decisions being made are

in their best interests. I look forward to hearing your testimony and answers to the committee today.

PREPARED STATEMENT OF SENATOR JEFFORDS

Mr. Chairman, I want to join you in welcoming Dr. Crawford before the HELP Committee. I've had the opportunity to meet with Dr. Crawford, and although there are some serious issues that need to be raised about the agency's ability to meet it's fundamental mission, I fully expect to support his nomination and to vote in favor of his appointment as the new Commissioner of the Food and Drug Administration.

Dr. Crawford, you may be the most important presidential appointee whose nomination this committee will have the opportunity to consider during this Congress. The members of this committee know well of the vital role that the Food and Drug Administration plays in the health and well being of our citizens, and we are also well aware of the impact the agency has on the industries you are charged to regulate.

The FDA also holds a special significance for many of us because of our involvement with passage of the FDA Modernization Act; a measure intended to guide the FDA in its mission to protect the American public. That act emerged after several years of debate over the appropriate role the FDA should have in approving the products it regulates

Many in industry and some in the consumer community argued that the agency was taking too long to approve new life saving medical devices and medicines; that the agency was acting as a roadblock to progress. More recently, new charges are emerging that the FDA is being too lax in its oversight of industry and that some of the products being approved are unsafe. What we need at the agency, and what I hope you will bring with your leadership is a better balance between these competing interests.

I had the privilege of being chairman of this committee when FDAMA passed and I continue to believe that that measure made substantial improvements to the agency. But, I will say again what I said then—I stand ready to work with FDA and my colleagues to ensure that the agency is able to meet its mission.

In some respects I view your, and the agency's, role to that of a traffic cop whose job is not just to stop the bad drivers, but is also to ensure that the good drivers get through unimpeded. This is not an easy task but I expect to hear you tell and convince this committee that you are up to that challenge.

PREPARED STATEMENT OF SENATOR MIKULSKI

Thank you for calling this prompt hearing on the vitally important nomination of Dr. Lester Crawford to be the Commissioner of the Food and Drug Administration (FDA).

The position of FDA Commissioner is critically important to the public health of the United States but it has been vacant for nearly 1 year. I am so pleased that Maryland is home to the FDA. FDA makes sure that safe and effective drugs, biologics, and devices come to the market to help save lives, help patients live longer, and help improve the quality of their lives.

FDA also plays a critical role in ensuring the safety and security of our country's food supply. FDA affects the lives of Americans everyday whether it is a pill you take or the food you eat. FDA-regulated products account for about 25 cents of every consumer dollar spent—a total of $1 trillion per year.

Criteria—My criteria for looking at each nomination are competence, integrity, and commitment to the mission of the agency.

I look forward to hearing from Dr. Crawford today about his vision and qualifications.

Competence—As head of the agency that regulates everything from food to the latest medication for heart disease, the FDA Commissioner must be knowledgeable about medicine and science. Management expertise is essential to effectively run FDA without red tape and bureaucracy.

FDA has over 9,000 dedicated employees. FDA has a budget of close to $1.8 billion and about 9,000 employees. Strong management skills and leadership to ensure that FDA can efficiently and effectively carry out its many responsibilities.

Recruiting and retaining the best and brightest employees at FDA is especially important as products reviewed by FDA become increasingly more complex and advanced.

Integrity—Well respected by patient/consumer groups and the industry so that FDA commands the respect of the public and the industry it regulates.

Honest broker and listener who can make tough calls on contentious issues.

Commitment to the Mission of the Agency—Decisions based on sound science and public health, not ideology. Maintaining the FDA gold standard of safety and efficacy. Ensuring timely approval of new therapies to save lives, help patients live longer, and improve their quality of life. Continual improvement in mammography quality and ensuring access to new screening and detection tools. Ensuring safety of our food supply.

Closing

While Dr. Crawford may have an unusual background for Commissioner of FDA. He could also bring a fresh perspective with new thinking and new ideas. I will evaluate Dr. Crawford, as I do each and every nominee, based on his competence, integrity, and commitment to the mission of the agency. Thank you again, Mr. Chairman, for convening this hearing on this critically important nomination to the health of this country.

LETTERS OF CONCERN

March 4, 2005.

DEAR SENATOR: We write to share our serious concerns about the President's nomination of Dr. Lester Crawford to serve as Commissioner of the U.S. Food and Drug Administration. The continued delay on a decision to make Plan B emergency contraception available without a prescription undermines public confidence in the Acting Commissioner's commitment to promoting the public's health and welfare.

Overwhelming scientific evidence shows that making emergency contraception easier to obtain would substantially reduce the incidence of unintended pregnancy and need for abortion. A recent study published in the Journal of the American Medical Association provides the latest evidence that Plan B should be made readily

available by demonstrating that using emergency contraception does not lead to more risky sexual behavior or other health risks for women.

In December 2003, following review of hundreds of studies, the FDA independent advisory committees voted 23–4 to approve Plan B for over-the-counter status. Based on FDA guidelines, a decision was anticipated in February 2004. Following a 90-day delay, on May 6, 2004 the FDA issued a non-approvable letter to Barr Pharmaceuticals, citing the lack of data concerning use in adolescents under age 16. The final decision was made by Acting Center Director Dr. Steven Galson, contrary to the recommendations of his own professional staff.

Barr Pharmaceuticals responded in good faith with a revised application supporting the marketing of Plan B as a prescription-only product for women 15 years of age and younger, and a non-prescription product for women 16 years of age and older. A decision was due on January 21, 2005, but instead the agency only gave notice of another delay and provided no reason for delay or date for completion of review.

Each day that this decision is delayed increases the serious health implications for women. The agency needs a leader who will ensure FDA decisions are based on scientific evidence and not political interests. To restore public confidence in the agency's integrity, Dr. Crawford must provide a full account of the decision processes that caused the FDA to go against the recommendations of the review panel and professional staff, share his assessment of the current situation, and provide assurances that a decision will be made on Plan B over-the-counter based totally on science and not politics. Until he provides this information and assurances, we urge you not to confirm him as Commissioner.

Sincerely,

National Partnership for Women and Families,
Reproductive Health Technologies Project.

Organizations: Advocates for Youth; American College of Obstetricians and Gynecologists; American Society for Emergency Contraception; Association of Reproductive Health Professionals; Campaign for Access to Emergency Contraception (Champaign, IL); Center for Reproductive Rights Center for Women Policy Studies; Champaign County Health Care Consumers; Clara Bell Duvall Project, ACLU of Pennsylvania; Family Planning Advocates of New York State; Family Planning Council (Philadelphia, PA) Feminist Majority Foundation; Florida NOW Young Feminist Taskforce; Gainesville Area National Organization for Women; Gainesville Women's Liberation Gynuity Health Projects; Ibis Reproductive Health; Institute for Reproductive Health Access; Massachusetts Emergency Contraception Network; Morning-After Pill Conspiracy; NARAL Pro-Choice America; NARAL Pro-Choice Colorado; NARAL Pro-Choice Massachusetts; NARAL Pro-Choice Texas; National Abortion Federation; National Association of Nurse Practitioners in Women's Health; National Family Planning and Reproductive Health Association; National Latina Institute for Reproductive Health; National Organization for Women; National Women's Health Network; National Women's Law Center; New York State Reproductive Rights Taskforce; People for the American Way; Pharmacy Access Partnership;Physicians for Reproductive Choice and Health; Planned Parenthood Federation of America; Population Connection; Redstockings Allies and Veterans, New York City; Religious Coalition for Reproductive Choice; Sexuality Information and Education Council of the United States (SIECUS); Students for Access to Emergency Contraception (IL); University of Florida Campus NOW; Women's Health Task Force (IL).

Individuals: Philip Corfman, M.D. (Bethesda, MD); Betty Farrell, CNM, MPH (Brooklyn, NY); Diana Romero, Ph.D. (Mailman School of Public Health, Columbia University.

CONSUMERS UNION,
CONSUMER FEDERATION OF AMERICA,
U.S. PUBLIC INTEREST RESEARCH GROUP,
March 15, 2005.

Hon. MICHAEL ENZI,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510.

DEAR MR. CHAIRMAN: This Thursday, the Senate Committee on Health, Education, Labor, and Pensions will consider the nomination of Dr. Lester Crawford to be the Commissioner of the Food and Drug Administration.

Before voting on his nomination, we urge you to ask, and get answers to, important questions about Dr. Crawford's record at FDA and his plans to achieve meaningful drug safety reform as Commissioner.

Dr. Crawford has served at the helm of FDA, as either Deputy or Acting Commissioner, for the last 3 years. During that time, the agency's high profile missteps and failure to take timely action to protect consumers from unreasonable drug safety risks have raised serious questions about his leadership, his ability to manage interagency conflicts and willingness to act in the best interest of consumers.

Dr. Crawford and Secretary of Health and Human Services Michael Leavitt recently announced the creation of an independent drug safety oversight board at FDA. Unfortunately the move offers no true substantive reform and bears little resemblance to the "emboldened new vision" it is supposed to represent. The Drug Safety Board does nothing to improve the agency's weak regulatory capacity or to address the inherent internal conflicts of interest that prevent FDA from identifying unreasonable safety risks and taking timely action to protect the public from them.

The agency's recent high-profile failings on the safety of widely used painkillers and antidepressants are symptoms of a larger problem that can only be resolved with critically needed new laws. First, FDA lacks authority to require drug companies to conduct safety studies once a drug is approved and to require timely protective action when unreasonable risks arise.

Second, the organizational structure of the FDA suffers from inherent conflicts of interest by allowing reviewers in the Office of New Drugs to make important determinations about the post-market safety of drugs they approve. In 2004, these conflicts discouraged public release of findings by reviewers in the Office of Drug Safety, who have no authority to take action on their own, nor even the right to ensure that FDA advisory committees, doctors and patients have access to their findings.

And third, patients and doctors don't have access to all clinical trial results, both good and bad, for widely prescribed medications. Meanwhile, drug makers are free to publish the positive results in medical journals, while downplaying less favorable findings.

In the face of widely publicized regulatory shortcomings at FDA, Dr. Crawford has not acknowledged the need for substantive changes to increase the FDA's ability to protect consumers.

Though he claims to have a bold vision for the FDA, the question is whether or not Dr. Crawford is committed to achieving substantive rather than symbolic drug safety reform. Such reforms must include full public disclosure of all clinical trial results, greater independence for the Office of Drug Safety, stronger authority to require additional studies on the safety of approved drugs, and increased capacity to take action to mitigate unreasonable risks when they arise.

Before the Senate HELP Committee reports his nomination, we urge you to compel Dr. Crawford to enumerate steps he will take to change the agency's culture and achieve meaningful administrative and legislative reforms to FDA's drug safety system.

Sincerely,

JEANNINE KENNEY,
Senior Policy Analyst,
Consumers Union.

TRAVIS PLUNKETT,
Legislative Director,
Consumer Federation of America.

LINDSEY JOHNSON,
Consumer Advocate,
U.S. Public Interest Research Group.

ASSISTANT SECRETARY FOR AGING
DEPARTMENT OF HEALTH AND HUMAN SERVICES
ADMINISTRATION ON AGING
WASHINGTON, D.C. 20201

2/17/05

Hon. Designate FDA Commissioner

Dear Dr. Crawford:

I was delighted to hear of your nomination for Commissioner of FDA by President Bush.

We wish you a speedy confirmation process. Look forward to serving alongside of you at HHS.

I am attaching a clipping from the Hawaii Herald I picked up while there of your announcement.

Good Luck!

Josefina Carbonell

1100

A. Gilbert, 464
THE WHITE HOUSE

Dr. Lester Crawford
U.S. Department of Health and Human Services
Parklawn Building, 5600 Fishers Lane, Room 14-71,
Rockville, MD 20857

FDA MAIL FACILITY
SCREENED

FEB 2 3 2005

THE WHITE HOUSE

02-23-05 03:56 RCVD

Les,

I wanted to send you a short note to congratulate you on your nomination. You have done a great job over these last few years. Your help and counsel during the flu vaccine shortage, and your continuing work on drug safety illustrates you are the right person for the job.

All the best!

Al Gilbert

1114

KENNETH J. HESELWOOD
RUE EMILE BOUILLIOT 2
BE - 1050 BRUSSELS
BELGIUM

23-th February 2005

03-08-05 05:33 RCVD

Dear Dr. CRAWFORD,

I am british with dual belgian nationality, born and raised in Belgium. Father was a british soldier who died when I was seven. Mother is belgian.
I am a retired police chief inspector at 58 because I am ill. I was a city policeman (Brussels) from 1968 to 2002.

I am very interested by the US Food and Drug Administration and I am writing to you, Sir, to congratulate you for your recent appointment as Commissioner of Food and Drugs by President Bush.

I wish you all the best in your new and very important position. I have a very great admiration for your career.

Allow me to wish you all the best for the future.

I have the honour to be,
Dear Dr. CRAWFORD,
your obedient servant.

Kenneth J. Heselwood

3299 K Street, NW, Suite 100, Washington, DC 20007 phone 202.944.6711 fax 202.333.7840 www.focr.org

FRIENDS of CANCER RESEARCH

March 3, 2005

The Honorable Michael B. Enzi
United States Senate
Russell Building 379A
Washington, DC 20510

Dear Senator Enzi:

As Chairperson and President of Friends of Cancer Research, a Washington, DC based non-profit organization dedicated to accelerating the nation's progress toward new technologies for the prevention, detection, and treatment of cancer, we wish to express our strong support for the President's nomination of Dr. Lester Crawford to the post of Commissioner of the Food & Drug Administration.

Dr. Crawford is, indeed, a true friend of cancer research. He understands the needs of our community from a patient perspective and has been one of the leading advocates for closer collaboration between government-based, academic, and pharmaceutical industry research and development. He also has been at the forefront of FDA's long overdue reorganization of the agency's oncology drug review functions.

In addition to our support for Dr. Crawford's nomination, we would like to applaud the thoughtful opening statement you provided during the March 1st HELP hearings entitled "FDA's Drug Approval Process: Up to the Challenge?" As you know, our organization partnered with Nancy Davenport-Ennis of the National Patient Advocate Foundation to present testimony as part of that hearing. She outlined our shared hope that smart FDA reforms will make the agency an even stronger ally in the war against cancer. We know that Les Crawford supports this agenda for change. He is a man of strong character and a voice for thoughtful reform.

Dr. Lester Crawford is a worthy navigator on the 21st century critical path and we strongly call for his speedy confirmation.

Sincerely,

Ellen V. Sigal, Ph.D.
Chair

Marlene A. Malek, RN
President

Alan J. Balch, Ph.D.
Executive Director

MAYO
Mayo Clinical Trial Services

Karen L. Johnson
Director of Regulatory Affairs

3050 Superior Drive NW
Rochester, Minnesota 55901
Voice 507-266-2028 Fax 507-538-0565
Email johnson.karen55@mayo.edu
Web mayoclinicaltrialservices.org

Dr. Les Crawford
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-0001

2/18/05

Dr. Crawford,

I recently saw the notice of your nomination to head the FDA and wanted to offer you my sincere congratulations. I have mixed emotions about your nomination and approval because I fear it will deprive your friends here at Mayo of your delightful company.

Steve Kopecky and I were discussing your nomination and he said, "Les will do an excellent job as Commissioner" and added, "what a thankless job!"

Please know that we appreciate all that you (and everyone) at FDA do on behalf of us, the public. Do let us know if we can

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be of support in any fashion.

I hope whenever your travels bring you to Minnesota, you will stop in and visit us here in Rochester.

All my best wishes for success in your new adventure.

Sincerely,
Karen Johnson
Regulatory Affairs
Mcsi

Hi Dr. Crawford,
Congratulations!
Larry Popke

UNIVERSITY OF GEORGIA ALUMNI ASSOCIATION,
ATHENS, GA 30602–6372,
February 17, 2005.

LESTER M. CRAWFORD,
U.S. Food and Drug Administration,
Rockville, MD 20852.

DEAR DR. CRAWFORD: Congratulations on being named Commissioner of the Food and Drug Administration. I wish you the best as you move forward with your appointment.

On behalf of the University of Georgia Alumni Association, I would like to extend our appreciation for your commitment to excellence. You bring honor to your alma mater.

If I may ever be of service, please do not hesitate to contact me.

Sincerely,

DEBORAH A. DIETZLER,
Executive Director.

AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS®,
BETHESDA, MD 20814,
February 16, 2005.

Hon. MICHAEL B. ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510.

DEAR CHAIRMAN ENZI: The American Society of Health-System Pharmacists (ASHP) is writing today to applaud the President's nomination of Lester M. Crawford to be Commissioner of the Food and Drug Administration (FDA). For more than 60 years, ASHP has helped pharmacists who practice in hospitals and health systems improve medication use and enhance patient safety. The Society's 30,000 members include pharmacists and pharmacy technicians who practice in inpatient, outpatient, home-care, and long-term-care settings, as well as pharmacy students.

The FDA has the enormous task of safeguarding our Nation's drug supply, ensuring that safe and effective products reach the market in a timely manner, monitoring products for continued safety after they are in use, and securing accurate,

science-based information about these products for consumers. Despite extraordinary efforts on the part of the FDA, more can and should be done. As a result, the FDA has come under significant fire in recent times to strengthen its focus on public health and safety.

The confirmation of a permanent FDA commissioner is an important step in positioning the FDA to fulfill its role. Dr. Crawford has exhibited the knowledge and leadership qualities that make him the right person for the job. During the confirmation process, we hope that you will request that Dr. Crawford put forward his plan for achieving this important goal. ASHP is particularly interested in FDA plans to enhance confidence in the integrity of the drug products reaching the pharmacy, increase drug safety information available to health professionals and the public, and facilitate the exchange of information to providers in times of product shortages or public health emergencies.

ASHP looks forward to continuing our work with Dr. Crawford in his new position. We encourage the committee and the Senate to confirm him quickly. PIease feel free to contact us at any time if we can be of assistance. Kathleen Cantwell, ASHP's Director of Federal Legislative Affairs and Government Affairs Counsel can be reached via e-mail at kcantwell@ashp.org or by phone at 301–664–8710.

Sincerely,

HENRI R. MANASSE, JR.,
PH.D., SC.D.,
Executive Vice President and
Chief Executive Officer.

NATIONAL RESTAURANT ASSOCIATION,
March 16, 2005.

Committee on Health, Education, Labor and Pensions,
U.S. Senate.

DEAR CHAIRMAN ENZI: I am writing to express the support of the National Restaurant Association for Dr. Lester Crawford, the nominee for Commissioner of the Food and Drug Administration. We hope the Senate Health Committee, without hesitation, will approve Dr. Crawford.

As Administrator of the USDA's Food Safety and Inspection Service, Dr. Crawford has an unique perspective on the important oversight role that both the FDA and USDA provide in maintaining a safe food supply—this is of the utmost importance to the National Restaurant Association.

In addition, Dr. Crawford's experience in life science, coupled with a laudable record of public service focused on those issues makes him the ideal candidate for this position. His previous roles as Acting FDA Commissioner, and Director for the FDA's Center for Veterinary Medicine, give him an unprecedented familiarity with roles and responsibilities of the FDA.

His commendable track record of successes in a variety of settings is ample evidence of Dr. Crawford's capabilities. We hope that the members of the Senate Health Committee, and the Senate overall, will confirm Dr. Crawford as FDA Commissioner.

Sincerely,

STEVEN C. ANDERSON,
President & CEO.

STROCK-WISE ANIMAL CLINIC P.A.,
CHARLESTON, SC 29412,
February 28, 2005.

DR. LESTER CRAWFORD,
U.S. Food and Drug Administration,
Rockville, MD 20857–0001.

DR. LESTER CRAWFORD: Congratualtions on your appointment to Commissioner of the FDA, I have been following your many accomplishments in the city by the Potomac and wanted to tell you what a great representative of the veterinary profession you have been throughout your professional career. If you are ever in Charleston, SC, please look me up.

I spoke with Roger Wilbur the other day; he sends his regards and congratulations also. Keep up the good work.

WILBUR WISE.

THE 60 PLUS ASSOCIATION,
ARLINGTON, VA 22209,
March 16, 2005.

Hon. MICHAEL B. ENZI,
U.S. Senate,
Washington, D.C. 20510–5004.

DEAR SENATOR ENZI: I am writing to express my support for Dr. Lester Crawford as the next Commissioner of the Food and Drug Administration. Dr. Crawford brings to the post a successful 1-year tenure as Acting Commissioner of the FDA as well as unique credentials and noteworthy achievements that qualify him for leadership of the agency's many and varied responsibilities.

As you may know, Dr. Crawford previously led the FDA as Deputy Commissioner as the agency stepped up to counter the threat of bioterrorism. He also served the FDA two other times in the past 30 years, as director of the agency's Center for Veterinary Medicine, from 1978 to 1980 and again from 1982 to 1985. Dr. Crawford's credentials are unmatched. He has dedicated his career to promoting safer products for the public; his vast experience positions him well to lead the agency going forward.

Today, the FDA's plate is full, brimming with challenges that when successfully accomplished will help 21st century Americans live longer, healthier and happier lives. Dr. Crawford has already demonstrated his leadership skills and his ability to deliver on the agency's core objectives, as measured by the FDA's unprecedented achievements toward its comprehensive strategic action plan.

In 2004, thanks to Dr. Crawford's inspired leadership, the FDA improved consumer protection by employing new bioterrorism countermeasures. The agency created regulations for safer dietary supplements. By applying innovative technologies, the agency bolstered protections against medical errors. And the FDA gave consumers the keys for improving their own health by educating people with better information about the foods they eat and the medicines they take. Of paramount importance to the 5 million senior citizens I represent, in 2004 the FDA gave citizens faster access to safe and affordable medicines.

But there's much more to be done. The FDA estimates it has completed about one-third of the work detailed in its strategic action plan. The agency has committed to completing three-quarters of the remaining work this year. A tall order, yes, but Dr. Crawford is the right leader at the right time, one who can focus the FDA's work and ensure that the FDA is not given burdensome responsibilities outside of its core mission that would dilute its purpose.

For example, the FDA has worked hard to reduce the time and expense of new drug approvals, steadily increasing the speed of its processes since the 1990s. But more improvements are needed, as the demand for safe, fast and affordable medication escalates, especially among seniors. Companies today may spend as much as $800 million to bring a new drug to market. That cost is prohibitive and discourages innovation, a problem that must be resolved.

In its role as health educator, the FDA should teach the American public, seniors in particular, about current discounts for prescription drugs. Discounts are available but not yet well understood by citizens. If the FDA were to leverage its credibility as the Nation's public health agency and primary consumer protection agency, it could launch an information campaign to advise citizens the best ways to avail themselves of the best prices on prescription medicines, and simultaneously cool down the drug reimportation issue.

Dr. Crawford's experience in regulating medical, agricultural and food product safety will serve well the FDA and the Nation. We welcome his vision, focus and leadership on the agency's fundamental imperatives, and hope that you will approve his nomination as the next Commissioner of the Food and Drug Administration.

60 Plus is an 11-year-old nonpartisan group with a less government, less taxes approach to seniors' issues. 60 Plus has become one of the fastest growing seniors groups in the country, doubling then tripling its support in the past year. 60 Plus now calls on support from nearly 4.5 million citizen lobbyists to print and mail millions of letters and petitions. 60 Plus publishes a newsletter, SENIOR VOICE, and a SCORECARD, bestowing a GUARDIAN OF SENIORS' RIGHTS award on lawmakers in both parties who vote "pro-senior." 60 Plus has been called "not only an increasingly influential lobbying group for the elderly," but also " the conservative alternative to the AARP.

Sincerely,

JIM MARTIN,
President.

UNIVERSITY OF FLORIDA,
COLLEGE OF VETERINARY MEDICINE,
GAINSVILLE, FL 32610–0136,
February 25, 2005.

DR. LESTER CRAWFORD,
U.S. Food and Drug Administration,
Department of Health and Human Services,
Rockville, MD 20857.

DEAR DR. CRAWFORD: Congratulations! I am excited that you were nominated by President George Bush for the position of Commissioner of the Food and Drug Administration. This is a tremendous accomplishment and demonstrates your hard work and dedication to our Nation. I am sure President Bush made a very wise choice and that you will excel in your new role as Commissioner.

Please accept my congratulations on your nomination and my very best wishes for your continuing success.

Sincerely,

DR. ELEANOR GREEN,
DVM, Dipl DACVIM, Dipl DABVP,
Professor and Chair, Chief of Staff.

ASSOCIATION OF AMERICAN VETERINARY MEDICAL COLLEGES,
WASHINGTON, D.C. 20005–3536,
March 7, 2005.

Hon. MICHAEL B. ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510.

DEAR MR. CHAIRMAN: The Association of American Veterinary Medical Colleges strongly supports President Bush's nomination of Dr. Lester M. Crawford to be Commissioner of the Food and Drug Administration. Dr. Crawford's unequaled experience, including his current tenure as Acting Commissioner and his previous positions as Deputy Commissioner and Director of the FDA's Center for Veterinary Medicine, make him eminently qualified for this position.

Dr. Crawford is one of the Nation's preeminent scientists and a world renowned leader in the veterinary medical profession. His recent election to the Institute of Medicine is evidence of his significant contributions to the advancement of the medical sciences and public health. In addition, Dr. Crawford's extensive experience in achieving cooperation and communication among numerous Federal Agencies and private organizations underscores his qualification for high public office.

The FDA is facing unprecedented challenges in ensuring the safety of foods, drugs and medical devices for all Americans. It is imperative to name a Commissioner with proven leadership ability and impeccable scientific acumen. Dr. Crawford embodies these traits and his appointment would provide the proper scientific basis of operation and exceptional communication skills in the position.

On behalf of the Nation's 28 colleges of veterinary medicine, the AAVMC urges the Senate to confirm Dr. Crawford's appointment as FDA Commissioner without delay.

Sincerely,

LAWRENCE E. HEIDER, DVM, DACVPM,
Executive Director.

CANADIAN FOOD INSPECTION AGENCY,
February 23, 2005.

DR. LESTER M. CRAWFORD,
Commissioner,
Department of Health & Human Services,
Food and Drug Administration,
Rockville, MD 20857.

DEAR LESTER: This is just a quick note to congratulate you on your appointment as Commissioner. The task will be a difficult one but I am certain you will do very well.

The follow-up to our Argentina PAHO Veterinary Project continues—next session will be in June 2005. Enclosed is a paper which Enrique collaborated on. I am sure you will be interested in the recommendations.

Kind Regards,

ANNE MACKENZIE,
Science Advisor, Science Branch,
Canadian Food Inspection Agency.

RETIRESAFE,
OAKTON, VA 22124.
March 15, 2005.

Hon. MICHAEL B. ENZI,
Chairman,
Hon. EDWARD M. KENNEDY,
Ranking Minority Member,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC 20510.

DEAR SENATOR ENZI AND SENATOR KENNEDY: On behalf of RetireSafe's 300,000 senior citizen supporters across America, I write to express our strong support for the nomination of Dr. Lester Crawford, Jr. to be the next Commissioner of the U.S. Food and Drug Administration (FDA). We believe the older Americans we represent, and the Nation as a whole, will be extremely well served by Dr. Crawford in his new role as FDA Commissioner. RetireSafe applauds Dr. Crawford's appointment by President Bush, and urges your swift confirmation of his nomination to this critical post.

Today, the FDA faces a host of challenges, as well as an expansion of responsibilities. It is vitally important that this agency have the benefit of a strong, experienced leader. Dr. Crawford, now serving as Acting Commissioner of the FDA, is more than qualified to fill that need. He is truly a champion of both food and drug safety, exactly the kind of individual FDA needs at the helm. This is evidenced by Dr. Crawford's work as an advisor to the World Health Organization and the United Nations, and as a leader in mandatory nutrition labeling and the control of chemical and microbiological contaminants of food.

Dr. Crawford's prior service at the FDA, as the Administrator of the Food Safety and Inspection Service (USDA), as Chair of the Physiology-Pharmacology Department at the University of Georgia, and as Director of the Center for Food and Nutrition Policy at Georgetown University and at Virginia Tech, all indicate that he is a person superbly qualified to head the FDA. As a Member of the National Academy of Science, a Fellow of the Royal Society of Medicine, and a Fellow of the International Society of Food Science and Technology, Dr. Crawford is very well respected in the scientific community.

With these outstanding qualifications, Dr. Lester Crawford is an excellent choice to serve as the Commissioner of the FDA. RetireSafe urges your strong support of Dr. Crawford, and the swiftest possible confirmation of his nomination.

Sincerely,

CHARLES G. HARDIN,
President.

LUPUS FOUNDATION OF AMERICA, INC.,
WASHINGTON, D.C. 20036,
March 16, 2005.

Hon. MIKE ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510.

DEAR MR. CHAIRMAN: On behalf of the Lupus Foundation of America, which represents the more than 1.5 million Americans with the disease lupus, their families and their health professionals, we are writing to express our enthusiastic support for the confirmation of Dr. Lester M. Crawford as Commissioner of the U.S. Food and Drug Administration (FDA). As Acting Commissioner, Dr. Crawford's focused

leadership has served the Agency and the Nation well during this period of transition.

While many national nonprofit voluntary health organizations have reason to provide input regarding this important position, the Lupus Foundation of America has a unique interest in the individual who will be confirmed by the Senate. As you may know, the FDA has not approved a new lupus medication in nearly 40 years. In recent years, drug development for lupus has entered a critical period in which an increasing number of biotechnology and pharmaceutical companies are developing new therapies for lupus. For individuals with lupus, the decisions of the FDA will have a great impact on their quality of life and survival.

Dr. Crawford has included lupus among the diseases that are part of the FDA's Critical Path Initiative that seeks to address unmet medical needs. Additionally, the Agency is preparing to release the first-ever industry guidance document on lupus. Under Dr. Crawford's on-going leadership, we believe the FDA will continue to take steps to ensure that patients with lupus will soon have access to new life-saving medicines aimed at bringing the disease under control. We applaud these efforts and look forward to working with him.

We urge you to confirm Dr. Crawford as the next Commissioner of the U.S. Food and Drug Administration. Thank you for your consideration of our views. Please let us know if we can be of assistance on this issue or any other matters.

Sincerely,

SANDRA C. RAYMOND,
President & CEO.

WOMENHEART,
WASHINGTON, D.C. 20006,
February 15, 2005.

WOMENHEART ENDORSES APPOINTMENT OF LESTER CRAWFORD AS FDA COMMISSIONER

Washington, D.C. (February 15)—WomenHeart: the National Coalition for Women and Heart Disease applauds President Bush's selection of Lester Crawford as the new Food and Drug Administration (FDA) Commissioner. It also urges Congress to swiftly approve his appointment.

"Dr. Crawford has many years of experience at FDA safeguarding the Nation's prescription drug and medical device approval processes, as well as our food supply," said Nancy Loving, WomenHeart's executive director. "We have worked very well with him on many important patient safety issues, including the need to include more women in clinical trials. He is an exceptional public servant."

Crawford, she noted, supported the Bioshield Act that ensured rapid FDA action for medical technologies that could improve the Nation's defense against bioterrorism threats and also efficiently secured sources to provide added flu vaccine in the 2004/2005 flu season.

WomenHeart is the Nation's only patient advocacy organization serving the 8,000,000 American women living with heart disease and provides them support, information and advocacy services. It is a public charity headquartered in Washington, D.C. Visit online at www.womenheart.org.

PAN AMERICAN HEALTH ORGANIZATION,
WASHINGTON, D.C. 20037–2895,
February 18, 2005.

LESTER CRAWFORD, D.V.M., PH.D.,
Acting Commissioner,
U.S. Food and Drug Administration (FDA),
Rockville, MD, 20857–1706.

DEAR DR. CRAWFORD: I am writing to congratulate you on your nomination as Commissioner of the Food and Drug Administration. Your advice and support of the Veterinary Public Health Program in PAHO has been greatly valued over the years, and I have also very much enjoyed our personal discussions.

It is a pleasure to see this recognition of your abilities. Best wishes for successful nomination hearings and subsequent work in your new role.

Sincerely,

STEPHEN CORBER, M.D.,
Area Manager,
Disease Prevention and Control.

PAN AMERICAN HEALTH ORGANIZATION,
WASHINGTON, D.C. 20037–2895,
February 18, 2005.

LESTER M. CRAWFORD, D.V.M., PH.D.,
Commissioner-Designate,
U.S. Food and Drug Administration,
Rockville, MD, 20557–1706.

DEAR DR. CRAWFORD: I wish to congratulate you on your recent nomination as Commissioner of the United States Food and Drug Administration (USFDA) by President George W. Bush.

I share the opinion of the Health and Human Services Secretary, Mr. Mike Leavitt, that you are "an outstanding choice" for the post. I am highly honored to have the head of one of the most important and prestigious U.S. health agencies as a friend who has provided steadfast advice to the Pan American Health Organization/World Health Organization (PAHO/WHO).

Please accept my best wishes for continued success in your new position.

Sincerely yours,

MIRTA ROSES PERIAGO,
Director.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY,
BEDFORD, MA 01730 USA,
February 26, 2005.

LESTER M. CRAWFORD, D.V.M., PH.D.,
Office of the Commissioner,
Food and Drug Administration,
Washington, D.C. 20204.

DEAR DOCTOR CRAWFORD: I wish to congratulate you on your many accomplishments and superb service to the government and society in general over the many years since you left the "lovliest village" of the plains in Auburn. Particularly significant is the most recent appointment at the FDA, a confirmation of your commitment to the protection and improvement of the health and well-being of all of us citizens. In all of the many assignments you have had you have brought, among other things, wisdom, integrity, and humor to sometimes difficult situations. For this, I for one, and for the entire Veterinary Profession in general thank you.

One event which affected me personally and which I've not forgotten was a meeting you were chairing somewhere in the western United States in the late 1970s. I presented the results on nitrate/nitrite studies conducted at MIT under contract to the FDA. Members of the pork producers in the audience was ready to tar and feather me for suggesting that the food industry might do as well with a little less nitrates and nitrites in our foods. You saved me from that rather miserable and unfortunate event and for that I have been eternally grateful.

I look forward to following your continuing remarkable career and to observe how you grapple with FDA problems, especially with what sometimes seems to be a pharmaceutical industry out of control. I've worked with the industry all of my active career and came to recognize many of their problems. However, if I were limited to only one suggestion as to how to improve the current situation in that regard, it would be to reduce the amount of direct to consumer advertising; this probably contributes more than any other single action to problems now under consideration by the Agency (i.e., cox-2 pain killers). As our old Professor, Will Bailey would say "you've done us proud." Keep up the good work and my best wishes.

Sincerely,

PAUL M. NEWBERNE,
D.V.M. M.Sc., Ph.D.,
Professor Emeritus,
Nutritional Pathology.

HEALTH CANADA,
OTTAWA, ONTARIO K1A 0L2,
February 17, 2005.

DR. LESTER M. CRAWFORD, D.V.M., PH.D.,
Acting Commissioner,
Food and Drug Administration,
Rockville, MD 20857–0001.

DEAR DR. CRAWFORD: On behalf of the Health Products and Food Branch of Health Canada, I would like to congratulate you on your nomination as FDA Commissioner, a position of enormous importance in the United States.

You come to this position with a very distinguished and outstanding career, and the FDA is fortunate to have your leadership in this position.We welcome your nomination and believe that you will continue to bring to the FDA programs, the vision and energy that had made you a success as FDA's Acting Commissioner over the past years.

Once again, I offer my sincere congratulations to you and look forward to a continued collaboration between our two organizations on a number of issues, and want you to know how much we have appreciated your leadership, support and insights in the past.

Yours sincerely,

DIANE C. GORMAN,
Assistant Deputy Minister.

THE TIPTON GROUP, INC.,
WASHINGTON, D.C. 20003,
February 23, 2005.

DR. LESTER M. CRAWFORD,
Acting Commissioner,
Food and Drug Administration,
Rockville, MD 20857.

DEAR LES: Congratulations! I am most pleased that President Bush has nominated you to be Commissioner of the Food and Drug Administration. In my view, you are clearly the correct choice, and you should have been nominated to the position much sooner.

I am already telling my friends on the Hill that you are the right person to take over leadership of FDA. If I can ever be of help to you on any specific issues or with Members of Congress, I would like the opportunity to try.

Again, my sincerest congratulations!

My best regards,

E. LINWOOD TIPTON,
Chairman & CEO.

FOOD MARKETING INSTITUTE,
WASHINGTON, D.C. 20005–5701,
March 16, 2005.

Senator MIKE ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510–6300.

CHAIRMAN ENZI: The Food Marketing Institute would like to offer its support for the nomination of Dr. Lester Crawford to be Commissioner of the Food and Drug Administration (FDA). FMI works with FDA on issues related to food safety, food security and nutrition on behalf of its 1,500 member companies—food retailers and wholesalers—in the United States and around the world. FMI's U.S. members—large multi-store chains, regional firms and independent supermarkets—operate approximately 26,000 retail food stores with a combined annual sales volume of $340 billion. Its international membership includes 200 companies from 50 countries.

Because of Dr. Crawford's present position as Acting Commissioner, as well as his previous experience as FDA's deputy commissioner, he would bring an unprecedented depth of knowledge to the job. His past experience as the U.S. Department of Agriculture's Food Safety Inspection Service (FSIS) Administrator and his tenure

at FDA guarantee that he understands the need for uniformity in food safety policy as well as how vital it is for FDA's Center for Food Safety and Applied Nutrition to work in tandem with its sister food safety department, FSIS.

Dr. Crawford also brings a unique perspective to the job of commissioner as he has a global view that he applies to U.S. food policy. He has seen firsthand how the amount of food products imported into the U.S. has increased and understands that developing food policy that applies only within our borders is no longer viable. His experience gives him the ability to see things with a wider lense, for example, he was instrumental in the formation of the World Trade Organization and has been an advisor to the World Health Organization of the United Nations for much of his career. He is a Fellow of the Royal Society of Medicine (UK) and a Fellow of the International Society of Food Science and Technology.

Not only does he have a special perspective on the world's food supply, he is also a scientist. He was Chair of the Department of Physiology-Pharmacology at the University of Georgia and he was the Director of the Center for Food and Nutrition Policy at Georgetown University and at Virginia Tech (where it moved in 2001). With his extensive knowledge regarding the control of chemical and microbiological contaminants of foods, Dr. Crawford is able to take his science background and use it to create practical solutions for food safety issues. In addition, he has also been involved with many of the major food safety initiatives in recent history; two of which were mandatory nutrition labeling and the recent bioterrorism act.

Dr. Crawford's distinguished career has also included his induction into the French Academy of Veterinary Medicine and he has been a recipient of the Wooldridge Award, the British Veterinary Association's highest award. Having a commissioner with a background in veterinary medicine is most timely as we face such critical issues as regulating animal feed and the rise of antimicrobial resistant stains of bacteria.

With Dr. Crawford's well-rounded career in food science and food policy it ensures that food issues will be given proper attention at FDA. Once confirmed, the food industry will look forward to sound, science-based policy and regulatory decisions under Dr. Crawford's guidance.

Sincerely,

TIM HAMMONDS,
President and CEO,
Food Marketing Institute.

MEDICAL DEVICE MANUFACTURERS ASSOCIATION,
WASHINGTON, D.C. 20006,
March 18, 2005.

Hon. MICHAEL ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510.

DEAR CHAIRMAN ENZI: On behalf of the Medical Device Manufacturers Association and the hundreds of manufacturers of medical devices, diagnostic products and health care information systems we represent, I wish to convey strong support for the prompt confirmation of Dr. Lester Crawford to be the Commissioner of the Food and Drug Administration so he can continue the important work of ensuring the public health safety of the Nation's citizens.

As a representative of the innovative sector of the medical technology industry, MDMA has worked closely with Dr. Crawford during his tenure at the FDA. He has always proven an able leader and has fought tirelessly to uphold the FDA's mission.

MDMA believes Dr. Crawford, as both a veterinarian and dedicated public servant, is uniquely suited to lead the FDA. With rapidly developing technologies and advancements in medicine it is imperative that FDA is led by a Commissioner who has the ability, dedication and integrity to lead the agency. Dr. Crawford has exhibited these qualities and it is our sincere hope that the Senate will move quickly to confirm him as the next FDA Commissioner.

Sincerely,

MARK LEAHEY,
Executive Director.

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION,
WASHINGTON, D.C. 20006,
March 1, 2005.

Hon. MICHAEL B. ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510.

DEAR SENATOR ENZI: The Consumer Healthcare Products Association (CHPA) sends this letter to express its support for the Senate confirmation of Dr. Lester M. Crawford to be Commissioner of Food and Drugs.

Dr. Crawford has devoted most of his career to public service, including his current term as Acting FDA Commissioner. The Food and Drug Administration has been hampered for too long by having an acting head.

Dr. Crawford is very familiar with the public health policy issues confronting the agency and his appointment will assure continuity in the leadership of FDA at a critical juncture. He has demonstrated a willingness to work cooperatively with stakeholders on important matters, and we believe that collaboration is a key to the credibility of the regulatory process. We urge the committee to give prompt consideration to Dr. Crawford's nomination.

Sincerely yours,

LINDA A. SUYDAM,
President.

UNIVERSITY OF CALIFORNIA, DAVIS,
DAVIS, CALIFORNIA 95616–8558,
February 24, 2005.

COMMISSIONER LES CRAWFORD,
Federal Drug Administration,
Rockville, MD 20857.

Re: Western U.S. FDA Center of Excellence

DEAR COMMISSIONER CRAWFORD: First, let me congratulate you on your nomination as Commissioner of the Food and Drug Administration (FDA). Your continued interest and investment in the future of our Nation's food supply certainly qualifies you for this critical leadership position. I look forward to working with you in the future.

As Chancellor of the University of California, Davis, I am very supportive of the opportunity to develop an FDA Center of Excellence on the Davis campus. As we lend our support for an added FDA research center of excellence, I would like to seek information from you regarding the FDA's level of interest in and priority for such an endeavor in the Western United States.

UC Davis established the Western Institute for Food Safety and Security (WIFSS) in 2002 to enhance our ability to provide a secure food supply by developing a research and training program in food defense. Through the Department of Homeland Security (OHS) cooperative agreement, we have been developing a region-wide training program for individuals and groups that are invested in the safety of our food supply, including the import of workers and food from Mexico, Canada, and the Pacific Rim.

Could you share with me those focus areas in which FDA would have a specific interest in a western FDA Center of Excellence?

The University of California, Davis has a long history for supporting agriculture and the extensive food systems in California through education, research and outreach. The University has been essential to California maintaining its leadership as the premier agricultural State in the Nation for over 50 years, We look forward to an opportunity to develop a strong collaborative research program with FDA in California.

The University recognizes its obligation to help the public, through industry, address the extraordinary challenges of improving and assuring food safety and food defense. For several years we have supported the California food industries' efforts to establish a FDA research center of excellence in the Western United States. By joining the talents we have assembled at the Western Institute for Food Safety and Security with those of FDA, we will be able to efficiently and effectively address the threats to our Nation's food systems and those that accompany the movement of food across our borders.

Again, I look forward to working with you on this endeavor and any focus areas in which FDA would have a specific interest in a western FDA Center of Excellence.

Sincerely,

LARRY N. VANDERHOEF,
Chancellor.

ADVANCED MEDICAL TECHNOLOGY ASSOCIATION (ADVAMED),
February 15, 2005.

APPOINTMENT OF PERMANENT FDA COMMISSIONER APPLAUDED

Washington, D.C.—AdvaMed welcomed the Bush Administration's appointment today of Lester M. Crawford as commissioner of the Food and Drug Administration. Crawford has served as Acting Commissioner since the departure of former FDA Commissioner Mark McClellan in March 2004.

"We look forward to continuing to work with Dr. Crawford," said Pamela G. Bailey, AdvaMed President. He understands the unique characteristics of the medical technology industry."

"Dr. Crawford's experience will be invaluable as Congress and FDA craft legislation this year that will add predictability and stability to the medical device user fee program and allow for the program's continuation beyond the current fiscal year," Bailey said.

Crawford served as Acting FDA Commissioner before Dr. McClellan joined the Agency in November 2002 and was involved in key negotiations that led to the landmark "Medical Device User Fee and Modernization Act of 2002."

AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems AdvaMed's more than 1,300 members and subsidiaries manufacture nearly 90 percent of the $75 billion of health care technology products purchased annually in the United States, and more than 50 percent of the $175 billion purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. Nearly 70 percent of our members have fewer than $30 million in sales annually.

ALLIANCE FOR AGING RESEARCH,
WASHINGTON, D.C. 20001,
February 16, 2005.

ALLIANCE ENDORSES DR. LESTER CRAWFORD'S NOMINATION AS FDA COMMISSIONER

WASHINGTON, D.C.: The Alliance for Aging Research, a not-for-profit organization, supports President Bush's nomination of Dr. Lester Crawford as the next FDA commissioner and encourages Congress to act swiftly in approving his appointment.

"Dr. Crawford is the perfect candidate to lead the FDA at this critical time," said Daniel Perry, Executive Director of the Alliance for Aging Research. "We are confident that Dr. Crawford will enhance the lives of our Nation's aging population by promoting better medical practices and guaranteeing the safety of drugs that affect our most vulnerable population."

"Dr. Crawford," continued Perry, "will use sound judgment and good science when dealing with drug safety. We look forward to continue working with him at the FDA in assuring the safety and efficacy of the next generation of therapies and treatments."

Crawford has been acting commissioner of the FDA since March of 2004 when Dr. Mark McClellan left the post to become administrator for the Centers for Medicare and Medicaid Services.

Founded in 1986, the Alliance for Aging Research is a nonprofit independent organization dedicated to supporting and accelerating the pace of medical discoveries to vastly improve the universal experience of aging. The Alliance combines the interests of top scientists, public officials, business executives and foundation and academic leaders to promote a greater national investment in research and new technologies that will prepare our Nation for the coming senior boom, and improve the quality of life for older Americans. Visit online at www.agingresearch.org.

ALLIANCE OF SPECIALTY MEDICINE.

Hon. MICHAEL LEAVITT,
Secretary,
U.S. Department of Health and Human Services,
Washington, D.C. 20201.

DEAR SECRETARY LEAVITT: The Alliance of Specialty Medicine supports the nomination of Lester M. Crawford Jr. for Commissioner of the Food and Drug Administration and urges the Senate to confirm him. Dr. Crawford has served the FDA with distinction since be was named to serve as deputy commissioner in 2002 and more recently as Acting Commissioner.

As specialty physicians, the more than 200,000 members of the Alliance of Specialty Medicine and the millions of patients they care for, support the critical role the FDA plays in assuring that the Nation's food is safe and properly labeled, The FDA also assures that pharmaceuticals, biological products and medical devices are safe, effective and properly labeled. Dr. Crawford has devoted his career to promoting safer products for the public. His leadership skills and experience equip him well for this important position.

We hope the Agriculture, Nutrition and Forestry Committee and full Senate will vote favorably on this nomination.

Sincerely.

AMERICAN SOCIETY FOR MICROBIOLOGY (ASM),
WASHINGTON, D.C. 20036–2594,
February 22, 2005.

LESTER M. CRAWFORD, PH.D.
Acting Commissioner,
Food and Drug Administration,
Rockville, M.D. 20857.

DEAR DR. CRAWFORD: We would like to thank you for the generous time you took to make such an excellent presentation to the ASM's Public and Scientific Affairs Board on February 11. Thank you for being so flexible with your schedule. Your presentation of issues and information related to the Food and Drug Administration was extremely valuable to ASM.

We would like to congratulate you on your appointment as Commissioner of FDA. The Society stands ready to assist you and the FDA on issues and policy.

With best wishes,

RUTH L. BERKELMAN, M.D.,
Chair, Public and Scientific Affairs Board.

ASSOCIATION OF AMERICAN VETERINARY MEDICAL COLLEGES,
CHICAGO, IL, 60610,
March 7, 2005.

Hon. MICHAEL B. ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510.

DEAR MR. CHAIRMAN: The Association of American Veterinary Medical Colleges strongly supports President Bush's nomination of Dr. Lester M. Crawford to be Commissioner of the Food and Drug Administration. Dr. Crawford's unequaled experience, including his current tenure as Acting Commissioner and his previous positions as Deputy Commissioner and Director of the FDA's Center for Veterinary Medicine, make him eminently qualified for this position.

Dr. Crawford is one of the Nation's preeminent scientists and a world renowned leader in the veterinary medical profession. His recent election to the Institute of Medicine is evidence of his significant contributions to the advancement of the medical sciences and public health. In addition, Dr. Crawford's extensive experience in achieving cooperation and communication among numerous Federal agencies and private organizations underscores his qualification for high public office.

The FDA is facing unprecedented challenges in ensuring the safety of foods, drugs and medical devices for all Americans. It is imperative to name a Commissioner with proven leadership ability and impeccable scientific acumen. Dr. Crawford em-

bodies these traits and his appointment would provide the proper scientific basis of operation and exceptional communication skills in the position.

On behalf of the Nation's 28 colleges of veterinary medicine, the AAVMC urges the Senate to confirm Dr. Crawford's appointment as FDA Commissioner without delay.

Sincerely,

LAWRENCE E. HEIDER, DVM, DACVPM,
Executive Director.

AMERICAN VETERINARY MEDICAL ASSOCIATION,
SCHAUMBURG, IL 60173–4350,
February 17, 2005.

Hon. MICHAEL ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
Washington, D.C. 20510.

DEAR MR. CHAIRMAN: The American Veterinary Medical Association (AVMA), on behalf of its more than 72,000 members, strongly endorses President Bush's nomination of Dr. Lester M. Crawford to be commissioner of the Food and Drug Administration (FDA). Dr. Crawford's exemplary record of service and leadership in public health, food safety, and regulatory medicine brings invaluable experience and a myriad of accomplishments in government, academia, and industry to this most esteemed position.

We echo Secretary Mike Leavitt's comments that Dr. Crawford is an "outstanding choice" for commissioner, especially as the FDA enters a new era of medicine and rapidly developing science.

Dr. Crawford's admirable public service at the FDA as Acting Commissioner mirrors his previous appointments as deputy commissioner of the FDA, director of the FDA Bureau of Veterinary Medicine, and director of the FDA Center for Veterinary Medicine. Noteworthy experience in his distinguished and varied Federal career is his appointment as administrator of the Food Safety and Inspection Service at the U.S. Department of Agriculture. Dr. Crawford's breadth and depth of experience in seeking out and facilitating cooperation and communication between numerous agencies and organizations underscores his qualifications for the office of commissioner.

In the academic venue, Dr. Crawford has served as the head of the Center for Food and Nutrition Policy at Georgetown University and Virginia Tech, chairman of the University of Georgia's Department of Physiology-Pharmacology, and executive director of the Association of American Veterinary Medical Colleges.

In addition, Dr. Crawford played a key role in the formation of the World Trade Organization has been an advisor to the World Health Organization of the United Nations for much career.

The AVMA is the recognized voice of the veterinary profession in presenting its views on veterinary medicine, including its relationship to public health, biological science, and agriculture, to government, academia, agriculture, pet owners, the media, and other concerned publics. As such, we strongly endorse Dr. Crawford and encourage the Senate to confirm his appointment as FDA commissioner.

Sincerely,

BONNIE V. BEAVER,
BS, DVM, MS, DACVB,
President.

AMERICAN MEDICAL ASSOCIATION,
CHICAGO, IL 60610,
March 15, 2005.

Hon. MICHAEL B. ENZI,
Chairman,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C. 20510–6300.

DEAR SENATOR ENZI: On behalf of the American Medical Association, I write to strongly endorse the confirmation of Lester M. Crawford, D.V.M., Ph.D., as Commissioner of the Food and Drug Administration (FDA). The FDA Commissioner plays

a crucial role in protecting the public from unsafe drugs and dangers associated with the Nation's food supply while ensuring that the United States remains a leader in medical innovation. Today's world of quickly evolving science and an increasing reliance on the healing power of prescription drugs calls for effective, seasoned leadership at the helm of the FDA. Dr. Crawford will provide that leadership.

Dr. Crawford has dedicated his career to advancing the public health, is well known for his work in food safety, and is a first rate scientist committed to public service. He has shown a strong commitment to improving patient safety, something that we as physicians value most highly. As a member of the National Academy of Sciences' Institute of Medicine he has contributed to providing accurate, scientifically sound information to the public. Importantly, Dr. Crawford has held several assignments at the FDA, serving as Deputy Commissioner, and most recently as Acting Commissioner. His expertise and experience will serve him well as Commissioner.

During his tenure as Acting Commissioner, Dr. Crawford has pursued initiatives to improve drug labeling standards to make it easier for physicians to read information critical to the safe and effective use of prescription drugs. He has continued the agency's increasing oversight of dietary supplements, and also has focused on slowing the growth of antibiotic resistance. Furthermore, he has worked to speed innovations to make medicines safer and more affordable to the American public. He has enhanced bioterrorism countermeasures to protect consumers, and is helping to empower Americans by providing more and better information about the medicines and food they consume every day, We have great confidence that Dr. Crawford's vision and leadership will continue to improve the FDA, and will benefit patients and the physicians we represent.

Sincerely,

ABXA,
MICHAEL D. MAYES,
Executive Vice President.

ADDITIONAL LETTERS OF SUPPORT

NOVARTIZ AG,
February 24, 2005.

LESTER M. CRAWFORD, D.V. M., PH.D.
Commissioner Designee,
U.S. Department of Health and Human Services,
Food and Drug Administration,
Parklawn—Room 1471,
3600 Fishers Lane,
Rockville, MD 20857.

DEAR DR. CRAWFORD: It is with great pleasure that I extend sincere congratulations on the announcement of your nomination to the post of Commissioner of Food and Drugs. It is not only an honor to be named for this high post, but an expression by President George W. Bush of his confidence in your education, skills, experience and judgment. You have clearly demonstrated an abiding commitment to the health and safety of U.S. citizens.

I wish for you a speedy and successful confirmation process and I look forward to continuing our cordial working relationship.

Best personal regards,

DANIEL VASELLA, MD.

U.S. OFFICE OF GOVERNMENT ETHICS,
WASHINGTON, D.C.,
March 1, 2005.

Mr. LESTER M. CRAWFORD,
Department of Health and Human Services,
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD.

DEAR MR. CRAWFORD: Congratulations on your nomination to the position of Commissioner, Food and Drug Administration, Department of Health and Human Services. I hope you will find that this position will be both challenging and rewarding.

Enclosed for your information is a copy of the letter sent to the U.S. Senate stating that the Office of Government Ethics has reviewed your financial dlsclosure report and that you are in compliance with applicable laws and regulations governing conflicts of interest. Also enclosed is "Ethics Starts Here: A Guide for Senior Officials" to provide you with an introductory guide to the government ethics rules. We hope you will find this overview helpful.

In addition, as you may already know, all Federal Agencies have a Designated Agency Ethics Official (DAEO). If, in the course of the confirmation process, you have any questions about conflicts of interest or other ethics related matters, you should contact your DAEO, Edgar M. Swindell, who can be reached at 202–690–7258.

I wish you all the best as you proceed through the confirmation process.

Sincerely,

MARILYN L. GLYNN,
Acting Director.

U.S. OFFICE OF GOVERNMENT ETHICS,
WASHINGTON, D.C.,
March 1, 2005.

Hon. MICHAEL B. ENZI,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C.

DEAR MR. CHAIRMAN: In accordance with the Ethics in Government Act of 1978, I enclose a copy of the financial disclosure report filed by Lester M. Crawford, who has been nominated by President Bush for the position of Commissloner, Food and Drug Administration, Department of Health and Human Services.

We have reviewed the report and have also obtained advice from the Department of Health and Human Services concerning any possible conflict in light of its functions and the nominee's proposed duties.

Based thereon, we believe that Mr. Crawford is in compliance with applicable laws and regulations governing conflicts of interest.

Sincerely,

MARILYN L. GLYNN,
Acting Director.

CENTER FOR BIOSECURITY, FOOD SAFETY, AND PUBLIC HEALTH,
Lakeworth, FL.

LESTER M CRAWFORD, DVM, PH.D.,
Acting Commissioner,
Food and Drug Administration,
Rockville, MD.

DEAR LESTER: Congratulations and best wishes for a speedy confirmation. You have been an outstanding professional, a dedicated public servant, and a perfect exemplar of how members of the veterinary profession can contribute to benefit one medicine.

You will be challenged daily in a manner that would test your inner strength. That is the price that you will pay as you continue to serve the needs of our Nation—it is a small price. Stay the course, but pace yourself and avoid as much as possible the stresses linked to the job. I wish you well. You are most deserving.

Sincerely,

DON A. FRANCO,
President.

CYSTIC FIBROSIS FOUNDATION,
WASHINGTON, D.C.,
February 18, 2005.

Hon. MICHAEL O. LEAVITT,
Secretary of Health and Human Services,
U.S. Department of Health and Human Services,
Washington, D.C.

DEAR SEC. LEAVITT: The Cystic Fibrosis Foundation supports the nomination of Dr. Lester Crawford as Commissioner of Food and Drugs. Representing 30,000 people with cystic fibrosis (CF) and their families, the CF Foundation is keenly aware of the importance of a strong leader at the FDA to ensure innovation and protect the public health.

Cystic fibrosis is a chronic, progressive, life-threatening, genetic disease that makes breathing difficult and impairs digestion of food, It creates abnormally thick, sticky mucus in the lungs and pancreas, which results in persistent coughing and chronic lung infections, as well as poor weight gain. A bacterial or viral lung infection that has a minimal impact on a healthy person could be life-threatening to someone with CF. While 30,000 people in the United States have CF, more than 10 million Americans are unknowing, symptomless carriers of a copy of the defective CF gene; individuals with CF have two copies of the gene.

Several new drugs for CF that have been approved in the last decade are the result of key incentives, including the Orphan Drug Act and the fast track approval process for life-threatening diseases. These drugs are critical to the people with CF who desperately need more effective medications to enjoy longer, healthier lives with this disease. Though we believe the FDA plays a vital role to ensure the safety of all medications, our community is well aware of the risk/benefits required and the impact on their own health of delaying approval of new technology. We hope that as Commissioner, Dr. Crawford will provide the essential leadership that will enable the FDA to maintain the priority on the timely approval of drugs to treat life-threatening diseases, such as CF.

We look forward to working with the Commissioner in the months and years ahead.

Sincerely yours,

ROBERT J. BEALL, PH.D.,
President and CEO.

FEDERATION OF AMERICAN HOSPITALS,
February 16, 2004.

FEDERATION COMMENDS NOMINATION OF DR. LESTER M. CRAWFORD FOR FDA COMMISSIONER

The Federation of American Hospitals commends President Bush's nomination of Dr. Lester M. Crawford as Commissioner of the Food and Drug Administration (FDA).

Dr. Crawford has an exemplary record of public service, with both the FDA and the U.S. Department of Agriculture, and has performed admirably as acting FDA Commissioner. Furthermore, Dr. Crawford has an extensive background in consumer health and safety issues, including safety issues with medicine and food. We believe Dr. Crawford is an excellent choice for FDA Commissioner and look forward to working with him on regulatory issues of mutual interest.

CHIP KAHN,
President.

5504 GOLDSBORO ROAD,
BETHESDA, MD,
February 14, 2005.

LESTER CRAWFORD, DVM, PH.D.,
Commissioner,
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD.

DEAR COMMISSIONER CRAWFORD: Congratulations on your well deserved appointment. You join a very distinguished list of individuals to hold this position.

It appears that this appointment will mark some significant firsts—first Deputy elevated to full Commissioner; first veterinarian trained professional to the post.

If my accounting is correct, there will have been chemists, physicians, a pharmacist, a zoologist and now a veterinarian.

My best wishes for success in what is one of the best and most difficult jobs in Washington.

Sincerely,

SHERWIN GARDNER.

GIRL SCOUTS OF THE USA,
March 14, 2005.

Hon. MICHAEL LEAVITT,
Secretary,
U.S. Department of Health and Human Services,
200 Independence Avenue, SW,
Washington, D.C.

DEAR MR. SECRETARY: On behalf of the Girl Scouts of the USA, I enthusiastically applaud the nomination of Dr. Lester Crawford to serve as the new Federal Drug Administration (FDA) Commissioner. Dr. Crawford has served the FDA with distinction as Deputy Commissioner and now Acting Commissioner, and we believe he will make an excellent Commissioner.

Throughout our 93-year history we have offered girls innovative programs in sports, nutrition and health. Our long-standing commitment to the health and well-being of girls gives our organization a profound understanding of the complex issue of obesity. From the beginning of his tenure at the FDA, Dr. Crawford recognized the need to respond to the increase in adolescent obesity and was instrumental in creating our Healthy Living partnership between your agency and the GSUSA to educate girls and their families about nutrition and the importance of physical activity. His leadership and guidance will help to ensure that this and other FDA initiatives regarding the health and well-being of children and families are successful.

We look forward to his confirmation and to continuing to work with Dr. Crawford to promote healthier lifestyles for all Americans.

Sincerely,

KATHY CLONINGER,
Chief Executive Officer.

GENERIC PHARMACEUTICAL ASSOCIATION,
February 14, 2005.

Hon. LESTER CRAWFORD,
FDA Commissioner.

Arlington, VA, Feb. 14 Newswire—The Generic Pharmaceutical Association (GPhA) today welcomed the White House's nomination of Dr. Lester M. Crawford to be Commissioner of the Food and Drug Administration (FDA). Dr. Crawford has served as Acting Commissioner since 2004,

"We're pleased that the White House has decided to nominate Dr. Crawford to this key position, A permanent, fully confirmed Commissioner will have the authority to move forward on many of the important tasks facing the FDA." said GPhA President and CEO Kathleen Jaeger. "GPhA has been working with Dr. Crawford in his current role and we are looking forward to continuing our conversations with him as the permanent Commissioner, once he is confirmed by the Senate."

Jaeger noted that because Dr. Crawford has served as Acting Commissioner for nearly 1 year, he already is familiar with many of the issues affecting the generic

industry. Those include the development of an abbreviated approval pathway for generic biopharmaceuticals, an end to the practice of authorized generics, the timely approval of generic medicines, and concerns with price controls/reimportation.

GPhA represents the manufacturers and distributors of finished generic pharmaceuticals, manufacturers and distributors of hulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic drug industry. Generics represent 51 percent of the total prescriptions dispensed in the United States, but less than 8 percent of all dollars spent on prescription drugs. For further information, please contact GPhA at 703–647–2480, or visit our web site at http://www.gphaonline.org/.

Sincerely,

KATHLEEN JAEGER,
President and CEO.

February 15, 2005.

The undersigned organizations are writing to express our support for Dr. Lester Crawford as Commissioner of the Food and Drug Administration.

Background: People with HIV/AIDS rely on the FDA for approval of a vast array of medical treatments. It is the major source of the prescription drugs that can forestall their illness and disability. It is also the major source of much of the diagnostic and preventive care, as well as treatment for those who become sick. We urge the confirmation of Dr. Crawford and look forward to his continued leadership.

Sincerely,

AIDS Action Project Northwest, AIDS Alliance for Children, Youth, AIDS Foundation of Chicago, AIDS Legal Council of Chicago, AIDS Project Los Angeles, AIDS Rochester, AIDS Services of Dallas, AIDS Survival Project, AIDS Treatment Activists Coalition, AIDS Treatment Data Network, 1AIDSmeds.com, Asian and Pacific Islander Wellness Center, Boulder County AIDS Project, Care for the Homeless, Cascade AIDS Project, Catholic Charities AIDS Services, Center for AIDS, Community HIV/AIDS Mobilization for Power (CHAMP), Critical Path AIDS Project, Doorways, an Interfaith AIDS Residence Program, Fenway Community Health Center, Florida Keys HIV Community Planning Partnership, foundation for Integrative AIDS Research (FIAR), Gay, Lesbian, Bisexual, and Transgender Community Center of Baltimore and Central Maryland, Harm Reduction Coalition, Health Education Resource Organization. Inc. (HERO), Hemophilia Association of New York, Hep-C Alert, Hepatitis C Action & Advocacy Coalition, Hepatitis C Caring Ambassadors Program, Hepatitis C Outreach Project, HIV/AIDS Alliance for Region Two, Inc, Housing Works, HUG-ME Program, Orlando Regional Healthcare, International Foundation for Alternative Research in AIDS (IFARA), Iris House, Inc. Latino Commission on AIDS, Latino Organization for Liver Awareness (LOLA), Lifelong AIDS Alliance, Long Island Association for AIDS Care (LIAAC), Metro St. Louis HIV Health Services Planning Council, McAuley Health Center, Minnesota AIDS Project, Montrose Clinic, Movable Feast, Inc., NAMES Project Foundation, Nashville CARES, National Healthcare for the Homeless Council, New York City AIDS Housing Network, Persons Living with HIV Action Network of Colorado, Philadelphia FIGHT, Positive Employment Options, Project Open Hand, Provincetown AIDS Support Group, Rochester Area Task Force on AIDS, San Francisco AIDS Foundation, San Mateo County AIDS Program, Seattle Treatment Education Project (STEP), Siouxland and Local Area AIDS Project, St. Louis Effort for AIDS, T.H.E. Clinic, Tennessee AIDS Support Services, Inc., The Health Association, Treatment Action Group, Treatment Access Expansion Project (TAEP), Vermont People With AIDS Coalition, Visionary Health Concepts, West Virginia HIV Care Consortium, Williamsburg/Greenpoint/Bushwick HIV CARE Network, Wilson Resource Center.

INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES,
WASHINGTON, D.C.,
February 16, 2005.

LESTER M. CRAWFORD, PH.D.,
Commissioner of Food and Drugs,
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD.

DEAR LES: What great news! Congratulations, and thanks for the continued leadership. It's terrific when good work is recognized, and that's clearly the case here. We all look forward to working with you. Meanwhile, warm wishes for great success.

Sincerely,

J. MICHAEL MCGINNIS, M.D., M.P.P.,
Senior Scholar.

INTERAMERICAN COLLEGE OF PHYSICIANS AND SURGEONS,
WASHINGTON, D.C.,
February 15, 2005.

The Interamerican College of Physicians and Surgeons was founded in 1979 to promote cooperation among U.S. Hispanic physicians and to advance their professional and educational needs. The ICPA reaches a vast majority of the Hispanic medical community in the United States and Puerto Rico—over 39,000 physicians—and a growing number of health professionals in Mexico, the Caribbean, Central and South America, and Spain. The ICPS is the largest association of Hispanic physicians in the Nation.

Today, the ICPS is writing to express our support for the nomination of Dr. Lester Crawford as FDA Commissioner. Dr. Crawford has a long and distinguished record of bringing safe and effective new treatments to all patients. His leadership and expertise will continue to guide the FDA to ensure safe regulation of food and medical products.

Again, ICPS urges confirmation of Dr. Crawford.

KIDNEY CANCER ASSOCIATION,
EVANSTON, IL,
February 15, 2005.

The Kidney Cancer Association is pleased to support the nomination of Lester M. Crawford to be Commissioner of Food and Drugs at the Department of Health and Human Services.

Dr. Crawford's track record with regard to regulation of medical products and ensuring timely access to safe, effective new tests and treatments is an indication of his commitment to patient safety. In addition, his FDA service record combined with his science based leadership in medical regulation should enable him to serve all Americans well—especially the hundreds of thousands with life threatening illnesses, such as kidney cancer, demand safe and efficacious treatments.

Sincerely,

WILLIAM P. BRO,
CEO.

NATIONAL ALLIANCE FOR THE MENTALLY ILL,
ARLINGTON, VA,
February 16, 2005.

Hon. MIKE ENZI,
Hon. EDWARD M. KENNEDY,
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, D.C.

DEAR CHAIRMAN ENZI & SENATOR KENNEDY: On behalf of the 210,000 members and 1,200 affiliates of the National Alliance for the Mentally Ill (NAMI), I am writing to urge support for the nomination of Dr. Lester Crawford as Commissioner of the Food and Drug Administration (FDA). As the Nation's largest organization rep-

resenting individuals with severe mental illnesses and their families, NAMI is pleased to support this important appointment.

In NAMI's view, Dr. Crawford brings unique qualifications to the important position of FDA Commissioner. He has a strong track record of working to ensure timely access to safe, effective new tests and treatments. This includes a long record of service at the FDA in both the Carter and Reagan administrations. He has a demonstrated record of effectiveness in promoting a science-based approach to patient safety.

NAMI urges the HELP Committee to act swiftly on this important nomination. It is critically important that the FDA have a strong leader in place address challenges faced by the agency with respect to safety and monitoring of medications.

Sincerely,

MICHAEL J. FITZPATRICK, MSW,
Executive Director.

NATIONAL MILK PRODUCERS FEDERATION,
ARLINGTON, VA,
March 9, 2005.

Senate Committee on Health, Education, Labor, and Pensions.

DEAR CHAIRMAN MICHAEL B. ENZI: I a writing to express the support of the National Milk Producers Federation for Dr. Lester Crawford, the nominee for Commissioner of the Food and Drug Administration. We hope the Senate Health Committee, following the necessary hearing and deliberations, will act quickly to approve Dr. Crawford.

Few commissioners in the history of the FDA have the depth and breadth of Dr. Crawford's experience in life science and food safety issues, coupled with a laudable record of public service focused on those issues. His two recent stints as Acting FDA Commissioner, coupled with his previous service as Director for the FDA's Center for Veterinary Medicine, give him an unprecedented familiarity with roles and responsibilities of the FDA.

By the same token, his past service as Administrator of the USDA's Food Safety and Inspection Service also provides him a unique perspective on the important oversight role that both the FDA and USDA provide in maintaining the public health.

On a personal note, I had the privilege of serving at FDA with Dr. Crawford early in my career and I have first hand knowledge of his capabilities, statesmanship and leadership. His early life growing up on a dairy farm in Alabama also serves him as a man of character, discipline, and fortitude.

His commendable track record of successes in a variety of settings is ample evidence of Dr. Crawford's capabilities. We hope that the members of the Senate Health Committee, and the Senate overall, will also acknowledge those capabilities by acting quickly to confirm Dr. Crawford as FDA Commissioner.

Yours truly,

JERRY KOZAK,
President and CEO.

RESPONSE TO QUESTIONS OF SENATOR BINGAMAN BY LESTER CRAWFORD, DVM, PH.D.

(1) Response to Letters

Question 1. We await responses to the March 2004 anthrax vaccine letter and the July 2004 letter sent with Senator Reed regarding drug trials. Can we obtain answers to these letters? What is the timeframe for such responses?

Answer 1. On June 4, 2004, the Food and Drug Administration (FDA or the Agency) responded to your letter of March 7, 2004. Although the response was limited due to pending litigation, additional public information has become available since our June 2004 response.

There is only one anthrax vaccine licensed in the United States, Anthrax Vaccine Adsorbed (AVA), also known as Biothrax, which is manufactured by BioPort Corporation, located in Lansing, Michigan. AVA was first licensed by NIH in November 1970. AVA is recommended for individuals who may come in contact with animal products that may be contaminated with *Bacillus anthracis* spores and for individuals engaged in diagnostic or investigational activities that may bring them in con-

tact with *Bacillus anthracis* spores. It is also recommended for persons at high risk, such as veterinarians and others handling potentially infected animals.

In an October 27, 2004 court order currently on appeal, the district court for the District of Columbia invalidated the January 5, 2004, final rule referenced in your letter. On December 29, 2004, in deference to the court, FDA republished a proposed rule and proposed order to provide notice and comment to give interested persons an opportunity for input. Comments were due by March 29, 2005. The proposed rule and order can be accessed on FDA's website: http://www.fda.gov/cber/vaccine/anthrax.htm.

In the December 29, 2004, proposed rule and proposed order, FDA categorized those bacterial vaccines and toxoids licensed before July 1972 according to the evidence of their safety and effectiveness, and issued a proposed response to recommendations made in an advisory panel's report. Pursuant to the FDA regulations Title 21, *Code of Federal Regulations* § 601.25, the advisory panel was convened on July 12, 1973, in an organizational meeting, followed by multiple working meetings until February 2, 1979. The Final Report of the advisory panel was completed in August 1979. The advisory panel's recommendations concern conditions relating to active components, labeling, tests required before release of product lots, product standards, or other conditions considered by the advisory panel to be necessary or appropriate for assuring the safety and effectiveness of the reviewed products.

FDA will be considering all comments submitted in response to the December 29, 2004, proposed rule and proposed order.

(2) Office of Drug Safety

Background

The Office of Drug Safety (ODS) is responsible for ensuring the safety of drugs already approved and on the market. It is housed within the Center for Drug Evaluation and Research (CDER). CDER is also home to the Office of New Drugs (OND), which is responsible for reviewing new drug applications and approving drugs for market.

There have been allegations that having both ODS and OND in the same component of the FDA creates conflicts. These conflicts stem from the fact that both offices are subject to the same management, which may not want drugs it has approved for market to be the subject of too much scrutiny, and also from the fact that OND and ODS staff are colleagues, which may create situations in which less than complete and impartial review of safety concerns occurs. The co-location of ODS and OND within CDER may have a chilling effect on raising and addressing safety concerns.

Question 2. Dr. Crawford, we have heard allegations about the conflicts that stem from the fact that the Office of Drug Safety (ODS) and the Office of New Drugs (OND) are co-located within the Center for Drug Evaluation and Research. There is some concern that drug safety concerns may not receive as much attention as they warrant given the potentially divergent missions of ODS and OND.

What are your thoughts on taking ODS out of CDER and putting it elsewhere within the FDA, like the Office of the Commissioner? Will that help foster scientific debate about drug safety? Will moving the Office of Drug Safety help ensure that drug safety concerns receive the appropriate amount of attention?

Are there other things that you would do to increase the FDA's commitment to drug safety? Are there other things you would suggest Congress do?

How do you intend to balance the need to expediently approve innovative drugs while ensuring the safety of consumers? Are you supportive of an independent office of drug safety?

Answer 2. Recently, I joined Secretary Leavitt to announce important efforts that we are undertaking with FDA to improve its ability to monitor and respond to emerging drug safety information. These steps will ensure both a better internal process of deliberation on drug safety issues that ensures appropriate and independent consideration of all issues, as well as a stronger ability to gather data about drug safety issues once a drug has been approved.

Most importantly, we are moving to encourage more transparency and to ensure that patients and physicians have the most up-to-date and complete information necessary to inform their treatment decisions. This new Drug Information Initiative will give patients, healthcare professionals, and other consumers quick and easy access to the most up-to-date and accurate information on medicines and make FDA's drug review, approval, and monitoring programs as transparent a possible.

This is in addition to FDA's Five Point Plan to Improve Drug Safety, a major initiative designed to improve the monitoring of drug products recently approved for marketing. The major components of this initiative include:

• Sponsoring a major study of the Drug Safety System by the Institute of Medicine;
• Implement a Program for Adjudicating Differences of Professional Opinion;
• Conducting a nationwide search to identify a permanent director for the Office of Drug Safety;
• Conducting a series of workshops and meetings on drug safety and risk management; and
• Publishing risk management guidance.

FDA's Office of Drug Safety (ODS), in the Center for Drug Evaluation and Research (CDER), is already an independent office separate from the Office of New Drugs, the office that reviews new drug applications. Both the Office of New Drugs and the Office of Drug Safety report directly to the Director of the CDER. ODS has independent authority to perform its own research and does so every day. To be valuable, this independent research must conform to widely accepted scientific standards and normal scientific procedures and peer review should not be bypassed. And when drug safety issues are identified, they must be factored into the risk-benefit equation so that safe and effective drugs remain available to patients who need them.

FDA has a longstanding commitment to provide a strong resource base for its drug safety program. The budget for fiscal year 2006 continues this commitment. The President has proposed a 24 percent increase for FDA's post-market safety program to help further ensure that America's drug product supply is safe and effective, and of the highest quality. Under this proposal, CDER's ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such as risk management, risk communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.

(3) Office of Orphan Products

Background

The Director of the Office of Orphan Products Development (OOPD), Dr. Marlene Haffner, is a respected and accomplished leader of OOPD. She is a highly dedicated public servant, respected by the pharmaceutical and biotechnology industry, by patient organizations, researchers, and by national drug regulatory authorities not just in the United States but throughout the world.

Through the office, there are 267 FDA approved orphan drugs and several "humanitarian" medical devices that treat at least 13 million Americans today—Americans who would otherwise have no treatment at all—and millions more throughout the world. Just last year, the FDA reported that the "program is widely viewed as a major success in assisting in development of treatments for rare diseases, at a very modest investment. FDA is conducting an internal review of how the successes of Orphan Products development research might be applied to other kinds of critical path problems."

It is our understanding that Dr. Haffner does not want to retire and continues to serve in the Public Health Service (PHS). Under her leadership, the FDA's orphan drug program has led the rest of the world in an international cooperative effort to address these devastating diseases. When Dr. Haffner decides to retire, the FDA should conduct a nationwide search for an individual with medical and/or pharmacy background and extensive knowledge of orphan products and rare diseases to ensure the continued growth and international influence of the FDA's Office of Orphan Products Development.

Question 3. The FDA Office of Orphan Drugs has a long successful history. It is my understanding that you are considering management changes in the office. If the office has been so successful, why are such changes being considered? What are your plans for ensuring that future management has the knowledge, subject expertise, and track-record necessary to ensure continued office and program success, including expertise in orphan drugs, biologics, or humanitarian use devices?

Answer 3. All FDA offices are required to have succession plans. The incumbent in the Office of Orphan Drugs has been in that position for 17 years. Traditionally, FDA leaders have rotated into other positions following lengthy periods in one position. This is the best for the institution and for the individual. No current Director, Associate Commissioner, or Deputy Commissioner has served for 17 years in one position. Finally, whenever FDA conducts recruitments for vacancies, we strive to

identify individuals that have the relevant management and subject matter expertise for the position.

(4) Labeling

The Food and Drug Administration's (FDA) Office of Nutritional Products, Labeling and Dietary Supplements (ONPLDS) is responsible for essential public health and consumer protection programs. ONPLDS develops policy and regulations for nutrition labeling, food standards, infant formula and medical foods. During hearings last year by the House Appropriations Subcommittee on Agriculture, Rural Development and Related Agencies, FDA stated that it would need 10–12 additional full time equivalents (FTEs) to complete five important projects, the majority of which are food labeling projects associated with reducing the costly rise in obesity among Americans. In addition, the Senate Committee on Appropriations last year recognized the important public health responsibilities of this Office and noted that its funding for activities other than the regulation of dietary supplements has remained level for several years. In Senate Report 108-340, the committee, therefore, encouraged "FDA to determine if additional funding is necessary for ONPLDS to more effectively carry out its important responsibilities, and if appropriate, increase funding for this office in its fiscal 2006 budget request."

Questions 4. Why did FDA fail to request additional FTEs in its 2006 budget for labeling activities when it told the House that it needed 10-12 additional FTEs and was encouraged by the Senate to determine if it needed more funding? If these matters are not addressed, how will FDA ensure that the market is not flooded with deceptive claims appealing to consumer's desire to control their weight especially in light of the cut in inspections?

Answer 4. FDA's Office of Nutritional Products, Labeling and Dietary Supplements' (ONPLDS) responsibilities continue to grow, including initiatives on infant formula review notifications, better-informed consumers, obesity, and allergen labeling. In addition, the Office has a continuing challenge to protect the safety and security of the food supply from tampering and from counterfeit products. The President's fiscal year 2006 budget request delineates FDA's priorities in this regard. FDA will continue to evaluate if additional funding is necessary for ONPLDS to more effectively carry out its important responsibilities.

(5) Food and Drug Administration Advisory Committees

The FDA relies on advisory committees to evaluate the scientific evidence supporting applications for new drugs, biologics, medical devices, and foods. Advisory committees also play a key role when drug safety issues come to the fore, as they have in the past year with the use of antidepressants in children leading to suicide and the cardiovascular risk from the newer arthritis pain relief medicines known as COX-2 inhibitors. Though the Federal Advisory Committee Act (FACA) prohibits outside scientists recruited to serve on these advisory panels from having conflicts of interest with companies whose products are under review, the FDA staff routinely waives such conflicts. These waivers are allowed under the law. Moreover, the staff usually waits until the eve of the advisory panel's meeting to release the names of the scientists who will be serving on the panel and the questions they will be asked, thus making it almost impossible for the public to scrutinize their choices to determine if the agency has met FACA's requirements for eliminating conflicts of interest and assuring that the committee is balanced with regard to points of view. The use of waivers reached a nadir at the recently concluded advisory panel on COX-2 inhibitors, where at least 10 of the 32 scientists on the panel had financial relationships with the companies involved. These conflicts were not disclosed at the meeting. Moreover, the FDA claimed that they didn't need to be disclosed because it was just a general discussion of the issue and not specific to any one company even though at the end of the 3-day meeting, specific votes were taken on three drugs.

Questions 5. Why did the FDA say at the advisory committee meeting that voted on specific COX-2 inhibitors that financial relationships with the companies making those drugs did not have to be disclosed? What efforts did the FDA make, prior to that COX-2 inhibitors meeting, to find additional experts who did not have a financial relationship with the manufacturers of those drugs? More generally, what do you intend to do at the FDA to clean up the advisory committee process for drugs, biologics, medical devices, and foods so that scientists who serve on your panels don't have conflicts of interest with the companies whose products are under review?

Answer 5. FDA screened the Advisory Committee members and other invited special Government employees (SGEs) for conflicts of interest according to the same strict ethics guidelines FDA applies to all its advisory committees. This transparent process requires the Agency to carefully weigh any potential financial interest with

the need for essential scientific expertise in order to protect and advance the public health. It is very difficult to obtain qualified advisory committee panel members who are totally free from any previous association with manufacturers. The Nation's experts (and in some cases, there are only a few experts on a particular topic) are sought after for consultation by both the Agency and industry because of the scarcity, and therefore the value, of their expertise. Utilizing less experienced or less highly qualified scientists in order to completely remove any potential conflict from the committee would hamper the Agency's ability to protect and advance the public health.

The Agency's staff examines all potential financial interests. The Agency's process is to evaluate the potential financial interests of members and other invited special government employees. FDA makes a determination as to whether the participation of an individual with some financial ties outweighs the need for the agency to understand the science on the topic before the committee. Although the Agency has guidelines for this process (see Waiver Criteria Document 2000 on the FDA website: *http://www.fda.aov/oc/advisory/conflictofinterest/intro.html.*), this is not a black and white process. It requires careful consideration of all facets of the issue in order to evaluate that balance. Congress, by permitting waivers for potential conflicts of interest, has ensured that the Agency and the public (through the advisory committee process) have access to the most knowledgeable individuals on the meeting topic.

Although 18 U.S.C. Section 208 provides that a copy of any waiver determination is available to the public upon request, the Agency may withhold from disclosure information that would be exempt under the Freedom of Information Act, 5 U.S.C. § 522(b). Under this provision, all of the information concerning conflicts of interest may be withheld as exempt pursuant to 5 U.S.C. § 522(b)(3) because the Ethics in Government Act prohibits release of the information. Nevertheless, in order to provide meaningful disclosure of conflicts of interest information, the Office of Government Ethics has concluded that, under section 208, Federal agencies have discretion to disclose information concerning the waived conflict of interest absent a foreseeable harm to be caused by the disclosure. The Office of Legal Counsel, United States Department of Justice (OLC), concluded that FDA may exercise its discretion in making disclosure to avoid making the disclosure requirement so intrusive or onerous as to make outside experts unwilling to serve on advisory committees.

In January 2002, the FDA issued draft guidance on "Disclosure of Conflicts of Interest for Special Government Employees Participating in FDA Product Specific Advisory Committee." The guidance provides information on the type and amount of information that will be disclosed to the public when a member is granted a conflict of interest waiver with the topic to be discussed by the committee. The guidance applies only to those advisory committee meetings at which a particular matter relating to a particular product is discussed (product specific meetings). The guidance does not apply to advisory committee meetings that provide advice on topics of general applicability (i.e., those meetings that could affect a class of products and their sponsors) even if the members on the committee received general matters waivers covering their participation on the committee.

The disclosure for particular matters identifies whether the interest is related to the sponsor or competitor that markets a product competing with the product at issue (without naming the competitor), the type of interest (stock, consulting, contracts/grants, patents/royalties/trademarks, expert witness, teaching, speaking, or writing), and the magnitude of the interest is described as a range.

After conducting the Agency's standard thorough review of the potential conflicts of interest for all potential members and invited SGEs on the advisory committee discussing the class of COX-2 inhibitors, several types of conflicts of interest were found. At least one potential participant was recused from the meeting entirely. In other cases, FDA found the conflicts not to be of sufficient magnitude to outweigh the need for the SGEs' specific scientific expertise for this public meeting. Accordingly, the Agency approved waivers to allow the participation of 19 scientists. The additional 16 participants did not require waivers.

SGEs who serve the public interest on advisory committee panels are world-class experts who are highly renowned and respected in their fields. Most consider it an honor and a privilege to serve on advisory committees. SGEs disclose all relevant personal and imputed financial information and members of the public may request copies of the waivers granted under 18 U.S.C. 208 through the Freedom of Information Act process. FDA has no reason to believe that any potential conflict affected the participant scientist's recommendations given our careful evaluation of all potential conflicts, selection of appropriate experts, and adherence to our standard process for granting and disclosing waivers where the need for essential scientific information for public discussion is so warranted.

FDA's process of evaluating potential committee members for conflicts is very extensive and transparent. At the beginning of each meeting, a conflict of interest statement is read into the record, which summarizes the results of the conflicts of interest screening. FDA has been commended by the Office of Government Ethics (1997) for serving as "a model for other Agencies to use in developing their own systems and procedures." Nonetheless it is always prudent to regularly assess the Agency program and determine if any improvements are warranted. In the near future, the Agency will review the advisory committee conflicts of interest disclosure process and consider if further improvements are necessary to make the disclosures more easily accessible to the public.

(6) Trans Fat in Partially Hydrogenated Vegetable Oils

Trans fat in partially hydrogenated vegetable oils is a major public health problem because it promotes heart disease. In July 2002 the Institute of Medicine ("IOM") of the National Academy of Sciences concluded that the consumption of trans fat is at least as unhealthful as the consumption of saturated fat and that consumption of trans fat in any amount increases the risk of heart disease. In December 2003 the IOM concluded that it is feasible to exclude from the diet trans fat from partially hydrogenated vegetable oil. In April 2004 the Nutrition Subcommittee of the Food and Drug Administration ("FDA") Food Advisory Committee concluded that trans fat is more conducive to coronary heart disease than is saturated fat. The January 2005 *Dietary Guidelines* recommended minimizing consumption of trans fat from both partially hydrogenated oils and meat and dairy products.

Questions 6. In addition to inclusion of trans fat information on Nutrition Fact labels by 2006, what other measures will be taken by FDA to promote public health in regard to trans fat intake?

Answer 6. FDA is requiring the declaration of *trans* fat amounts directly under the saturated fat line on the nutrition facts panel (without a %DV). This requirement goes into effect January 1, 2006. (The *trans* fat labeling rule, which was published on July 11, 2003, in the Federal Register, can be found at *http://www.cfsan.fda.gov/-acrobat/fr03711a.pdf*). We believe this information will allow consumers to lower their intake of *trans* fat. We estimate that 3 years after the January 1, 2006 effective date, *trans* fat labeling will result in approximately 600 to 1,200 fewer cases of coronary heart disease and 240–480 fewer deaths each year, saving $900 million to $1.8 billion per year in medical costs, lost productivity, and pain and suffering.

FDA understands the important public health concern associated with the consumption of products that contain cholesterol-raising lipids such as *trans* fat which, in turn, may increase the risk of coronary heart disease. We encourage consumers to choose foods with lower amounts of saturated fat, *trans* fat and cholesterol as part of a healthy diet (see FDA's education material entitled "Trans Fat Now Listed with Saturated Fat and Cholesterol on the Nutrition Facts Label" on the web at *http://www.cfsan.fda.gov/-dms/transfat.html*). FDA also recommends that saturated and *trans* fats be replaced with mono- and polyunsaturated fats because mono- and polyunsaturated fats do not raise LDL (or "bad") cholesterol levels and have health benefits when eaten in moderation. The 2005 *Dietary Guidelines* for Americans contain these same recommendations. The FDA has worked closely with other offices within the Department of Health and Human Services to foster the incorporation of these messages into consumer education materials as it relates to nutrition labeling. To further disseminate FDA's consumer message about *trans* fat and other cholesterol raising fats, we are planning additional outreach efforts, including a Newsflash that can be incorporated into consumer magazines and other publications.

The Agency has no regulation defining nutrient content claims or a reference value for *trans* fat. In the near future, we hope that we will be able to establish definitions for claims such as "*trans* fat free" and in response to an ANPRM that published the same day as the *trans* fat labeling final rule (*http://wvvw.cfsan.fda.gov/-Ird/fr03711b.html*). Soon, FDA will be conducting consumer research to determine consumer perception of *trans* fat labeling including nutrient content claims and a possible footnote statement. Currently, the label or labeling may contain a statement about the amount of *trans* fat provided the statement is not false or misleading and in no way characterizes the level of *trans* fat in the food. For example, "0 g *trans* fat/per serving" and "2 g *trans* fat/per serving" are appropriate when, in fact, the nutrition facts panel represents these same amounts of *trans* fat per serving.

FDA is also working to develop educational strategies and partnerships to support appropriate messages and teach people, particularly children, how to lead healthier lives through better nutrition.

Fostering the development of healthier food products for American consumers is an important aspect of public health. FDA is aware of the impact labeling *trans* fat has on the manufacturer (e.g., by creating an incentive to reformulate), and the alternative ingredients or processing techniques under consideration for reducing *trans* fat. FDA is monitoring industry progress in this effort.

(7) Nutrition Education Strategy

Background

In commenting on the Calories Count report of March 2004, you (FDA Deputy Commissioner Lester M. Crawford, D.V.M., Ph.D.) said, "Our report concludes that there is no substitute for the simple formula that "calories in must equal calories out" in order to control weight. We're going back to basics, designing a comprehensive effort to attack obesity through an aggressive, science-based, consumer-friendly program with the simple message that "Calories Count." Thus far, we have seen that education campaign in the form of the updated nutrition facts label website and the consumer brochure that accompanied the release of the 2005 Dietary Guidelines for Americans.

Question 7. What "aggressive, science-based, consumer friendly" strategies do you have planned for the future?

Answer 7. FDA believes that all parties, including the packaged food industry, restaurants, academia, and other private and public sector organizations in addition to government agencies at all levels, have an essential role to play in communicating the report's messages to the public. FDA is focusing its science-based, consumer friendly strategies in 3 areas at this time:

- Developing education materials and partnerships to promote appropriate weight management messages.
- Evaluating the need for changes to the food label to make it easier for consumers to understand the calories and portion sizes they are consuming.
- Working with a third party facilitator to begin a national policy dialogue, seeking consensus-based solutions, on the obesity problem and away-from-home foods.

FDA is working to develop educational strategies and partnerships to support appropriate messages and teach people, particularly children, how to lead healthier lives through better nutrition. We are starting work with the Girl Scouts of the USA, under terms of a Memorandum of Understanding signed this past fall, to provide outreach and education in a science-based initiative to focus on improving health, nutrition, and physical activity. In addition, FDA's field offices are participating in local partnerships to reach and teach children. For example, in Central Florida, FDA's SE Region is part of the Seminole County Healthy Kids Partnership to promote positive opportunities for school-aged children in Seminole County to learn healthy nutrition and the value of increased daily physical activity. These are examples of how FDA is working to leverage its ability to convey appropriate messages on obesity to the public with the goal of changing behavior and ultimately reversing obesity trends in the United States.

FDA has published advance notices of proposed rulemaking (ANPRMs) addressing prominence of calories on the label and certain provisions of the nutrition labeling regulations related to serving size.

FDA also stresses that the regulatory scheme for claims in food labeling, whether health claims, nutrient content claims, or other types of claims, must be science based. We continue to consider modifications to our regulations to keep up with recent scientific developments. A benefit of standardized, science-based terminology (e.g., terminology concerning fat content) is that it allows consumers to compare across products and it encourages manufacturers to compete based on the nutritional value of the food. FDA, however, does not regulate television and other media marketing of food products.

In June 2004, FDA signed a contract with the Keystone Center, a nationally recognized facilitator for policy and scientific issues, to begin a dialogue on away-from-home foods and the pediatric obesity (education) issue. The goal of the away-from-home foods dialogue will be to consider what can be done, given the best available evidence to date, to support consumers' ability to manage energy intake with respect to preventing undue weight gain and obesity. The dialogue will produce a report to FDA and options for a range of actions by diverse stakeholders, including government, industry, voluntary health agencies, consumer organizations, and others. Keystone will convene its first plenary meeting of stakeholders, to include representa-

tives from the restaurant industry, academia, consumer groups and government on April 26–27, 2005.

The final Keystone report, and comments received on the two ANPRMs, in combination with other information, will provide FDA with information on which to base future activities.

(8) Scientific Evidence vs. Personal or Political Ideology

Questions 8. Do you have a personal commitment to keep politics or political ideology out of the FDA approval process? If so, how do you plan to accomplish this?

Answer 8. The law is clear that FDA approval decisions should be based on science, and the requirements of the law, not ideology or opinion. Sometimes the science is not adequately developed to provide for a clear decision, and decisions have to be deferred until adequate information is available.

I am committed, if confirmed, to ensuring that during my tenure as commissioner, FDA's decisions will be based on science and the requirements of the law and that the basis for FDA's decisions are open and transparent to the public.

My vision for the future of FDA is one of transformation. And one aspect of that transformation will be ensuring an agency culture of transparency, collaboration, and cutting-edge thinking.

RESPONSE TO QUESTIONS OF SENATOR BURR BY LESTER CRAWFORD, DVM, PH.D.

Question 1. On Monday, March 14, 2005, the NIH inadvertently posted on its website at 2:22 p.m. the results of a large clinical trial that showed a Genentech drug helped certain lung-cancer patients live longer. The NIH was supposed to publish those results at 4 p.m., after the close of trading. Due to the mistake, Genentech's stock shot up 25 percent and the NYSE halted trading in the shares just before 3:30 p.m.—but in the preceding 10 minutes, 4.7 million shares had changed hands. There has been some discussion around the drug safety issue about putting more clinical trial data on the web. Shouldn't we consider examples like what happened on March 14 and think twice about putting more and more clinical trial data on the web?

Answer 1. As you know, I recently joined Secretary Leavitt to announce important efforts that we are undertaking with FDA to improve its ability to monitor and respond to emerging drug safety information.

These steps will ensure both a better internal process of deliberation on drug safety issues that ensures appropriate and independent consideration of all issues, as well as a stronger ability to gather data about drug safety issues once a drug has been approved.

Most importantly, we are moving to encourage more transparency and to ensure that patients and physicians have the most up-to-date and complete information necessary to inform their treatment decisions. This new Drug Information Initiative will give patients, healthcare professionals, and other consumers quick and easy access to the most up-to-date and accurate information on medicines and make FDA's drug review, approval, and monitoring programs as transparent as possible.

You raise an important point, and I agree that it is important that we make this information available in a meaningful, accurate and responsible manner, and I hope to continue to work with this committee as we move forward.

Question 2. FDA and USDA have joint responsibility over the Food Emergency Response Network. Who at the FDA will be in charge of working on that Network and how directly will they report to you?

Answer 2. As you know, the Food Emergency Response Network (FERN) is a nationwide laboratory network that integrates existing Federal and State food testing laboratory resources by utilizing standardized diagnostic protocols and procedures. FERN is the collaborative work of USDA and FDA with support from the Department of Homeland Security (DHS), Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), Federal Bureau of Investigation (FBI), Customs and Border Protection (CBP), and the Environmental Protection Agency (EPA). By increasing our laboratory search capacity, FERN will enhance the Nation's ability to respond swiftly to a terrorist attack.

The FERN Steering Committee, which includes Federal and State representation, was established in September 2003 and is jointly chaired by Patrick C. McCaskey, Senior Executive for Laboratory Services within the Office of Public Health Sciences in USDA's Food Safety and Inspection Service and John R. Marzilli, Deputy Associate Commissioner for Regulatory Affairs in FDA's Office of Regulatory Affairs (ORA). FERN Subcommittees have also been formed which provide guidance and ex-

pertise regarding the development and implementation of FERN programs to Messrs. McCaskey and Marzilli specifically, and the steering committee, in general.

Participating FERN laboratories fall within one of five geographically based Regional Coordination Centers (RCCs), otherwise known as regional "hubs". The regional hubs include the Northeast RCC, the Southwest RCC, the Southeast RCC, the Pacific RCC and the Central RCC. Each RCC is led by an Interdisciplinary Scientist who receives direction from, and reports directly to, the FERN National Program Office (NPO) located within FDA's/ORA's Division of Field Science. Scientists within the Division of Field Science who have oversight of FERN programs subsequently advise, inform and notify Mr. Marzilli of all issues involving FERN laboratories. FDA's Center for Food Safety and Applied Nutrition also assists the FERN initiative by providing specialized scientific expertise, laboratory capabilities, and research capabilities, as well as training, proficiency, and logistics support.

Mr. Marzilli reports to his immediate supervisor, the Associate Commissioner for Regulatory Affairs who, in turn, reports directly to the Commissioner of Food and Drugs.

Question 3. The DOD and USDA use the Carver Analytical Tool to perform threat assessments and understand where vulnerabilities are in a particular system. Will the FDA also use the Carver Analytical Tool on the food system? I would think that there could be better coordination between the DOD, USDA and FDA if everyone is using the same tool to perform threat assessments.

Answer 3. I agree with your statements. To perform threat assessments, the Agency has been using the CARVER + Shock Analytical Tool since April 2003. In preparing for the CARVER + Shock analysis, FDA worked with DOD, CIA, FBI, and our colleagues at USDA/Food Safety Inspection Service to develop a design basis threat (i.e., what a party intent on doing damage could do based on their capability, intent, and past history). The CARVER + Shock analyses for two food products have now been classified as SECRET. Furthermore, seven other products under FDA jurisdiction are currently being finalized using the CARVER + Shock Analytical Tool. In addition to these assessments, FDA has been working with selected higher risk commodity industry groups to initiate threat assessment and identify preventive measure options using a CARVER + Shock approach. Also, FDA has collaborated with USDA using the CARVER + Shock Analytical Tool on specific commodities that are of joint interest in relation to the school lunch program.

Question 4. The FDA's Core Mission covers a wide spectrum, including:

- Maintaining the safety of the Nation's food supply from threats such as BSE or "mad-cow" disease;
- Ensuring that vaccines are safe and in ready supply for the American public;
- Reviewing the safety and efficacy studies for new medical drugs and devices; and
- Monitoring approved medical drugs and devices for unforeseen health consequences, to name a few.

Does FDA possess adequate resources and expertise to carry out these core missions?

Do you believe there are other areas not currently within the agency's purview that it should address?

If so, is the regulation of tobacco one of those areas?

If there are other areas, how would you expect to allocate FDA's limited resources to address these new areas without impacting the agency's ability to carry out its core mission?

Answer 4. FDA has a highly motivated and well-trained staff. Our resource levels have been sufficient to meet critical needs and requirements and have been augmented by Congress when new demands are identified as occurred, for example, with the fiscal year 2002 Counter Terrorism supplemental appropriations. Our mission involves the regulation of food and medical products that are valued at more than 20 percent of every consumer dollar spent in the U.S. The Administration's budgets are set at a level to effectively accomplish FDA's core mission. If new needs arise, the Administration will work with Congress to address them.

Question 5. Critics have argued that FDA cannot be trusted to safeguard the American drug supply and that we need to set up an independent drug safety office, separate from the FDA and the FDA personnel who review and approve drug products, to oversee drug safety. Do you believe that an independent drug safety is necessary? Is there, in fact, some benefit to having the drug safety review function remain within FDA even after approval? What is the FDA doing internally to enhance the independence of its drug safety oversight?

Answer 5. Recently, I joined Secretary Leavitt to announce important efforts that we are undertaking with FDA to improve its ability to monitor and respond to emerging drug safety information.

These steps will ensure both a better internal process of deliberation on drug safety issues that ensures appropriate and independent consideration of all issues, as well as a stronger ability to gather data about drug safety issues once a drug has been approved.

Most importantly, we are moving to encourage more transparency and to ensure that patients and physicians have the most up-to-date and complete information necessary to inform their treatment decisions. This new Drug Information Initiative will give patients, healthcare professionals, and other consumers quick and easy access to the most up-to-date and accurate information on medicines and make FDA's drug review, approval, and monitoring programs as transparent as possible.

This is in addition to a major initiative designed to improve the monitoring of drug products recently approved for marketing. The major components of this initiative, including the IOM study, include:

- Conducting a nationwide search to identify a permanent director for the Office of Drug Safety;
- Conducting a series of workshops and meetings on drug safety and risk management; and
- Publishing risk management guidance.

FDA has a longstanding commitment to provide a strong resource base for its drug safety program. The budget for fiscal year 2006 continues this commitment. The President has proposed a 24 percent increase for FDA's post-market safety program to help further ensure that America's drug product supply is safe and effective, and of the highest quality. Under this proposal, CDER's ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such as risk management, risk communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.

With regards to an independent drug safety office, FDA's Office of Drug Safety (ODS), in the Center for Drug Evaluation and Research (CDER), is already an independent office separate from the Office of New Drugs, the office that reviews new drug applications. Both the Office of New Drugs and the Office of Drug Safety report directly to the Director of the CDER. ODS has independent authority to perform its own research and does so every day. To be valuable, this independent research must conform to widely accepted scientific standards and normal scientific procedures and peer review should not be bypassed. And when drug safety issues are identified, they must be factored into the risk-benefit equation so that safe and effective drugs remain available to patients who need them.

FDA will await the views and findings of the IOM study before making any major structural changes with regard to ODS. The benefits of having both OND and ODS under one FDA center are many. Most importantly, the current structure allows important risk information on drugs to be shared rapidly between the two offices that are most familiar with the benefits and risks of the drug. It is this close collaboration that allows FDA to make the critical decisions with regard to a drugs benefit-to-risk profile.

Question 6. In November 2002, the FDA disbanded its Medical Imaging Drugs Advisory Committee (MIDAC), ending the 25 year existence of that body. Medical imaging drugs are now the only significant class of drugs for which FDA does not have a standing advisory committee. We understand that FDA is currently obtaining expert medical imaging advice by retaining medical imaging experts on an *ad hoc* basis and assigning them to existing standing committees as temporary members for particular meetings. In its notice terminating the MIDAC, FDA said this system would be "more effective" than a standing MIDAC, but did not explain why. It is difficult to understand how this *ad hoc* system would be more effective than having a cohesive group of imaging experts with appropriate continuity meeting as a standing committee at regular intervals. Please explain how the current system of assigning experts ad hoc to existing committees on a meeting-by-meeting basis is "more effective" than having a standing committee.

Answer 6. The MIDAC met only infrequently in the preceding years. The decision to terminate MIDAC was based on several factors. We believe that the FDA advisory committee assessment of the risks and benefits to patients of a new imaging procedure is enhanced through the perspective of physicians who are providing di-

rect care to patients, and, as part of that direct patient care, are ordering all imaging procedures for their patients. As part of the assessment of a patient's care, these attending physicians must determine the risk and benefit to their patients of all imaging procedures. As such, the current FDA advisory committee assessment of a new imaging procedure is performed by the advisory committee that represents the specialty of patient care physicians that will order the new imaging procedure, in conjunction with all other imaging procedures. We believe we can continue to obtain the essential external advice from imaging trained specialty physicians for the FDA advisory committees by supplementing the membership of our patient care specialty advisory committees. For example, medical imaging special government employees (SGEs) were part of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee that occurred in February 2004 to discuss the use of imaging drugs in conjunction with cardiac imaging procedures in the pediatric population. They were also part of the November 2002 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee on the role of brain imaging as an outcome measure in Phase 3 drug trials in Alzheimer's disease. Most recently, they were also part of the March 2005 Oncology Drugs Advisory Committee that assessed the performance of lymph node imaging in patients with possible metastatic cancer.

Please be assured that the Agency believes it possesses the scientific expertise required to perform thorough reviews of applications pertaining to these drug products and make informed decisions, and can supplement that expertise with outside input. In addition, we are committed to resolving scientific issues regarding medical imaging in a timely manner.

Question 7. I have always been concerned that a generic biologic would not pass the FDA's gold standard safety test, especially without the FDA using protected information from other companies' biologic applications. Where does the generic or follow-on biologic process stand at the FDA?

Answer 7. As you know, FDA is conducting a public process to examine the many questions, including scientific and legal issues, that must be answered regarding these products and to ensure that all interested parties have an opportunity to comment. When this process is complete, FDA intends to provide guidance to industry to clarify, consistent with its legal authority, the approval pathway and principles for review of such products, which will protect the public health.

Question 8. Since the implementation of the Generally Recognized as Safe (GRAS) notification process at the Center for Food Safety and Nutrition, what has been the number of full time employees (FTEs) involved in the review and safety evaluation of food ingredients before and after GRAS notification, how many food ingredients have been reviewed under GRAS notification compared to immediately prior to implementation of GRAS and what is the average review time for GRAS petitions submitted under GRAS notification before and after implementation? Would implementation of GRAS notification at the Center for Veterinary Medicine be possible? If not, please explain.

Answer 8. FDA published a proposed rule to establish a GRAS notification program in 1997 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe; the GRAS proposal). Under the GRAS proposal, FDA evaluates whether each submitted notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the Agency to question whether use of the substance is GRAS. Following this evaluation, FDA responds to the notifier by letter.

The Center for Food Safety and Applied Nutrition (CFSAN) implemented a pilot GRAS notification program and received its first notice for a food ingredient in 1998. Through the end of 2004, CFSAN had filed 162 notices (ranging from 12 to 30 notices per year, with an average of 23 per year) and had completed its response to 155 of them. CFSAN has responded to 80 percent of the filed GRAS notices within 180 days (ranging from 7 to 643 days, with an average of 163 days). Over the past 3 years, CFSAN estimates that approximately 7 to 8 FTE's were devoted to support the review of GRAS notices.

In regard to review times of GRAS affirmation petitions submitted before and after implementation of the GRAS notification program, CFSAN last filed a GRAS affirmation petition in 1997 (62 FR 10285; March 6, 1997). Prior to the implementation of the GRAS notification program, CFSAN published an average of 5 affirmations of GRAS status in the Federal Register per year for 1995 and 1996. The time elapsed since CFSAN filed the petition until CFSAN published the final rule ranged from just under 3 years to more than 13 years. CFSAN estimates that approximately 5 or fewer FTE's were devoted the GRAS affirmation petition process prior to implementation of the GRAS notification program (i.e., a time when CFSAN had

re-allocated resources to reduce the backlog of food and color additive petitions). The GRAS affirmation petition process required rulemaking, and was far more resource-intensive than the GRAS notification process, so that fewer responses were achieved per FTE.

While it would be possible for the Center for Veterinary Medicine (CVM) to implement GRAS notification before publication of a final rule, CVM has not done so because an alternative process has existed for many years through establishment of feed ingredient definitions by the Association of American Feed Control Officials (AAFCO) and implementation of a notification program would require significant reallocation of resources currently allocated to high priority programs. CVM has participated in the AAFCO process by serving in a technical scientific review capacity ensuring that the listed ingredients are safe and function as claimed. No comparable process exists for human food. In addition, CVM traditionally has received only a small number of GRAS affirmation petitions and currently does not have resources dedicated for review of GRAS submissions. Implementation of a GRAS notification program at CVM also would be complicated by other issues. CVM, for example, is responsible for many animal species, and review of GRAS notices would need to address the different physiologies and the potential for toxicity in each species. CVM also would need to review whether a notified substance would produce residues that raise human food safety concerns when these substances are fed to livestock species. Addressing complex issues such as these would place significant additional demands on resources. Affected resources would include both personnel and implementation technologies, such as CVM computer systems, which would require modification and support to implement publicly available database of GRAS notices and their ultimate disposition. CVM has met recently with two major feed trade associations on GRAS notification and is reviewing its options, which may include implementing a notification program that uses longer timeframes in consideration of its resource limitations.

RESPONSE TO QUESTIONS OF SENATOR CLINTON BY LESTER CRAWFORD, DVM, PH.D.

Question 1. In your opinion, what are the appropriate roles of the scientific advisory committees and the senior staff of the FDA, if not to make recommendations about the safety and efficacy of drugs like Plan B?

Answer 1. Advisory committees at the Food and Drug Administration (FDA or the Agency) are designed to offer a wide range of views on topics that are discussed in a public forum and to be advisory in nature. FDA seeks and appreciates the recommendations made by the committees. By law, however, the final determination on a drug application, however, remains with the Agency. Although the Agency frequently makes final decisions concerning a new drug application (NDA) that are consistent with an advisory committee's recommendations, FDA is not bound to follow their recommendations. Ultimately, a final decision is based on FDA's evaluation of the data, taking into account all of the views expressed.

Question 2. In your opinion, under what circumstances is it appropriate for the FDA to overrule such a strong, united, scientifically-based recommendation?

Answer 2. The Agency considers the recommendations made by advisory committees very carefully and takes the suggestions made very seriously. However, as noted above, by law, the Agency has final decision-making authority on a drug application. Although the Agency frequently makes final decisions about NDAs that are consistent with advisory committee recommendations, the recommendations are not binding, and FDA may make a different decision.

Occasionally, there are differences of opinion among staff at the Agency on a particular issue. The scientific interchange of ideas is widely encouraged during the review process to ensure a thorough vetting of the issues. Decisions on drug reviews, however, cannot be made by simple majority or with the Agency feeling obligated to rubber stamp an advisory committee vote. None of the advisory committee members are permanent FDA employees with the same responsibilities as our permanent staff. Ultimately, a final decision must be made based on the Agency's evaluation of the scientific data, taking into account all of the views expressed. The greatest responsibility for a final decision concerning an NDA falls on the Center Director or other FDA staff who must put his or her signature on the final action on an NDA and will be the primary individual with the responsibility to defend that decision in the future.

Question 3. As you may be aware, the agency's decision on the EC application last May was widely decried as politically influenced. In fact, my colleague Senator Kennedy and I organized 15 of our colleagues to initiate a GAO investigation into the

process, and we are looking forward to the results. Can we count on you to ensure that the GAO has the FDA's full cooperation in the investigation? What steps will you take to ensure that medical and scientific evidence, not politics, is the basis for the agency's future decisions? Can we count on greater transparency in the FDA's decision-making process?

Answer 3. The Agency makes every effort to fully cooperate with the GAO, and we are doing so with regards to the study that you and Senator Kennedy et al., initiated concerning the Barr/Plan B application.

Additionally, FDA now publishes on its Internet site full information about the Agency's review process on an application if the application is approved. Included in this information is the medical and scientific evidence taken into account when reviewing the application.

Question 4. On November 5, 2004, you pledged to fill the position of Director at the Office of Drug Safety. Can you please update us on the status of this search, over 4 months after you made this pledge?

Answer 4. The Agency has experienced difficulty in recruiting high quality candidates for the position of Director, Office of Drug Safety, through traditional mechanisms such as scientific journal advertisements and government vacancy announcements. We are committed to using all available resources to ensure a systematic, inclusive recruitment process for this critically important position. To that end, FDA has partnered with the recruitment and staffing professionals at the Office of Personnel Management (OPM), Center for Talent Services, to develop and manage a recruitment strategy that we are confident will yield a sizable number of strong candidates and ultimately, a top-notch director. We feel that the additional time and resources invested in a thorough analysis of the leadership and technical competencies required to successfully manage the drug safety program, including input from internal and external subject matter experts and stakeholders, will be time well spent.

Question 5. During your tenure as either Acting Commissioner or Deputy Commissioner of the FDA, the agency placed a black box warning on antidepressant medications because several studies linked this medication to increased risk of suicidal ideation. While the FDA has little control over the off-label use of drugs, the Pediatric Rule, if applied to its fullest extent, could have helped prevent much of the controversy around pediatric antidepressant safety. Could you please tell me how you plan to increase FDA reliance upon the Pediatric Rule, as well as the Best Pharmaceuticals for Children Act, as tools to increase the safety of drugs for Americans?

Answer 5. As of February 2005, FDA has requested studies on 298 products under the Best Pharmaceuticals for Children Act (SPCA), has received the results of those studies on over 117 products, and has added new labeling to 87 products. Most importantly, about 25 percent of the time, when these products that were being used in the pediatric population were studied, we discovered the following: a need for a change of dosing, a new pediatric specific safety concern, or a lack of pediatric efficacy. In fact, most of the pediatric studies conducted to assess the efficacy and safety of the selective serotonin reuptake inhibitors (SSRI) antidepressants were performed utilizing the SPCA process. The data collected for these studies allowed FDA to evaluate the risk of suicidality (thoughts or attempts) in children who have taken these products.

As you know, in December 2003 the Pediatric Research Equity Act (PREA) became law and established FDA's authority to implement the principles of the Pediatric Rule. Since PREA was enacted, the Agency has required evaluation of the pediatric need for drug and biologic product applications that are submitted for an adult indication. Through this process, the Agency determines if pediatric studies are required, may be deferred, or should be waived for each product for the specified indication. Waivers are granted, for example, if the disease or condition to be treated does not occur in pediatrics, such as prostate cancer or Alzheimer's disease. Once a pediatric need determination is made, the sponsor is informed if pediatric studies are required, have been deferred, or are waived.

The BPCA and PREA work together as powerful FDA tools for obtaining important safety, efficacy, and dosing information for pediatric patients.

Question 6. Following the flu vaccine shortage that occurred in fall 2004, which was the third shortage experienced by our Nation since 2000, several questions were raised about the FDA's oversight of vaccine manufacturing facilities, especially after it was revealed that the agency had been aware of contamination issues at the Chiron facility prior to the shutdown of this facility by British drug regulators. With the loss of this production capacity, the U.S. vaccine supply for the 2004 flu season

was effectively cut in half. If you are confirmed as Commissioner, how will you work to ensure, from the regulatory standpoint, that future flu shortages do not occur? What activities will you undertake to assist manufacturers who are currently in or who enter the flu vaccine market with producing a safe, reliable and uncontaminated vaccine product? What other steps can the FDA take to ensure an adequate supply of flu vaccine on an annual basis?

Answer 6. FDA is working with manufacturers and its regulatory counterparts in anticipation of having an ample supply of influenza vaccine for the coming season and annually thereafter.

FDA is using a dual-track strategy. FDA's first track is to facilitate Chiron's effort to correct its manufacturing problems. FDA and MHRA, the British regulatory agency, have an agreement with Chiron that allows full information sharing. FDA has used that agreement to collaboratively review Chiron's remediation plans and activities, and the Agency is providing continuing and extensive feedback to both Chiron and MHRA. In addition, FDA signed an information sharing agreement with MHRA that will, among other things, permit advance communication on important issues. The agreement was effective February 14, 2005.

FDA is actively communicating on inspection activities. Only after passing MHRA and FDA inspections will Chiron be able to provide vaccine to the U.S. market. In the spring when critical stages of manufacturing are taking place, the Agency plans a comprehensive inspection to verify whether Chiron has adequately addressed its problems. While much work remains to be done, it appears that Chiron is making progress.

FDA's second track is to facilitate overall greater capacity and diversification in the U.S. influenza vaccine supply. It is important to recognize that the demand for vaccine and other economic issues are primary factors that determine whether a manufacturer will seek and maintain a license in this country.

CDC and FDA are working to encourage vaccination throughout the flu season, including January and February. To increase the total doses available, manufacturers can produce vaccine over a longer time period, and that becomes available during these months. Because influenza cases usually continue well after November and December when most people are seeking immunization, later vaccination is beneficial. The Public Health Service is working to better communicate this important public health message.

In addition, FDA has been working to stimulate manufacturers not licensed in the U.S. to provide or, where needed, develop the safety and effectiveness data to obtain U.S. licensure. The Agency has actively engaged several interested companies. FDA has informed manufacturers that the Agency is willing to consider all approaches to licensing, including accelerated approval based on surrogate markers, e.g., the patients' immune response to the vaccine. In addition, Sanofi Pasteur and MedImmune have indicated their willingness, if needed, to do what they can to increase production.

Very importantly, FDA has challenged itself to identify other lessons learned from this year's influenza season and is evaluating how this experience could be used to prevent similar events in the future. While there are some elements that FDA cannot control, the Agency is making significant changes. For example, FDA plans to conduct inspections of influenza vaccine manufacturers on an annual basis, and the Agency is completing or has completed agreements that allow information sharing with numerous foreign regulatory agencies. In addition, FDA has recently engaged in a confidentiality agreement with MHRA that covers exchange of information for all inspections.

Question 7. There are many clinical areas where the synthesis and evaluation of existing research, as well as better, more definitive research, could improve the quality of care and reduce costs. The Agency for Healthcare Research and Quality (AHRQ) has recently begun a program of comparative effectiveness studies, for which my colleagues and I managed to secure $15 million dollars in funding last year. One of the first studies to be initiated under this comparative effectiveness program is a systematic review of the Cox-2 drugs, which will be completed in August 2005. Could you please comment on the ways in which such comparative effectiveness reviews can be used to enhance the work of the Office of Drug Safety?

Answer 7. We are more than willing to use any information that may be discovered by the comparative effectiveness studies to assist the Office of Drug Safety. Although such studies are not necessarily designed to identify unknown safety concerns, it is certainly possible that valuable information may be identified. We would want to evaluate the results and data before we can comment as to whether such studies will enhance the work of the Office of Drug Safety.

Question 8. Several questions have been raised as to whether the FDA has the legislative and regulatory authority it needs to carry out its mission. What additional authority would you identify as necessary to enable the FDA to ensure the safety and efficacy of the drugs, medical devices and foods manufactured and sold in our Nation?

Answer 8. FDA is fully capable of carrying out its mission under its current statutory and regulatory authority. If we identify gaps in our authority as we move to implement our various initiatives, we will work with the Administration and the Congress to address those. We have worked with Congress on many legislative efforts including MDUFMA, generic and pediatric exclusivity provisions, food allergens, minor use and minor species for animal drugs, and bioterrorism protections—all of which have enhanced our ability to help protect public health.

Question 9. Do you feel the FDA has adequate access to clinical and scientific expertise in the full range of specialties and sub-specialties? If not, what steps can the agency take to improve this access? How can the agency better utilize the scientific and medical resources in our Nation in a way that will not raise the conflict of interest issues for which the FDA has been criticized in its experiences with both the Cox-2 and silicone breast implant advisory panels?

Answer 9. The Food and Drug Administration (FDA) has a responsibility to regulate products that comprise approximately one fourth of the Nation's consumer expenditures. Within the United States there are only a limited number of experts on any given topic; these experts usually work together through effective scientific collaboration. Most of the Nation's scientists are honored to serve their country by becoming members of FDA's advisory committees and, consequently, the Agency has little trouble recruiting the foremost experts in the field to serve on such advisory committees. Inherent in the process of clinical product development and evaluation is the competition for the Nation's experts. FDA staff evaluates the potential for financial conflict of interest and weighs these facts with the need for the Agency to use the most qualified experts to gain the necessary scientific information upon which to evaluate decisions that impact the public health.

Question 10. At a hearing of the House Appropriation Committee's Subcommittee on Agriculture on March 11, 2004, you stated: "The FDA is overwhelmed by imports, which have increased fivefold since 1994. It's difficult for us and we are missing the mark, but we pledge to do better." The FDA's proposed budget for 2006 includes a 5 percent cut for food-safety inspections. How do you plan to ensure the safety of FDA-regulated food imports? What percentage of food shipments should FDA be inspecting and on what basis do you make that determination?

Answer 10. The fiscal year 2006 Budget does not reduce field examinations of imported food. FDA will continue to examine about 93,000 import lines in fiscal year 2006 as well as in fiscal year 2005. To manage the ever-increasing volume of imported food shipments, FDA is using risk management criteria to achieve the greatest food protection with our available resources. While we cannot physically inspect every shipment, it is important to note that every shipment containing FDA-regulated products entered through the Bureau of Customs and Border Protection (CBP's) automated system is electronically reviewed by FDA's system and those FDA-regulated products requiring further investigation are identified. FDA's Operational and Administrative System for Import Support (OASIS) determines if the shipment meets identified criteria for physical examination or sampling and analysis or warrants other review by FDA personnel. This electronic screening allows FDA to concentrate its limited enforcement resources on high-risk shipments while allowing low-risk shipments to proceed into commerce.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 provided a significant new tool that enhances FDA's ability to electronically review all FDA-regulated imported shipments. That law requires that FDA receive prior notice before food is imported or offered for import into the United States. Advance notice of import shipments, called "Prior Notice," allows FDA, with the support of the CBP, to target import inspections more effectively and help protect the Nation's food supply against terrorist acts and other public health emergencies. With the new prior notice requirement, specific information mandated by the Bioterrorism Act must be submitted to FDA before the imported food arrives in the United States. This not only allows the electronic system to review and screen the shipments for potential serious threats to health (intentional or otherwise) before food arrives in the United States, but it also allows for FDA staff review of prior notices for those products flagged by the systems as presenting the most significant risk. FDA worked very closely with CBP in developing this screening system. FDA receives approximately 27,000 prior notice submissions about incoming food ship-

ments every day. The Prior Notice Interim Final Rule became effective December 12, 2003. At the time of the statement you mentioned, FDA had not yet had much experience with the new prior notice requirement. Since then, FDA's experience with the prior notice system has been that it permits FDA to further refine our risk-based targeting and allocate resources for inspections more effectively.

The fiscal year 2006 budget requests an increase of $30 million for food defense activities. Twenty million dollars of this increase will support a national laboratory network known as the Food Emergency Response Network (FERN). A critical component of controlling threats from deliberate food-borne contamination is the ability to rapidly test large numbers of samples of potentially contaminated foods for a broad array of biological, chemical, and radiological agents. FERN will increase our laboratory surge capacity through a nationwide network of Federal and State laboratories capable of testing the safety of thousands of food samples, thereby enhancing the Nation's ability to swiftly respond to a terrorist attack. The additional $10 million will be used for targeted food defense research, for continued coordination and sharing of data with the Department of Homeland Security as part of the government-wide Bio-Surveillance Initiative, and for upgrades in FDA's crisis management capabilities.

Question 11. Section 130 of the Food and Drug Administration Modernization Act requires sponsors to report annually on the status of post-marketing commitments. In what ways has such reporting improved the FDA's ability to engage in post-approval safety monitoring? How can the system be improved so as to avoid the confusion that arose among patients and providers following the recent Cox-2 controversy?

Answer 11. This authority assisted FDA greatly in considering the risk/benefit profile of marketing drugs. For example, FDA recently convened a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committees to discuss overall benefit to risk considerations for COX-2 selective non-steroidal anti-inflammatory drugs. The Advisory Committees analyzed all available information, much of it post marketing data obtained through this authority, from recent studies of Vioxx, Celebrex, Bextra, naproxen, and other data for non-selective NSAIDs and COX-2 selective products. The Advisory Committee issued recommendations that the Agency is promptly and carefully reviewing before taking further action.

Recently, I joined Secretary Leavitt to announce important efforts that we are undertaking with FDA to improve its ability to monitor and respond to emerging drug safety information.

These steps will ensure both a better internal process of deliberation on drug safety issues that ensures appropriate and independent consideration of all issues, as well as a stronger ability to gather data about drug safety issues once a drug has been approved.

Most importantly, we are moving to encourage more transparency and to ensure that patients and physicians have the most up-to-date and complete information necessary to inform their treatment decisions. This new Drug Information Initiative will give patients, healthcare professionals, and other consumers quick and easy access to the most up-to-date and accurate information on medicines and make FDA's drug review, approval, and monitoring programs as transparent as possible.

This is in addition to FDA's Five Point Plan to Improve Drug Safety, a major initiative designed to improve the monitoring of drug products recently approved for marketing. The major components of this initiative include:

- Sponsoring a major study of the Drug Safety System by the Institute of Medicine;
- Implement a Program for Adjudicating Differences of Professional Opinion;
- Conducting a nationwide search to identify a permanent director for the Office of Drug Safety;
- Conducting a series of workshops and meetings on drug safety and risk management; and
- Publishing risk management guidance.

FDA's Office of Drug Safety (ODS), in the Center for Drug Evaluation and Research (CDER), is already an independent office separate from the Office of New Drugs, the office that reviews new drug applications. Both the Office of New Drugs and the Office of Drug Safety report directly to the Director of the CDER. ODS has independent authority to perform its own research and does so every day. To be valuable, this independent research must conform to widely accepted scientific standards and normal scientific procedures and peer review should not be bypassed. And when drug safety issues are identified, they must be factored into the risk-benefit

equation so that safe and effective drugs remain available to patients who need them.

FDA has a longstanding commitment to provide a strong resource base for its drug safety program. The budget for fiscal year 2006 continues this commitment. The President has proposed a 24 percent increase for FDA's post-market safety program to help further ensure that America's drug product supply is safe and effective, and of the highest quality. Under this proposal, CDER's ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such as risk management, risk communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.

Question 12. In light of concern that FDA activities are influenced unduly by factors other than science, what assurances can you provide that your leadership and your leadership team will pursue a science-based agenda, rather than an ideological-based agenda? What qualifications are most important to you when assembling your leadership team? Who are you considering as possible members of your leadership team?

Answer 12. FDA has often been in the position of making decisions that have strongly motivated interests in favor or opposed to a product approval decision. While social factors and economic interests, for example, may result in opposing decision preferences, FDA's statute is clear that decisions should be based on science, and the requirements of the law, not ideology or opinion. Sometimes the science is not adequately developed to provide for a clear decision, and decisions have to be deferred until the adequate information is available. I am committed, if confirmed, to ensuring that, during my tenure as commissioner, FDA's decisions will be based on science and the requirements of the law and that the basis for FDA's decisions are as open and transparent to the public as possible, consistent with the law.

My vision for the future of FDA is one of transformation. Internally at FDA, we're transforming from domestic-focused, paper-based processes, employing yesterday's technologies, to global, electronic data-driven decisions that apply the latest science. And we're transforming our culture to one of transparency, collaboration, and cutting-edge thinking.

As you know, I have recently appointed new Associate Commissioners for the Office of Management and for the Office of Policy and Planning. The qualifications that are most important to me as I assemble my leadership team are the qualities that support transformation: scientific and management ability, innovation and cutting-edge thinking, ability to confer and collaborate internally and externally and to ensure transparency of our processes, ability to manage organizational change effectively, and vision to see leveraging opportunities that yield public health protection.

RESPONSE TO QUESTION OF SENATOR ENSIGN BY LESTER CRAWFORD, DVM, PH.D.

There is currently a major dispute between independent compounding pharmacists and the Food and Drug Administration (FDA) regarding the very legality of pharmacy compounding.

The FDA appears to be taking the position that when a pharmacist compounds a prescription drug pursuant to a lawful order from a physician, veterinarian or medical practitioner, that this is a new drug that technically needs to be submitted through the new drug approval process. This interpretation, which does not seem to be based on existing statutes or recent court decisions, would effectively outlaw compounding and would deny patients necessary medical care.

Recently, the FDA has been aggressive in its enforcement against compounded medications for non-food animals, arguing that these compounded medications are new drugs that must be submitted to an Abbreviated New Drug Application (ANDA) process. Additionally, the FDA has asserted that it is illegal to use bulk ingredients when compounding for non-food animals. Since the vast majority of drugs compounded for use by non-food animals utilize bulk ingredients, this would result in the denial of medical care to countless animals.

Question. Can you please provide the committee with a clear statement as to the FDA's current position on pharmacist compounding for both human and non-food animals, including actual statutory citations for the FDA's position?

Answer.—**I. Statutory Authority: General Overview**

Sections 201(p) and (v) of the Federal Food, Drug, and Cosmetic Act (the act) respectively define the terms "new drug" and "new animal drug" as products that are not generally recognized among qualified experts as safe and effective for use under the conditions recommended in their labeling. With respect to human drugs, section 505(a) prohibits the introduction or delivery for introduction into interstate commerce of "new drugs" that have not been pre-approved by FDA as safe and effective for their intended uses. Similarly, new animal drugs that have not been pre-approved by FDA are deemed unsafe within the meaning of section 512(a)(1) of the act and, therefore, adulterated under section 501(a)(5) of the act. Where the compounding is for food or non-food animals and is from approved animal or human drugs, it is permitted if it complies with sections 512(a)(4) and (5) of the act and 21 CFR Part 530.

Sections 301(a)–(d) and (k) of the act prohibit, among other things, the introduction, delivery, and receipt for distribution of unapproved, adulterated, or misbranded drugs in interstate commerce. Because the drugs compounded in pharmacies typically are not "generally recognized as safe and effective" within the meaning of sections 201(p) and 201(v), they meet the act's definition of "new drugs" and "new animal drugs." Accordingly, they are also technically subject to the act's pre-approval requirements for "new drugs" and "new animal drugs."

II. FDA's Current Approach to Human Drug Compounding

In light of the preceding statutory analysis, Congress attempted to legalize certain aspects of traditional pharmacy compounding by amending the act in the mid-1990s. Section 127 of the Food and Drug Administration Modernization Act of 1997 amended the act by adding section 503A, which specified certain conditions under which compounded human drugs could be exempt from certain requirements of the act, including the aforementioned requirement under section 505 that all new drugs be pre-approved by FDA as safe and effective for their intended uses before being introduced into interstate commerce. In April 2002, however, the United States Supreme Court struck down as unconstitutional the commercial speech restrictions that Congress included in section 503A of the act. See *Thompson* v. *Western States Medical Center*, 535 U.S. 357 (2002). The Court left in place the Ninth Circuit's holding that the unconstitutional restrictions could not be severed from the rest of section 503A, and that the provision (including its exemptions) was therefore invalid in its entirety.

As a result, the agency now uses its longstanding policy of exercising its enforcement discretion to permit certain types of pharmacy compounding. This policy is articulated in Compliance Policy Guide (CPG), section 460.200, issued on June 7, 2002. FDA recognizes that pharmacists traditionally have extemporaneously compounded reasonable quantities of drugs. This traditional practice follows the receipt of a valid prescription for an individually identified patient from a licensed practitioner. The compounding is performed at the pharmacy site for nearly immediate dispensing or administration to the patient. FDA has long expressed the view that such compounding serves an important medical purpose, and FDA has no intention of eliminating or frustrating this historical practice.

FDA believes, however, that some pharmacies are engaged in practices that fall outside the bounds of traditional pharmacy compounding. These pharmacies are engaged in manufacturing and distributing unapproved new drugs in violation of the act. Many of these pharmacies make large quantities of unapproved drug products in advance of receiving a valid prescription for them, and copy commercially available drug products when there is no medical need for these compounded products. It is appropriate that pharmacies engaged in activities analogous to manufacturing drugs for human or animal use be held to the same provisions of the act as drug manufacturers.

FDA's CPG contains factors that the agency considers in deciding whether to exercise its enforcement discretion with respect to pharmacy compounding. One factor is whether a firm is compounding drugs for third parties who resell them to individual patients. Another is whether a firm is compounding drugs in anticipation of receiving prescriptions, except in very limited quantities. Another is whether a firm is compounding a copy, or essentially a copy, of a commercially available FDA-approved drug product. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved, commercially available drug. In these circumstances, however, FDA may consider whether there is documentation of patient-specific medical need for the compounded product. Other factors in the CPG include whether a firm is compounding drugs from active ingredients that are not components of FDA approved drugs, whether a firm is compounding drugs that are like drugs that were

withdrawn or removed from the market for safety reasons, or whether a firm is not in compliance with applicable State law regulating the practice of pharmacy.

III. FDA's Current Approach to Animal Drug Compounding

As in the case of human drugs, FDA recognizes that some compounded animal drugs serve an important purpose in the practice of veterinary medicine. Accordingly, FDA continues to evaluate the appropriateness of different animal drug compounding and to use its enforcement discretion in applying the provisions described above. Under its policy described in Compliance Policy Guide (CPG) 7125.40, FDA is most likely to pursue enforcement action when the scope and nature of the compounding activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the act. As with human drug compounding, the CPG contains factors that the agency considers in deciding whether to exercise its enforcement discretion with respect to animal drug compounding. The 13 factors described in the CPG include whether a firm is compounding drugs for third parties who resell them; whether a firm is compounding drugs in anticipation of receiving prescriptions, except in very limited quantities; whether a firm is compounding a copy, or essentially a copy, of a commercially available FDA-approved drug product; and whether a firm is compounding from bulk active ingredients, except where the use of the bulk active ingredient is of low regulatory concern either in general or on a case-by-case basis.

FDA is revising the CPG to further explain its enforcement policies with respect to the compounding of drugs for food and non-food animals. A number of groups, including the International Academy of Compounding Pharmacists, the American Veterinary Medical Association, the American Association of Equine Practitioners, and other affected groups, have met with the Agency to discuss their concerns with the current CPG and to suggest changes to it. In revising the CPG, FDA wants to make sure that it provides the clarity that the regulated industry believes is lacking in the current CPG.

RESPONSE TO QUESTIONS OF SENATOR FRIST BY LESTER CRAWFORD, DVM, PH.D.

Question 1. Americans have tremendous confidence in the United States' prescription drug supply due to our closed regulatory system, which includes rigorous safety and efficacy standards enforced by the Food and Drug Administration (FDA). Following the worldwide withdrawal of Vioxx, some have questioned the FDA's ability to maintain the public's trust and confidence, and have argued that the FDA has not been sufficiently concerned about the safety of Cox-2 inhibitors and other prescription drugs. As Commissioner, what steps would you take to strengthen the FDA's drug safety program and better protect public health? Are there actions the FDA could take to improve its post-market surveillance of prescription drugs?

Answer 1. I take very seriously the questions that arise concerning safety and efficacy of drugs both before and after approval. FDA approves a drug only when the demonstrated benefit outweighs its known risk for an intended population. However, the Agency cannot anticipate all possible effects of a drug during the clinical trials that precede approval. Occasionally, FDA identifies serious adverse effects after approval either in post-marketing clinical trials or through the Agency's strong post-market drug safety program.

Recently, I joined Secretary Leavitt to announce important efforts that we are undertaking with FDA to improve its ability to monitor and respond to emerging drug safety information.

These steps will ensure both a better internal process of deliberation on drug safety issues that ensures appropriate and independent consideration of all issues, as well as a stronger ability to gather data about drug safety issues once a drug has been approved.

Most importantly, we are moving to encourage more transparency and to ensure that patients and physicians have the most up-to-date and complete information necessary to inform their treatment decisions. This new Drug Information Initiative will give patients, healthcare professionals, and other consumers quick and easy access to the most up-to-date and accurate information on medicines and make FDA's drug review, approval, and monitoring programs as transparent as possible.

This is in addition to a major initiative designed to improve the monitoring of drug products recently approved for marketing. The major components of this initiative include:

- Sponsoring a major study of the Drug Safety System by the Institute of Medicine;
- Conducting a nationwide search to identify a permanent director for the Office of Drug Safety;

• Conducting a series of workshops and meetings on drug safety and risk management; and
• Publishing risk management guidance.

FDA's Office of Drug Safety (ODS), in the Center for Drug Evaluation and Research (CDER), is already an independent office separate from the Office of New Drugs, the office that reviews new drug applications. Both the Office of New Drugs and the Office of Drug Safety report directly to the Director of the CDER. ODS has independent authority to perform its own research and does so every day. To be valuable, this independent research must conform to widely accepted scientific standards and normal scientific procedures and peer review should not be bypassed. And when drug safety issues are identified, they must be factored into the risk-benefit equation so that safe and effective drugs remain available to patients who need them.

FDA has a longstanding commitment to provide a strong resource base for its drug safety program. The budget for fiscal year 2006 continues this commitment. The President has proposed a 24 percent increase for FDA's post-market safety program to help further ensure that America's drug product supply is safe and effective, and of the highest quality. Under this proposal, CDER's ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such as risk management, risk communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.

Question 2. The National Institute for Health Care Management (NIHCM) estimates that spending on direct-to-consumer advertising increased to $2.5 billion on 2000, compared to $791 million in 1996. What is the FDA's role in regulating prescription drug advertising? In particular, has the FDA conducted recent studies or surveys of physicians or consumers regarding the impact of direct-to-consumer advertising on prescription drug utilization, cost, and quality of care? And if so, what have been the results? Based on the results of the FDA's own analysis, and the analysis of others, what is your view regarding the impact of direct-to-consumer adverting on utilization, costs, quality of care, and patient education?

Answer 2. Section 502(n) of the Federal Food, Drug, and Cosmetic (FD&C) Act (or the act) provides the Agency with authority to regulate prescription drug advertisements. Implementing regulations (Title 21, Code of Federal Regulations [CFR] section 202.1) provide specifics about the content of such advertisements. Nothing in the law or regulations prohibits direct-to-consumer (DTC) promotion in any advertising medium. Also, the advertising provisions of the act do not address the issues of pharmaceutical coverage by insurance companies, advertising costs, or drug product price.

FDA believes consumer-directed advertisements can play an important role in advancing the public health by encouraging consumers to seek treatment of diseases that may be under-treated and diseases for which patients may not be aware of treatment options. We have conducted research that confirms that DTC advertising, when done correctly, can serve positive public health functions, such as increasing patient awareness of diseases that can be treated, and prompting thoughtful discussions with physicians that result in needed treatments being prescribed—often, not the treatment in the DTC advertisement. Results of our research shows that many physicians believe that DTC can play a positive role in their interactions with patients and that many physicians thought that DTC ads made patients more involved in their healthcare.

At FDA, CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC) is responsible for regulating prescription drug promotion. DDMAC's mission is to protect the public health by helping to ensure that prescription drug information is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering optimal communication of labeling and promotional information to both health care professionals and consumers.

In February 2004, we issued three draft guidance documents, addressing: (1) consumer-friendly options for presenting risk information in consumer-directed print advertisements for prescription drugs; (2) criteria FDA uses to distinguish between disease awareness communications and promotional materials; and, (3) a manner in which restricted device firms can comply with the rules for disclosure of risk information in consumer-directed broadcast advertising for their products.

FDA adopted a comprehensive, multi-faceted, and risk-based strategy for regulating consumer-directed advertising of medical products, which emphasizes the use of warning letters, untitled letters, development of guidance that facilitate voluntary compliance, frequent informal communications with industry and advertisers, and research on the public health effects of consumer-directed promotional materials.

While we believe the survey results discussed above confirm our belief that DTC ads help increase patient awareness about the availability of effective treatments for their health problems, we will continue to ensure that our DTC policies help prevent potential misperceptions about benefits and risks of the advertised treatment and promote the importance of prescribing decisions being made with the intervention of a health care professional.

Question 3a. Last year, the British Medicines and Healthcare products Regulatory Agency (MHRA) suspended Chiron's license to manufacture influenza vaccine, resulting in a loss to the U.S. influenza vaccine supply. As we approach the 2005–06 influenza season, recent events highlight the pressing need to stabilize, protect, and strengthen our vaccine supply. What are the FDA's plans to prevent a future potential shortage?

Answer 3a. Recent experiences, particularly those of the past 7 months, have taught us important lessons about manufacturing and inspectional activities with respect to influenza vaccine. Although FDA has always interacted extensively with influenza vaccine manufacturers throughout the vaccine production cycle, the annual changes in the flu vaccine and the increased dependence on a smaller number of manufacturers highlight the risks of unexpected manufacturing difficulties. For these reasons, in 2005 and the future, we plan to conduct inspections of influenza vaccine manufacturers on an annual basis, with additional interactions with manufacturers and, in the case of foreign facilities, their regulatory agencies where appropriate, based on findings or events that raise concerns.

FDA is working with manufacturers and its regulatory counterparts in anticipation of having an ample supply of influenza vaccine for the coming season through a dual-track strategy.

FDA's first track is to facilitate Chiron's effort to correct its manufacturing problems. FDA and MHRA, the British regulatory agency, have an agreement with Chiron that allows full information sharing. FDA has used that agreement to collaboratively review Chiron's remediation plans and activities, and the Agency is providing continuing and extensive feedback to both Chiron and MHRA. In addition, FDA signed an information sharing agreement with MHRA that will, among other things, permit advance communication on important issues. The agreement was effective February 14, 2005.

FDA is actively communicating on inspection activities. Only after passing MHRA and FDA inspections will Chiron be able to provide vaccine to the U.S. market. In the spring when critical stages of manufacturing are taking place, the Agency plans a comprehensive inspection to verify whether Chiron has adequately addressed its problems. While much work remains to be done, it appears that Chiron is making progress.

FDA's second track is to facilitate overall greater capacity and diversification in the U.S. influenza vaccine supply. It is important to recognize that the demand for vaccine and other economic issues are the primary factors that determine whether a manufacturer will seek and maintain a license in this country.

CDC and FDA are working to encourage vaccination throughout the flu season, including January and February. To increase the total doses available, manufacturers can produce vaccine over a longer time period, and that becomes available during these months. Because influenza cases usually continue well after November and December when most people are seeking immunization, later vaccination is beneficial. The Public Health Service is working to better communicate this important public health message.

In addition, FDA has been working to stimulate manufacturers not licensed in the U.S. to provide or, where needed, develop the safety and effectiveness data to obtain U.S. licensure. The Agency has actively engaged several interested companies. FDA has informed manufacturers that the Agency is willing to consider all approaches to licensing, including accelerated approval based on surrogate markers, e.g., the patients' immune response to the vaccine. Sanofi Pasteur and Med Immune have indicated their willingness, if needed, to do what they can to increase production.

FDA has challenged itself to identify other lessons learned from this year's influenza season and is evaluating how this experience could be used to prevent similar events in the future. For example, as mentioned above, FDA plans to conduct inspections of influenza vaccine manufacturers on an annual basis, and the Agency

is completing or has completed agreements that allow information sharing with numerous foreign regulatory agencies.

Question 3b. What policy proposals are necessary to increase domestic production capacity and advance research and development? And, what is the status of new technologies such as animal cell culture and reverse genetics?

Answer 3b. HHS has announced that it plans to spend $439 million department-wide on influenza related activities in fiscal year 2006. This amount is an increase of nearly $400 million over the fiscal year 2001 level of $41 million, and represents the Administration's commitment to addressing this important public health concern.

The Administration is making the largest investment ever made by the Federal Government to protect against influenza. We welcome the continued support of Congress for this work, and view influenza preparedness as a critical responsibility as well as an important opportunity. The Department has announced two Requests for Proposals designed to encourage U.S.-based influenza vaccine manufacturers to have both the capacity and raw materials necessary to produce large quantities of vaccine using current egg-based methods, which are efficient and have a long and generally successful history. In November 2004, HHS awarded a contract to Sanofi Pasteur to help ensure year round availability of an increased egg supply in case it is needed for a pandemic or for future vaccine shortages. These contracts and other research supported by HHS through NIAID will also help us move from dependence solely on egg-based production technology to the development of U.S. licensed cell-culture based and/or recombinant protein and DNA-based vaccines. While work remains to obtain sufficient vaccine yields and evaluate cell-based vaccines for their safety and effectiveness, moving from an egg-based production to a cell-culture production can potentially shorten the time needed to produce vaccine as well as decrease the risk of contamination inherent in egg-based production.

In an important new development, HHS is supporting development of vaccines against potential pandemic strains. Through this effort we hope to obtain experience in the formulation and use of such a vaccine and to prepare in the event that these strains become pandemic. As part of HHS' efforts to support pandemic preparedness, NIAID contracted for the production of pilot lots of potential pandemic vaccines from the two licensed U.S. manufacturers of inactivated influenza vaccine. HHS contracted for the production of 2 million doses of vaccine against H5NI avian flu, the influenza type of current concern in Southeast Asia. NIAID is preparing to initiate clinical studies of the first H5N1 vaccine under INDs that FDA oversees, and both agencies will be working together to evaluate the results. While much work remains, these steps to produce and evaluate pandemic influenza vaccines are a critical component of our preparedness efforts. Reverse genetics is a method that can lead to more rapid generation of reference strains needed to manufacture influenza vaccines. This methodology was used to manufacture the H5N1 investigational vaccine noted above. In addition, studies supported by the National Institutes of Health and FDA will try to develop vaccine strategies that could lead to longer lived immunity and to vaccines that help protect against multiple strains of influenza. FDA is actively engaged with sponsors and manufacturers that are interested in developing such new technologies and has approved cell-based and recombinant vaccines for prevention of other infectious diseases such as chicken pox, rubella, polio, and hepatitis.

Question 4. In May 2004, the Institute of Medicine's (IOM) Immunization Safety Review Committee examined the hypothesis that vaccines, specifically the measles-mumps-rubella (MMR) vaccine and thimerosal-containing vaccines, are causally associated with autism. The committee concluded that the evidence favors a rejection of a causal relationship between thimerosal-containing vaccines, or the MMR vaccine, and autism.

In a joint statement in 1999, the U.S. Public Health Service, which includes the FDA, and the American Academy of Pediatrics urged vaccine manufacturers to reduce or eliminate thimerosal in vaccines. The U.S. Public Health Service and the American Academy of Pediatrics noted that they "are working collaboratively to assure that the replacement of thimerosal-containing vaccines takes place as expeditiously as possible while at the same time ensuring that our high vaccination coverage levels and their associated low disease levels throughout our entire childhood population are remained."

To date, what process has been made in reducing or eliminating thimerosal in vaccines? What does scientific evidence show regarding the affect of trace amounts of this preservative? What are the FDA's current efforts to reduce child exposure

to mercury? And, what is your view of the current scientific evidence regarding a relationship between vaccines and autism?

Answer 4. FDA actions have resulted in a marked reduction in mercury exposure from thimerosal in vaccines. Since 2001, all vaccines routinely recommended for children 6 years and under (DTa), hepatitis B, Haemophilus b conjugate (Hib), pneumococcal conjugate, IPV, MMR, and varicella) manufactured for the U.S. market have contained no thimerosal or only trace amounts, with the exception of inactivated influenza vaccine.

In 2004, the Advisory Committee on Immunization Practices recommended routine use of influenza virus vaccine in children 6 to 23 months of age. FDA has approved preservative-free formulations (which contain either no or only trace amounts of thimerosal) for each of the two licensed inactivated influenza vaccines. These influenza vaccines continue to be marketed in both the preservative-free and thimerosal-preservative-containing formulations. Of the two licensed inactivated influenza vaccines, Sanofi Pasteur's (Fluzone) is approved for use in children down to 6 month's of age; Chiron's Fluvirin is approved for individuals 4 years of age and older. The live attenuated influenza vaccine (FluMist, manufactured by MedImmune) contains no thimerosal, and is approved for individuals 5–49 years of age. In addition, pediatric vaccines such as DT, which are administered only to children for whom DTaP is not indicated, are also available in thimerosal-preservative-free formulations, as are Td vaccines, which are indicated for individuals 7 years of age and older.

In addition to FDA's actions outlined above, the PHS agencies have collaborated with various investigators to initiate further studies to better understand any possible health effects from exposure to thimerosal in vaccines. In 2001, the Institute of Medicine (IOM), at the request of CDC and NIH, convened the Immunization Safety Review Committee (the committee) to review selected issues related to immunization safety. This committee has completed two reviews of studies addressing a potential link between thimerosal-containing vaccines and autism. In its first review, conducted in 2001, the committee concluded that the evidence is inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder, and speech or language delay. The committee believed that the effort to remove thimerosal from vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible."

In 2004, the IOM's Committee reviewed this topic again, including new data that had accumulated since its review in 2001. These data included several epidemiological studies conducted in the U.S., Denmark, Sweden, and the United Kingdom, and studies of biologic mechanisms related to vaccines and autism. The committee concluded that this body of evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism, and that hypotheses generated to date concerning a biological mechanism for such causality are theoretical only. Further, the committee stated that the benefits of vaccination are proven and the hypothesis of susceptible populations is presently speculative, and that widespread rejection of vaccines would lead to increases in incidences of serious infectious diseases like measles, whooping cough, and Hib bacterial meningitis.

FDA has succeeded in reducing children's exposure to mercury from vaccines during the first 6 months of life and continues to work toward reducing everyone's thimerosal exposure through vaccines. With the exception of the inactivated influenza vaccine, which was recently added to the list of routinely recommended pediatric vaccines, all routinely recommended licensed pediatric vaccines that are currently being manufactured for the U.S. market contain no thimerosal or only trace amounts of thimerosal. FDA, together with our colleagues within the other Health and Human Service agencies, will continue to study data relating to the incidence and etiology of autism.

Question 5. This month the World Health Organization (WHO) confirmed 10 new cases of human infection with H5N1 avian influenza virus, as reported by the Ministry of Health in Viet Nam. Since January 2004, 69 human cases of H5N1 infection have been reported, 46 cases of which have been fatal. Earlier this year, Senator Gregg, myself and others unveiled S. 3, the Protecting America in the War on Terror Act of 2005, which includes biodefense provisions to better protect and strengthen our public health infrastructure in the event of a pandemic outbreak. What is the FDA's role in ensuring pandemic preparedness? Are there actions the FDA Commissioner could take to improve our preparedness and response capabilities?

Answer 5. FDA's goal is to establish a process to produce pandemic influenza vaccine in the shortest amount of time possible and protect the largest number of peo-

ple, using a vaccine that is safe, effective and easy to deliver. The full details of the draft Pandemic Influenza Preparedness and Response Plan are located on the HHS website at: *http://www.dhhs.gov/nvpo/pandemicplan/annex5.pdf.* Through all these efforts, and with enhanced global surveillance by CDC and its partners, we have the unique opportunity to effectively intervene and potentially blunt a global pandemic, should one occur.

FDA is actively participating in the HHS efforts for pandemic planning as highlighted in our response to Question 3.

Question 6. Over the past 20 years, the number of people who are obese nearly doubled in the United States. An estimated 30 percent of U.S. adults are now classified as obese and over 60 percent are classified as overweight. The number of obese children between the ages of 6 and 11 has tripled over the past 3 decades. During the 108th Congress, I introduced two pieces of legislation, the Improved Nutrition and Physical Activities (IMPACT) Act and the Childhood Obesity Reduction Act. Both were intended to help address this serious and significant public health threat.

Last year, the Department of Health and Human Services (HHS) unveiled a strategy to combat obesity. As a part of HHS' comprehensive strategy, the FDA's Obesity Working Group released a report which proposes a series of recommendations, including developing a national education campaign, encouraging the availability of nutritional information at restaurants, enhancing the calorie information on food labels, and strengthening the coordination of obesity research. Where does this FDA initiative stand today? What have been its results? Are there additional steps the FDA could take in order to combat the ever-rising tide of obesity across this Nation?

Answer 6. There is no simple solution to the problem of obesity. Achieving success in reducing and avoiding obesity will occur only as a result of efforts over time by individuals as well as various sectors of our society. Most associations, agencies, and organizations believe that diet and physical activity should be addressed together in the fight against overweight and obesity.

Obesity is a growing and urgent public health problem in the United States. Today, almost two-thirds of all Americans are overweight and over 30 percent are obese. To help confront the problem of obesity in the U.S. and to help consumers lead healthier lives through better nutrition, in August 2003, FDA created an Obesity Working Group (OWG), which was charged with preparing a report that outlines an action plan to cover critical dimensions of the obesity problem from FDA's perspective and authorities. FDA's "Calories Count" report was released on March 12, 2004.

The OWG report provides a range of short and long-term recommendations to address the obesity epidemic. For FDA's actions the emphasis is on calories. Progress to date follows:

We have published two advance notices of proposed rulemaking (ANPRMs), in response to the recommendations in the OWG report, seeking comments on the following:

- How to give more prominence to calories on the food label, for example, increasing the font size for calories, including a column in the Nutrition Facts panel of food labels for percent Daily Value for total calories, and eliminating the listing for calories from fat. In addition, the Agency is seeking comment on the reformulation of the foods or redesign of packaging that may occur if any changes are made to the food label;
- Whether to amend certain provisions of the nutrition labeling regulations concerning serving size, such as for multiple-serving packages that may reasonably be consumed in a single eating occasion.

We continue to encourage manufacturers to take advantage of the flexibility in current regulations on serving sizes to label as a single-serving those food packages where the entire contents of the package can reasonably be consumed at a single eating occasion. We also continue to encourage manufacturers to use appropriate comparative labeling statements that make it easier for consumers to make healthy substitutions. Since release of the OWG report, the Agency, in meetings with industry, has made a point to encourage manufacturers to take advantage of the existing flexibility in serving size regulations, and companies are responding. For example, Kraft Foods is instituting dual column labeling for all its packaged foods containing 2–4 servings per package.

FDA continues to encourage restaurants voluntarily to provide point-of-sale nutrition information to customers, including calorie information on a nationwide basis.

FDA is also working to develop educational strategies and partnerships to support appropriate messages and teach people, particularly children, how to lead healthier lives through better nutrition. We are starting work with the Girl Scouts of the USA, under terms of a Memorandum of Understanding signed this past fall, to pro-

vide outreach and education in a science-based initiative to focus on improving health, nutrition, and physical activity. In addition, FDA's field offices are participating in local partnerships to reach and teach children. For example, in Central Florida, FDA's South East Region is part of the Seminole County Healthy Kids Partnership to promote positive opportunities for school-aged children in Seminole County to learn healthy nutrition and the value of increased daily physical activity.

Also, FDA's Center for Drug Evaluation and Research (CDER) will continue to work with pharmaceutical sponsors to facilitate development of effective therapies to address the important public health issue of obesity and its attendant morbidities. An advisory committee meeting was held on September 8, 2004 to discuss the draft guidance on Clinical Evaluation of Weight-Control Drugs. The Agency is working to finalize the guidance.

We believe that, when implemented, the report's recommendations will make a worthy contribution to confronting our Nation's obesity epidemic and helping consumers lead healthier lives through better nutrition.

RESPONSE TO QUESTIONS OF SENATOR JEFFORDS BY LESTER CRAWFORD, DVM, PH.D.

Emergency Contraception Questions

Dr. Crawford, while you have been the Acting Commissioner of the FDA the agency has failed to approve Barr Laboratories' application to make Plan B emergency contraception available over-the-counter. This is despite the recommendations of the FDA's own advisory panels, the support of major professional medical associations, and overwhelming scientific evidence supporting the move. I have a series of questions I would like to ask on this issue:

Question 1a. Please explain how the FDA failed to approve the application when the independent medical and scientific review performed by the FDA Advisory Committees overwhelmingly approved the application?

Answer 1a. Advisory committees at the Food and Drug Administration (FDA or the Agency) are designed to be only advisory in nature. Advisory Committees offer a wide range of views on topics, usually in a public forum. FDA seeks and appreciates the recommendations made by the committees. The statutory responsibility for making a final decision on a drug application, however, remains with the Agency. Although the Agency frequently makes final decisions concerning new drug applications (NDAs) that are consistent with advisory committee recommendations, FDA is not bound to follow their recommendations. Ultimately, a final decision is based on FDA's evaluation of the data, taking into account all of the views expressed.

At the joint advisory committee meeting held December 16, 2003, to review the Barr/Plan B OTC application, the Chairman of the Advisory Committee on Over-the-Counter Drugs as well as other members of the joint committee expressed concerns regarding whether the actual use data in the application were generalizable to the overall population of nonprescription users, chiefly because they felt the data showed inadequate sampling of younger age groups. Their concerns were strong enough for them to vote against approving the application, and the Center Director felt these concerns were important enough to seek further information from the sponsor on that issue. It is his job to see that the data meet the standards for safe and effective OTC use before a final decision is made.

Question 1b. To better understand how this decision on Plan B was reached, can you provide a full account of the decision processes that caused the FDA to go against the recommendations of the review panel and professional staff?

Answer 1b. After completing review of the supplemental application, FDA concluded that the application could not be approved at this time because: (1) adequate data were not provided to support the conclusion that young adolescent women can safely use Plan B for emergency contraception without the professional supervision of a licensed practitioner and (2) a proposal from the sponsor to change the requested indication to allow for marketing of Plan B as a prescription-only product for women under 16 years of age and a non-prescription product for women 16 years and older was incomplete and inadequate for a full review. The supplemental application that was submitted proposed OTC status for both adults and children based primarily on an actual-use study in 585 subjects. Only 29 of the 585 subjects enrolled in the study were 14–16 years of age, and none was under 14 years of age. Therefore, FDA concluded that the application was not approvable during that review cycle.

In its letter notifying the sponsor of this decision, the Agency stated the following:

"Before this application can be approved, you would have to provide data demonstrating that Plan B can be used safely by women under 16 years of age without the professional supervision of a practitioner licensed by law to administer the drug. Alternatively, you could supply additional information in support of the revised indication to allow for marketing of Plan B as a prescription-only product for women under the age of 16 years and a non-prescription product for women 16 years and older, including draft product labeling. If you take the latter approach, your response to this letter would have to include details of how you propose to implement simultaneous prescription and non-prescription marketing of Plan B for women of different ages in a single packaging configuration while complying with all relevant statutory and regulatory requirements for labeling and marketing of this product. We will have to assure ourselves that your proposed approach is consistent with our statutory authority. If you pursue the alternative approach, we also would request details of your proposed program to educate consumers, pharmacists, and physicians about the dual marketing of Plan B as both a prescription and non-prescription product, as well as your proposed program to monitor implementation of this novel approach."

The issuance of the Not Approvable letter in May 2004 did not mean that a supplemental application could not be approved in the future. The Not Approvable letter described what the applicant would need to do to obtain approval for its initial supplemental application. In this case, the applicant chose to revise its application and requested to market Plan B as prescription-only for women under the age of 16 and as nonprescription for women 16 years of age and older. FDA is reviewing this latest supplemental application.

Question 1c. Barr Pharmaceuticals has submitted a revised proposal to the FDA, but even though a deadline has passed, they have not been notified of any outstanding questions or requests for information. Can you tell us what the reason is for the delay at this point, why the review was not completed on time and when a decision could be expected?

Answer 1c. The Prescription Drug User Fee Act (PDUFA) goal date for the Barr Laboratories/Plan B OTC supplemental application was January 22, 2005. Because of the complexities involved, the application is under review at the Center.

Use of PDUFA Funding for Drug Safety

In the past, the Congress has authorized the FDA to accept user fees to augment its ability to review drug and medical device products. Some have urged that some of those fees should be directed to ensuring the safety of these products. Thus far, the Congress has agreed with the industries' position that post-market product safety review is the responsibility, and should be paid for, through general revenues.

Question 2. I would like to hear your thoughts on how you plan to provide funding for post market product safety. Failing the availability of appropriations, would some portion of user fees be a reasonable source of funding?

Answer 2. Under the current system of user fees, a portion of fees is used for drug safety activities. Drug safety activities are a cornerstone of the drug approval process, and PDUFA user fees support these activities. Moreover, under PDUFA III, Congress authorized the use of user fees for certain post-market risk management activities. Thus, user fees already fund drug safety activities, and the Agency supports the use of fees for this essential activity.

Clinical Trials Database

Dr. Crawford, clinical trials are an important part of the drug approval and use process. Information that comes out of clinical trials continues to be of vital concern to doctors, patients, manufacturers and regulators. To that end, it seems like a good idea to expand the amount of information about trials that is available.

Question 3. What is your response to the idea of creating a mandatory clinical trials registry, modeled after clinicaltrials.gov, which makes information available about all clinical trials? Would having complete information, including results information, available publicly help doctors and patients make better decisions about medications?

Answer 3. I believe that patients and health professionals should have as much information possible to inform their treatment decisions. That is why I joined Secretary Leavitt to announce important efforts that we are undertaking with FDA to improve its ability to monitor and respond to emerging drug safety information.

Importantly, we are moving to encourage more transparency and to ensure that patients and physicians have the most up-to-date and complete information necessary to inform their treatment decisions. This new Drug Information Initiative

will give patients, healthcare professionals, and other consumers quick and easy access to the most up-to-date and accurate information on medicines and make FDA's drug review, approval, and monitoring programs as transparent as possible.

Moreover, clinicaltrials.gov is the world's largest source of information about federally- and privately-sponsored clinical trials throughout the United States and abroad, making critically important public health information available to patients and the healthcare community. Working together and in collaboration with our sister agencies in the HHS, FDA implemented section 113 with the establishment of ClinicalTrials.gov in February 2000. Today, ClinicalTrials.gov contains information on more than 11,000 publicly and privately funded trials. Recent public attention to the increasing availability of clinical trial information has made pharmaceutical companies more aware of the responsibility to list clinical trials in ClinicalTrials.gov. Moreover, many companies that previously listed "pharmaceutical company" in the drug sponsor field are now identifying themselves by their company name.

Moreover, the agency has been making information from drug approval packages publicly available for some time. Drug approval packages, which include medical, chemistry, pharmacology, statistical, and clinical pharmacology/biopharmaceutics reviews, are posted on the FDA website Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) and are made available in response to requests under the Freedom of Information Act after certain trade secret, confidential commercial or other privileged information has been redacted in accordance with relevant legal requirements. The Best Pharmaceuticals for Children Act (BPCA) requires FDA to make available to the public a summary of the medical and clinical pharmacology reviews of the pediatric studies conducted for supplements submitted under the BPCA. This information can be found at: http://www.fda.gov/cder/pediatric/Summaryreview.htm. Additional information is also available from questions and answers posted on FDA's website and can be found at: http://www.fda.qov/cder/drugsaffda/FAQ.htm.

Protecting First Responders

In order to ensure that first responders are prepared to respond to a chemical terrorist attack, the Congress and Department of Homeland Security have worked hard to ensure that funding is available and that the first responders and the public have the best possible equipment and medical countermeasures. The military for decades has used effective countermeasures against chemical, biological, radiological or nuclear (CBRN) threats. There is concern about how the FDA is transitioning use of these products from the battlefield to the domestic sector as terrorist threats have expanded.

*Question 4a.*Please explain what FDA is currently doing to ensure the chemical, biological, radiological or nuclear (CBRN) medical countermeasures are reviewed and approved without jeopardizing the safety of the general public.

Answer 4a. FDA is working diligently to speed the development and availability of safe and effective medical products to protect Americans from the harmful effects of chemical, biological, radiological, and nuclear (CBRN) agents. The Agency is coordinating and collaborating with the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Department of Defense (DOD), academia, and industry regarding novel medical countermeasures (MCMs) and new (counterterrorism) indications for approved medical products for the public and the U.S. military. An important part of this effort is FDA's participation in several interagency working groups to address scientific and policy issues related to medical countermeasure development.

FDA has a number of mechanisms that may be used to expedite approval and access to MCMs. These include the familiar processes for fast track, priority review, and accelerated approval, as well as innovative new tools, such as the "Animal Rule." Under the Animal Rule, animal efficacy data may be used for product approval when human efficacy studies are not ethical or practical and when safety is established through human studies. FDA continues to play a critical role in the design and analysis of animal models that mimic disease progression in humans, recognizing that the lack of established animal models for the study of CBRN agents and associated medical products is a key impediment to future MCM development.

Though not an approval process, FDA also is implementing new authority to allow the use of unapproved medical products and unapproved uses of approved medical products to protect the public and U.S military forces during a declared emergency involving a heightened risk of exposure to a CBRN agent. FDA may issue an Emergency Use Authorization (EUA) for a medical product only if certain statutory criteria are met, including a requirement that the known and potential benefits out-

weigh the known and potential risks. The Agency may impose certain conditions on the EUA and may revoke the authorization if appropriate to protect public health or safety.

FDA's current activities on specific CBRN agents and MCMs include the following:

- Ongoing development efforts associated with a new preventative anthrax vaccine and therapies to treat anthrax infections; a new and safer preventative smallpox vaccine and therapies to treat active smallpox infections; a vaccine to protect against botulinum toxin; therapies for plague; and treatments for special populations, such as children, pregnant women, and those with weakened immune systems, when standard therapies are not advised.
- Continuing an Interagency Agreement (IAG) with CDC for clinical trials to collect human data on plague in African countries to label an antibiotic that would otherwise require an investigational new drug application for product deployment.
- Funding, with the National Institute for Allergies and Infectious Disease, the development of a non-human primate model of pneumonic plague.
- Conducting workshops and meetings to discuss strategies for developing therapeutics for certain CBRN agents.
- Drafting guidance on MCMs for anthrax toxins.
- Working on animal model studies for radiation-related countermeasures.
- Maintaining a database of approved and investigational products that may be candidates for medical countermeasures against Category A agents.

Many of the CBRN threats demand immediate medical treatment, which creates substantial medical and first responder logistical challenges.

Question 4b. Please tell us what FDA's position is regarding the expanded availability of existing medical countermeasures, including the availability of these countermeasures through prescription for individuals, before a terrorist incident occurs.

Answer 4b. The Department of Health and Human Services (HHS) has a lead role in protecting Americans from the effects of terrorist attacks by enhancing public health preparedness and response capabilities. Within HHS, the CDC works with provider and first responder organizations on terrorism prevention and preparedness efforts. FDA's role is to speed the availability of new medical countermeasures through responsive regulatory review of these medical products.

Within the scope of the Agency's statutory authority and mission, FDA participates in and collaborates with HHS and other Federal Agencies on certain public health preparedness and response activities. These include working with CDC in the Cities Readiness Initiative (CRI), a pilot program to aid cities in increasing the capacity to deliver medicines and medical supplies during a large-scale catastrophic event. CRI participants include City/State medical, bioterrorism, and emergency responders, Health Resources and Services Administration (HRSA), Department of Homeland Security Federal Emergency Management Agency (DHS-FEMA), Strategic National Stockpile (SNS), the Department of Justice (DOJ), the Federal Bureau of Investigation (FBI), the Veteran's Administration (VA) and the United States Postal Service (USPS).

FDA also works closely with CDC's SNS, which stockpiles large quantities of medicine and medical supplies to protect the American public if there is a public health emergency (terrorist attack, flu outbreak, earthquake) severe enough to cause local supplies to run out. Once Federal and local authorities agree that the SNS is needed, medicines will be delivered to any State in the United States within 12 hours. Each State has plans to receive and distribute SNS medicine and medical supplies to local communities.

Post Marketing Study Commitments Under Fast Track

When Congress passed the Food and Drug Modernization Act in 1997, we included new authorities for FDA to provide fast-track approval for drugs to treat serious and life threatening diseases. The law was intended to ensure that innovative new treatments would be made available to patients in a timely manner while at the same time ensuring they were both safe and effective. We did that by empowering FDA to mandate additional post approval studies on both safety and efficacy without delaying the approval process. Instead, FDAMA provided the agency with the authority to withdraw approval of a fast-track drug if the drug sponsor failed to conduct a required study with due diligence.

The law has clearly been effective in getting new life-saving treatments on the market. But I'm concerned about reports concerning drug maker compliance with post-approval study commitments those studies are an important piece of the safety and efficacy picture. Now however, questions are being raised about how many of those fast track studies are actually completed.

*Question 5a.*Please provide a summary on the status of each fast track studycommitment, including the date of the drug's approval and the expected date of the study fulfillment. For those that have not yet been initiated, please provide an explanation as to why.

Answer 5a. FDA has approved 38 products under fast track review. Nineteen of the approved fast track products were approved under accelerated approval. All fast-track products that FDA approved under accelerated approval (based on a surrogate endpoint or on a clinical endpoint other than survival or irreversible morbidity) must complete post-marketing confirmatory studies (refer to 21 CFR 314.510). There are 19 such approvals, listed in the answer to question. These products are: Alimta (NDA 21677 only), Erbitux, Velcade, Iressa, Fabrazyme, Fuzeon, Arimidex, Eloxatin, Zevalin, Viread, Gleevec, Campath, Kaletra (NDAs 21226 and 21251), Agenerase (NDAs 21007 and 21039), Ziagen (NDAs 20977 and 20978), and Sustiva.

Twenty three percent (18/80) of accelerated approval confirmatory studies are proceeding according to or ahead of the original schedule. Twenty-six percent (21/80) of accelerated approval confirmatory studies are considered "pending." Many older postmarketing study commitments (e.g., those established prior to FDAMA 1997) did not have study schedules specified at the time of approval. A commitment cannot be deemed "delayed" unless the progress of the study has fallen behind the original study schedule (21 CFR 314.81(b)(2)(vii)). Because some of these older commitments do not have an original study schedule on which compliance may be based, they cannot be considered "delayed." Studies remain "pending" for a variety of reasons; typically while a study is "pending," FDA and the applicant are working together to design a study that will adequately address the objective of the commitment.

Four percent (3/80) of accelerated approval confirmatory studies are considered "delayed." Studies are considered "delayed" if they are proceeding, but not meeting the original study schedule. Studies can be considered "delayed" for a variety of reasons (e.g., enrollment problems, ongoing analysis of study results, or submission of the final study report later than the scheduled date). The review divisions work proactively with sponsors to design trials that will provide the required information and to identify obstacles to completing the trials as they are initiated and begin accrual. However, when unexpected or unavoidable obstacles are encountered and the study becomes "delayed," FDA continues to work with the sponsor to address and try to resolve the reasons for the delay. Sometimes when the obstacles associated with the original study design cannot be readily resolved, new confirmatory studies with defined study schedules are established. One percent (1/80) of accelerated approval confirmatory studies are considered "terminated." FDA encourages sponsors to submit final study reports for "terminated" studies as soon as the reports are completed.

Final study reports have been "submitted" for 60 percent (48/80) of accelerated approval confirmatory studies. Of these 48 PMCs, FDA has reviewed 45 (94 percent) of them and determined that the terms of the commitment have been met (i.e., "fulfilled"); a fulfillment letter has been issued for these PMCs. Three are currently considered "submitted" while the other 45 are considered "fulfilled" according to 21 CFR 314.81(b)(2)(vii). All of the studies for which final study reports were submitted were completed (i.e., none of the final study reports were submitted for "terminated" studies).

Question 5b. Have you ever withdrawn a fast track drug for failure to conduct a required study? What factors guide the FDA in making these decisions?

Answer 5b. For drugs approved under accelerated approval or the animal efficacy provisions, FDA may withdraw approval (described further under 21 CFR 314.530 and 314.620) if:

A post-marketing clinical study fails to verify clinical benefit;

The applicant fails to perform the required post-marketing study with due diligence;

Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

If a manufacturer fails to submit a supplemental application containing the information or request for approval of a pediatric formulation within the time specified by FDA (i.e., deferred pediatric studies under PREA), the drug product may be considered misbranded or an unapproved new drug or unlicensed biologic.

To date, FDA has not undertaken an enforcement action in any of the scenarios described above; however, FDA actively monitors the completion of the required post-marketing commitments and works with individual sponsors to address factors that may delay timely completion of the required studies (e.g., slow enrollment, changes in practice or disease patterns).

Question 5c. Can you tell us what you'll do as Commissioner to ensure drug makers make good on fast-track study commitments in a timely manner.

Answer 5c. In addition to the enforceable post-marketing study commitments described above, the Food and Drug Administration Modernization Act of 1997 (FDAMA) provided FDA with additional authority for monitoring the progress of post-marketing studies. Section 130(a) of Title I of FDAMA added a new provision (section 506B) on post-marketing studies to the Federal Food, Drug, and Cosmetic Act 356b ("the act") (21 U.S.C. 356b). This new provision required sponsors of approved drugs and biological products to report to FDA annually on the progress of their post-marketing study commitments. In addition, FDA was required to do the following:

- Develop and publish regulations prescribing the format of the reports sponsors are to submit to FDA.
- Report annually in the Federal Register on the performance of post-marketing commitment studies.
- Report to Congress on the studies.

After receiving and considering public comments on its proposed rule, FDA published the final rule on October 30, 2000 (65 FR 64607) and the regulations, promulgated under 21 CFR 314.81(b)(2)(vii), became effective in April 30, 2001. In the preamble to the proposed and final rules, FDA announced its intention to make basic information about the status of each post-marketing study commitment available to the public on the Internet. In May 2003, the Agency launched this website. The website is updated quarterly. It includes a searchable database of information on post-marketing studies for drugs and biological products. The database is maintained internally and tracks the progress of all post-marketing study commitments; including those that are required and those that are agreed upon by applicants. FDA's Report to Congress was delivered to Congress in March 2002, and there have since been three annual reports (fiscal year 2002, fiscal year 2003, and fiscal year 2004) on the performance of post-marketing commitment studies published in the Federal Register.

Publication Bias

Among the controversies FDA has faced in recent years is the question of antidepressants prescribed to children. In one now well-publicized case, the drug sponsor had results of several pediatric studies of its widely prescribed drug an off-label use—only one of which demonstrated efficacy in treating major depressive disorder. That single study was published and promoted to doctors, while the other studies, including some submitted to FDA were not publicized.

While I understand the importance of "off label" use drugs to the practice of medicine, I'm equally concerned about cases in which FDA has the results of failed efficacy trials for an off-label use and knows the drug remains widely prescribed for that use.

*Question 6.*What is FDA's obligation to the public and healthcare providers to proactively inform them about information the agency has that contradicts published studies about the safety or efficacy of off-label uses?

Answer 6. FDA makes every effort to keep the public and healthcare providers proactively informed about information concerning the safety and efficacy of drugs that they use. In fact, under our new safety initiative, we plan to release important new information about safe and effective product use, and we intend to make information about emerging risks regarding drug uses available earlier. This will include information such as known and potential safety issues based on reports of adverse events, new information that may affect prescribing of the drug, and the approved indications and benefits of the drug. Under this initiative, we want to make emerging safety information available to practitioners and to patients, so they may consider the information themselves.

RESPONSE TO QUESTIONS OF SENATOR ROBERTS BY LESTER CRAWFORD, DVM, PH.D.

Question 1. Currently, a decision is pending in the commissioner's office regarding the use of an FDA approved antimicrobial for the treatment of severe respiratory outbreaks in poultry. While I understand you cannot comment on this case, many experts in poultry science, veterinary medicine, risk assessment and medical epidemiology have questioned the validity of FDA's evaluation which has been challenged as not being compliant with the Information Quality Act. Further, it appears that the potential benefits to food safety and human health associated with the use of this product were presented to FDA but not considered. As commissioner, will you

subject such assessments and decisions to unbiased scientific peer review to ensure that the best science is used in making decisions that support food safety and protect human health, yet not taking away the ability of livestock and poultry producers to judiciously use the valuable tools that they need?

Answer 1. FDA is committed to using the best available science in its decision-making and has, like other HHS agencies, developed guidelines concerning the Data Quality Act. We are also working, as are other Federal Agencies, to implement where applicable the OMB's Peer Review Bulletin. Moreover, as you know, the formal process for withdrawing approval of a new animal drug gives the drug's sponsor the opportunity to present evidence and legal arguments in support of keeping the drug on the market. In such cases, I review the sponsor's evidence and legal arguments before reaching my determination, and I am not required to follow the rulings by the Administrative Law Judge.

Question 2. We appreciate your leadership last year in FDA moving forward with the draft guidance for the Early Food Safety Assessment. Given the importance of final guidance to assisting USDA in working with our trading partners to keep our international grain markets open, could you give us an indication on when we could expect to see the FDA Early Food Safety Evaluation guidance be published in its final form?

Answer 2. We are currently analyzing over 2000 comments the Agency received on the proposed guidance on the Early Food Safety Evaluation of New Proteins Produced by New Plant Varieties, and we intend to finalize the guidance by the end of the year. FDA's commitment to finalize this document is reflected in the Center for Food Safety and Applied Nutrition 2005 Program Priorities list, or yellow book, where the guidance is an "A-list" goal slated for completion by the end of 2005.

Question 3. The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) required reprocessors of certain types of previously cleared reprocessed medical devices originally intended for single use only to submit to FDA supplemental cleaning, sterility, and functionality data demonstrating that the device functions "like new" in order for the FDA to provide continued market clearance for the device. Approximately 1,800 models of reprocessed SUDs required validation data under MDUFMA. The FDA announced toward the close of 2004 that it had completed its review of supplemental validation data submitted by reprocessors and determined that a significant number of these devices can no longer be commercially distributed. In light of the FDA's determination that at least 33 percent of these submissions failed to demonstrate substantial equivalence, would it not be in the interest of patient safety to require reprocessors to submit validation data for all reprocessed single use devices in order for them to remain marketable?

Answer 3. In the Medical Device User Fee and Modernization Act of 2003/P.L.107-250 (MDUFMA), Congress specified a detailed process by which FDA was to re-evaluate previously-cleared reprocessed single use medical devices (SUDs). In accordance with the intent of Congress, FDA has expended significant resources to accomplish the following:

Premarket Review

On April 30, 2003, FDA identified certain reprocessed SUDs for which 510(k)s must now include "validation data . . . regarding cleaning and sterilization, and functional performance" to show that the devices remain substantially equivalent to predicate devices after all intended reprocessing. FDA issued a guidance document on July 8, 2003 (revised June 1, 2004), describing the types of validation data that would satisfy this MDUFMA requirement.

For devices in this category that already had cleared 510(k)s, validation data (referred to as "Supplemental Validation Submissions (SVSs)") were required to be submitted to FDA by January 30, 2004. FDA received 44 SVSs for reprocessed SUDs for which the 510(k)s had already been cleared. This represented approximately 1,800 previously cleared reprocessed SUDs. Regulatory decisions on all but two of these SVSs were issued by November 1, 2004 as outlined below.

- Fifty-two percent of these devices were determined to be substantially equivalent (SE) to a legally-marketed predicate device and may continue to be marketed.
- An additional 33 percent of the models were determined to be Not Substantially Equivalent (NSE) to a legally marketed predicate device based on the failure to submit supplemental data OR the submission of inadequate supplemental data to FDA. These devices may no longer be legally marketed since they are no longer cleared for commercial distribution in the United States at this time. Reprocessors of these devices may seek clearance for the subject devices anytime in the future by submitting a new 510(k) premarket notification to FDA that satisfies the Agency's premarket requirements including supplemental validation data.

• Approximately 15 percent of previously cleared reprocessed SUD models were withdrawn by the reprocessor. These devices may no longer be legally marketed at this time. Also, FDA conducted field inspections to verify discontinuance of marketing.

In November, 2004, FDA posted, on its website, the status of previously-cleared, reprocessed SUDs that were subject to supplemental validation data requirements described above. This allows hospitals and other interested parties to verify the status of reprocessed devices for use in their facilities. The website includes lists of devices found to be Substantially Equivalent based on a review of the supplemental data. These devices appear under the heading of "Legally Available." In addition, the website lists those devices which may no longer be legally marketed because supplemental data were required but not received, subject 510(k)s were withdrawn by the sponsor, or supplemental data were determined by FDA to be inadequate. These devices are listed as "No Longer Legally Marketed".

On April 30, 2003, FDA also published a list of "critical" reprocessed SUDs whose exemption from premarket notification requirements was terminated. Reprocessors of the devices on this list were required to submit 510(k)s, including the types of validation data described above, by July 30, 2004. No reprocessors of the critical reprocessed SUDs provided any submissions. FDA will conduct follow-up inspections to verify that the firms have stopped marketing these reprocessed devices.

On April 13, 2004, FDA published a list of "semi-critical" reprocessed SUDs whose exemption from premarket notification requirements was terminated. Reprocessors of the devices on that list are required to submit 510(k)s, including validation data, by July 13, 2005.

MDUFMA created a new type of premarket submission, a "premarket report" (PMR), for reprocessed SUDs that otherwise would have required premarket approval applications. Among other items, a PMR must include data on reprocessing procedures, such as validation data regarding cleaning, sterilization, and functional performance.

Adverse Event Reporting

In accordance with MDUFMA, FDA revised the mandatory and voluntary MedWatch report forms to incorporate the reporting of information on incidents related to reprocessed SUDs. FDA posted the revised forms on the MedWatch website in October 2003, along with revised instructions for mandatory reports, and, in early 2004, published a Federal Register notice announcing the availability of the revised MedWatch forms.

Inspections/Enforcement

Since MDUFMA was enacted, FDA has inspected over 150 third-party reprocessors and hospitals engaged in reprocessing. As a result of the information collected, CDRH's Office of Compliance has issued two Warning Letters (to a hospital and a third-party reprocessor).

In fiscal year 2004, FDA inspected over 100 U.S. hospitals and found none currently reprocessing single use devices. FDA has also issued an inspection assignment in fiscal year 2005 for five firms that reprocessed SUDs to ensure that they have discontinued marketing of the devices that were NSE. The five inspections have just been completed and inspection reports are being prepared.

Next Steps

FDA will continue to review submissions for reprocessed single use devices as they are received. FDA has received comments on the lists of critical and semi-critical reprocessed SUDs whose exemption from premarket notification requirements was terminated, and we are currently reviewing these comments. Finally, FDA will continue to inspect reprocessors as appropriate and will inspect new hospital or third-party reprocessors as they are identified.

RESPONSE TO QUESTIONS OF SENATOR GREGG BY LESTER CRAWFORD, DVM, PH.D.

Question 1. In response to controversies surrounding FDA's actions taken with the popular pain-management drugs Vioxx and Celebrex and other medications, FDA recently announced new initiatives to improve drug safety monitoring. Among the initiatives is a plan to provide emerging safety information to physicians and patients. What will be FDA's scientific threshold for determining whether "emerging" safety information should be communicated? Will FDA consider factors surrounding the use of the drug, including risks associated with patients avoiding the use of potentially life-saving medicines based on the preliminary data and whether there are alternative treatments available? Does FDA need any additional authority to ensure the safety and efficacy of new and marketed drugs?

Answer 1. An emerging risk, or emerging safety concern, is a possible serious new side effect, potentially related to a drug on the market, that has been reported to FDA and that FDA is analyzing. A side effect is considered new when, for example, the effect was not seen (or the rate or severity of the effect was not seen) during clinical testing, but was identified after the drug went on the market. For example, sometimes, after a drug is approved, rare but serious side effects may emerge as the drug is more widely used. Sometimes drugs are prescribed for new uses (off-label uses) with unanticipated results. If FDA receives information that a drug interacts with another drug, and this interaction may be causing a serious side effect, this information would be considered emerging.

FDA will consider factors surrounding the use of the drug, including risks associated with patients avoiding the use of potentially lifesaving medicines based on the preliminary data and whether there are alternative treatments available.

I do not believe new statutory authority is needed. We will use all existing regulatory authority and enforcement powers when negotiating label changes with drug companies or when monitoring or managing drug safety issues.

Question 2. Shortly after the Bioterrorism Act was signed into law, the FDA and Customs entered into a Memorandum of Understanding concerning increased coordination and communication over the prior notice requirement for imported foods. What is the status of the implementation of that MOU? To what extent are FDA and Customs and Border Protection (CBP) coordinating with the increased inspections and reinspections of food products? Can you identify what are the barriers to establishing a mechanism for providing prior notice without a manufacturer's facility registration number for food products that are imported for analytical testing or research and development activities that do not involve consumption by humans or animals?

Answer 2. FDA and Customs and Border Protection (CBP) signed the Memorandum of Understanding on December 3, 2003. It allows FDA to commission CBP inspectors to assist FDA in the implementation of the Prior Notice provisions contained in Section 307 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107-188.) This assistance includes coordinating examination and sampling operations with local FDA personnel. At ports that are not staffed by FDA personnel, this assistance includes responding to requests from FDA's Prior Notice Center to examine and sample suspect shipments arriving at such ports. As of March 2005, FDA has commissioned approximately 9,500 CBP inspectors who have received the requisite training. Joint FDA and CBP prior notice activities are coordinated by FDA's Prior Notice Center, which is co-located at CBP's National Targeting Center. This collaboration allows both agencies to share each others' data and targeting systems to evaluate high-risk shipments.

With respect to food imported for quality assurance, research or analysis purposes, FDA stated, in the November 2004 revision of the Compliance Policy Guide for Prior Notice, that it intends to exercise broad enforcement discretion if, after a good faith effort, the person submitting prior notices does not know the registration number of the facility that manufactured the food and instead provides the name and full address of the facility that manufactured the food. FDA has had a version of this policy in effect since August 2004. FDA is also considering this issue, and the comments it has received on it, as it develops the final rule on prior notice.

Question 3. The Federal Food Drug and Cosmetic Act does not include provisions to allow for abbreviated biologics license applications (otherwise known as generic biologics). Can you identify the steps—including steps related to scientific knowledge—needed to proceed with the approval of follow-on versions of biological drugs? Do you agree that any approval requires separate Congressional authorization?

Answer 3. As you know, FDA is conducting a public process to examine the many questions, including scientific and legal issues, that must be answered regarding these products and to ensure that all interested parties have an opportunity to comment. When this process is complete, FDA intends to provide guidance to industry to clarify, consistent with its legal authority, the approval pathway and principles for review of such products, which will protect the public health.

In recent years—and with increasing frequency—questions about generic or follow-on proteins have arisen in response to scientific advances, impending patent expirations, and the ability to better characterize and understand biological products.

Acknowledging scientific and legal limitations in this area, yet also recognizing the public health need to move forward to assist industry and make more products available to the public, FDA is conducting a public process to examine the scientific, and related issues regarding follow-on biologics. This process will ensure that sci-

entific considerations and issues related to Agency authority are fully examined and that all interested parties have an opportunity for input.

Question 4. The media has alleged that there exists a conflict of interest on the part of many qualified specialists who serve on FDA advisory committees. Despite that it is beneficial for both industry and FDA to consult with top experts concerning a drug, device or biologic, critics allege that because they have received compensation by industry during their professional career or because they have used a drug, device or biologic in their professional practice, they are assumed to have conflicts which affect their professional judgment. Would the FDA be able to have an effective advisory committee process without the use of experts who have worked with the drug, device or biologic of interest? Describe the process that FDA has in place to screen and make public potential conflicts of interests before an expert serves on an advisory committee.

Answer 4. It would not be possible for FDA to have an effective advisory committee process without the use of experts who are familiar with the technology related to new proposed drugs, devices or biologics of interest. Due to the scarcity of the specific expertise necessary to evaluate complex scientific issues, these experts are often sought after for consultation by both the Agency and industry. Utilizing junior scientists who are less experienced or less highly qualified in order to completely remove any potential conflict from the committee would hamper the Agency's ability to protect and advance the public health.

The Agency's process is to evaluate the potential financial interests of members and other invited special government employees. FDA makes a determination as to whether the participation of an individual with some financial ties outweighs the need for the agency to understand the science on the topic before the committee. Although the Agency has public guidelines for this process, this is not a black and white process. It requires careful consideration of all facets of the issue in order to evaluate that balance. By permitting waivers for conflicts of interest, Congress has ensured the Nation that the Agency and the public (through the advisory committee process) has access to the most knowledgeable individuals on the meeting topic.

FDA's process of evaluating potential committee members for conflicts is very extensive and transparent. Our methodology is articulated in an extensive document that is publicly available on the agency's Web site (http://www.fda.00v/oc/advisory/conflictofinterest/intro.html). At the beginning of each meeting, a conflict of interest statement is read into the record, which summarizes the results of the conflicts of interest screening. FDA has been commended by the Office of Government Ethics (1997) which stated that it was "impressed with FDA's Program for protecting SGEs from COI . . ." and that FDA is "a model for other Agencies to use in developing their own systems and procedures." Nonetheless it is always prudent to regularly assess the Agency program and determine if any improvements are warranted and in the near future, the Agency will review the advisory committee conflicts of interest disclosure process and work to make the disclosures more easily accessible to the public.

Question 5. As you know, there are no FDA approved drugs to treat some major conditions of companion animals and horses. Despite that many species of animals cannot be successfully treated with currently available FDA approved drugs, the Center for Veterinary Medicine prohibits pharmacists from filling prescriptions for animals by compounding the prescribed drug from bulk drugs. Their policy permits no exceptions even for non-food animals, such as cats, dogs, and horses. Critics of this policy say that, were this ban to be fully implemented and enforced, many animals would suffer or die needlessly. As Commissioner would you permit licensed veterinarians to prescribe drug products which must be compounded and pharmacists to compound such prescriptions for non-food animals when medically warranted from bulk?

Answer 5. FDA has had a longstanding policy of exercising its enforcement discretion regarding certain types of pharmacy compounding. This policy is articulated in Compliance Policy Guide (CPG), section 7125.40, issued in July 2003. FDA recognizes that pharmacists traditionally have extemporaneously compounded reasonable quantities of drugs. This traditional practice follows the receipt of a valid prescription for an individually identified patient from a licensed practitioner. The compounding is performed at the pharmacy site for nearly immediate dispensing for administration to the animal or animals. FDA has long expressed the view that such compounding serves an important medical purpose, and FDA has no intention of eliminating or frustrating this historical practice.

FDA believes, however, that some pharmacies are engaged in practices that fall outside the bounds of traditional pharmacy compounding. These pharmacies are en-

gaged in manufacturing and distributing unapproved new animal drugs in violation of the act. It is appropriate that pharmacies engaged in activities analogous to manufacturing drugs for animals be held to the same provisions of the act as drug manufacturers.

FDA's CPG contains factors that the agency considers in deciding whether to exercise its enforcement discretion with respect to animal drug compounding. The 13 factors described in the CPG include whether a firm is compounding drugs for third parties who resell them; whether a firm is compounding drugs in anticipation of receiving prescriptions, except in very limited quantities; whether a firm is compounding a copy, or essentially a copy, of a commercially available FDA-approved drug product; and whether a firm is compounding from bulk active ingredients, except where the use of the bulk active ingredient is of low regulatory concern either in general or on a case-by-case basis. Thus, for example, where a pharmacist contemporaneously compounds reasonable quantities of drugs from bulk active ingredients for non-food animals in response to a valid prescription for an individually identified patient, FDA has typically not taken enforcement action.

FDA is revising the CPG to further explain its enforcement policies with respect to the compounding of drugs for food and non-food animals. A number of groups, including the International Academy of Compounding Pharmacists, the American Veterinary Medical Association, the American Association of Equine Practitioners, and other affected groups, have met with the Agency to discuss their concerns with the current CPG and to suggest changes to it. In revising the CPG, FDA wants to make sure that it provides the clarity that the regulated industry believes is lacking in the current CPG.

Question 6. On November 16, 2004, I wrote a letter to you recommending the establishment of descriptive claims for whole grains on food labels. Do you agree that establishing descriptor claims such as "excellent source," "good source," and "made with" for whole grain content can provide information so that consumers can make better dietary choices that could lead to the prevention of some diet-related diseases? I understand that the FDA is currently considering a petition requesting descriptive claims for whole grains on food labels. When does FDA expect to act on that petition?

Answer 6. FDA is committed to the goal of making available to consumers more and better information about the health benefits of foods. HHS and the U.S. Department of Agriculture developed the 2000 Dietary Guidelines for Americans and the Food Guide Pyramid, which contain guidelines for increased consumption of whole grain foods. On May 11, 2004, FDA received a petition asking the Agency to establish the descriptive claims "excellent source", "good source", and "made with" for whole grain content of foods. That petition is under review in our Center for Food Safety and Applied Nutrition.

Question 7. Under the proposed reorganization of CDER, the Ophthalmology Sub-Division would be completely absorbed by the Division of Anti-Infective drugs. This proposed merger could potentially have a harmful impact to the review of ophthalmic drugs. As ophthalmic products are merged into anti-infectives, will staff with ophthalmic experience maintain management and review of ophthalmology drugs and final approval recommendations for such products? If not, how does this represent a more efficient structure to ensure the safety and efficacy of ophthalmic drugs?

Answer 7. We expect that individuals with expertise in ophthalmology will continue to play a critical role in reviewing new ophthalmology products, and the reorganization will not affect the timely approval of treatments and drug therapies available to eye care practitioners and their patients. All drug review processes for all products will continue to be held to existing PDUFA goals and timelines during and as a result of the reorganization.

Question 8. FDA has a key role to play in evaluating and approving effective treatments for tobacco dependence, like the nicotine gum, lozenge, and patch. However, more can be done within FDA's existing authority to help smokers who are trying to quit. Such actions include "fast track" status to applications involving products to treat tobacco dependence and considering alternative indications for nicotine replacement therapies, including relapse prevention, relief of cravings, and extended use for those smokers who wish to gradually wean off of tobacco consumption. What steps is FDA taking to expand access to these promising therapies?

Answer 8. The Food and Drug Administration (FDA or the Agency) is committed to employing tools to facilitate the development and marketing of products that may represent important public health advances for smoking cessation. FDA would evaluate for fast track designation and/or priority review status novel products that

have the potential to truly represent a significant advance in the treatment of tobacco dependence. This accelerated development/review is a highly specialized mechanism for speeding the therapies for serious or life-threatening illnesses or for illness for which no therapy exists.

FDA approved Nicorette Gum (nicotine polacrilex), manufactured by GlaxoSmithKline, on January 13, 1984, under accelerated review (6 months). This product received accelerated review because it was a new molecular entity with a therapeutic advantage over existing therapies for smoking cessation. FDA switched Nicorette Gum to over-the-counter status on February 9, 1996. All other approved products underwent standard review because they did not demonstrate a significant benefit over Nicorette Gum.

Question 9a. The FDA approval of RU-486 has raised many concerns regarding the safety and efficacy of the drug regimen.

(a) Please describe why RU-486 was approved under Subpart-H, which is reserved for drugs in treating serious or life-threatening illnesses, such as AIDS and cancer?

Answer 9a. As you know, Mifeprex (sometimes referred to as RU-486) was approved in September 2000 under a previous Commissioner. I am therefore unable to fully respond to this question.

FDA has received reports of serious bacterial infection, bleeding, ectopic pregnancies that have ruptured, and death. In response, in November 2004, FDA announced new safety changes regarding the labeling of Mifeprex. The new warnings to health care providers and consumers include changes to the existing black box on the product to add new information on the risk of serious bacterial infections, sepsis, and bleeding and death that may occur following any termination of pregnancy, including use of Mifeprex.

We will continue to closely monitor the safety of this and all drugs on the market.

Question 9b. Would you also describe why the FDA approved RU-486 for pediatric patients but waived the pediatric rule?

Answer 9b. As you know, RU-486 was approved in September 2000 under a previous Commissioner. I am therefore unable to fully respond to this question. As noted above, the FDA is carefully monitoring adverse events related to this and all drugs on the market.

Question 9c. Please describe information that you have that the product is being promoted by the manufacturer, or by providers on publicly accessible websites, for "off-label" uses. What actions has the agency taken in response to such information?

Answer 9c. The Agency is not aware of the manufacturer promoting off label use of Mifeprex on publicly available websites. FDA's authority to regulate advertising is directed at advertising by the manufacturers, packers or distributors of regulated products.

Question 10. Aside from Mifeprex, in the past 20 years how many new drug applications has FDA approved based solely on data from uncontrolled clinical trials? In the past 20 years how many new drug applications has FDA approved based solely on data from historically controlled trials? For each answer please provide the name of any drugs listed, the NDA number, and a brief description of the trials. With respect to historically controlled trials, please describe the control group used.

Answer 10. Below is a brief summary of FDA's policy regarding control groups for clinical trials intended to support an effectiveness claim for a new drug.

An adequate and well-controlled investigation must be designed to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is substantial evidence to support the claims of effectiveness for new drugs. By definition, an adequate and well-controlled study uses a design that permits a valid comparison with a control to provide a quantitative assessment of the drug effect. Generally, we recognize the following types of controls (21 CFR 314.126(b)(2)):

- Placebo concurrent control
- Dose-comparison concurrent control
- No treatment concurrent control
- Active treatment concurrent control
- Historical control

"No treatment concurrent control" is defined as trials where objective measurements of effectiveness are available and placebo effect is negligible. In such trials, the test drug is compared with no treatment. Such trials usually include randomization. In "historically controlled trials," the results of treatment with the test drug are compared with experience historically derived from the adequately documented

natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

In contrast, uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. However, such studies, if carefully conducted and documented may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. (21 CFR 314.126(e))

As noted above, uncontrolled studies are not an acceptable basis for establishment of a claim of effectiveness, therefore, we cannot cite any examples of drugs approved solely based on uncontrolled trials. With regard to historical controls, FDA does not capture information on the type of control used in clinical investigations to support a demonstration of effectiveness in our databases. Therefore, we are not able to provide a comprehensive list of applications approved based on historical controls in response to your question. However, the following are examples to illustrate experience (NOTE: This is not intended to be a comprehensive listing of all such approvals.):

Example of a product approved using "no treatment concurrent control":

NDA 50-747 Synercid (quinupristin/dalforpristin) for the treatment of vancomycin resistant Enterococcus faecium bacteremia. Four non-comparative studies were conducted. Three of the trials were prospective; the fourth consisted of a collection of individual emergency-use requests.

Examples of products approved using historical controls:

• NDA 20-645 Ammunol (sodium benzoate/sodium phenylacetate) for the treatment of urea cycle disorders. Efficacy was compared to historical data from published literature to evaluate percent survival with therapy compared to how these patients fared in other cohorts before such therapy was available on an investigational basis.

• NDA 21-227 Cancidas (caspofungin acetate) for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies, on the basis of a historically controlled trial with the control developed from hospital records by the sponsor. The approval was supported by information on safety from trials in candida infections.

• BLA STN 103737 Rituxan (rituxumab) and BLA STN 125011.0 Bexxar (tositumomab plus13'I-labeled tositumomab) for the treatment of non-Hodgkin's lymphoma. Approvals for both products were based on multicenter, single-arm studies. The historical control is based on knowledge of the natural history of untreated non-Hodgkin's lymphoma, a disease that does not have spontaneous remissions.

Question 11. Aside from Mifeprex, how many drugs has FDA approved in which an off-label, unapproved use for a second drug is mandated as part of an approved regimen? If there are any others, please provide the name of the drugs, the NDA numbers in which such use was mandated, and any documents from FDA requiring such use.

Answer 11. We do not track information about references to the use of other drugs as part of the approved labeling for drug products. Therefore, we are not able to provide a comprehensive response to your question. The following examples illustrate FDA's experience: (NOTE: This is not intended to be a comprehensive listing of all such products.)

Examples of products approved in combination with another drug for a use that was not sought by the sponsor of the second product and for which a change in labeling of the second product was not required include:

• NDA 20-954 Busulfex (busulfan), in combination with cyclophosphamide, for hematopoietic stem cell transplant.

• NDA 20-509 Gemzar (gemcitabine hydrochloride), in combination with cisplantin, for treatment of non-small cell lung cancer.

• NDA 20-388 Navelbine (vinorelbine tartrate), in combination with cisplantin, for treatment of non-small cell lung cancer.

• NDA 20-262 Taxol (paclitaxel), in combination with cisplantin, for treatment of ovarian cancer and non-small cell lung cancer, and for use with Adriamycin (doxorubicin) plus Cytoxan (cyclophosphamide) in adjuvant breast cancer.

• NDA 20-638 Vistide (cidofovir), for the treatment of CMV retinitis in patients with AIDS, has a boxed warning which states that it must be administered with probenecid to reduce nephrotoxicity.

• BLA STN 103792.0 Herceptin (traxtuzumab), in combination with paclitaxel, for first-line treatment of metastatic breast cancer.

• NDA 21-462 Alimta (pemetrexed disodium), in combination with cisplantin, for the treatment of mesothelioma.
• NDA 21-663 Menopur (menotropins), for use in female infertility in which pituitary suppression is required. Dosage instructions are given for patients who have received a GnRH agonists; however, GnRH agonists are not approved for this use.

RESPONSE TO QUESTIONS OF SENATOR HARKIN BY LESTER CRAWFORD, DVM, PH.D.

Post Market Surveillance

Question 1. On February 15th, the Food and Drug Administration announced the formation of the Independent Drug Safety Oversight Board. The purpose of the Board is to get information to doctors and consumers about safety concerns with drugs that have already been approved. However, the board has no regulatory authority and is only advisory in nature. In addition, the Board is not truly separate from the Office of New Drugs, the entity responsible for action if a problem is found with a drug after market approval. Shouldn't there be a separate entity charged with post-market surveillance and evaluation of approved drugs? Should this entity have the authority to make label changes or take other actions designed to protect the consumer? What actions could FDA take to inform physicians and consumers about the risks associated with specific drugs after drug approval? What resources would be necessary to maintain this advisory role for FDA?

Answer 1. The make up of the Drug Safety Oversight Board (Board) and the vesting of decision-making authority in the Center Director ensure that the Board's deliberations will be independent of the drug approval process. Representatives of the Office of New Drugs comprise only three of the Board's 15 voting members. To the extent possible, we will ensure that none of the three voting members has been involved in the actual decision-making concerning a particular drug coming to the Board. If they have been involved in the actual decision-making process, they will not be allowed to vote. The Board will make recommendations to the Center Director who will make the final decisions on drug safety issues. The Center Director and the Deputy Center Director are not normally involved in the approval of new drugs. Decisions made by the Center Director, based on recommendations made by the Board, will be implemented through the appropriate program office. The Center Director retains final authority for Center decisions. A dissenting Office Director may appeal the Board's recommendations to the Center Director before the Center Director makes a final decision.

The Office of Drug Safety (ODS) is charged with post-marketing surveillance of approved drugs. ODS is already an independent office separate from the Office of New Drugs, the office that reviews new drug applications. Both offices report directly to the Acting Director of CDER. ODS has strong support within both CDER and the Agency and has been a vital part of FDA's efforts to ensure drug safety. In addition, ODS has independent authority to perform its own research and does so every day.

Regarding the issue of informing physicians and consumers about the risks associated with specific drugs after approval, FDA will share drug safety information sooner and more broadly, including information on potential safety problems even before the Agency has reached conclusions that would prompt a regulatory action. The new communications include:

• The Proposed Drug Watch "Web" Page

At the direction of the new Drug Safety Oversight Board, this Web page will include emerging information about possible serious side effects or other safety risks.

• Healthcare Professional Information Sheets

We have also started developing and making these sheets available to better communicate emerging risk information to the medical community. We will continue to develop these information sheets, or will update existing ones, as we become aware of possible serious new side effects for a drug. The sheets will contain an FDA Alert describing emerging information.

• Patient Information Sheets

We have already begun to develop and make available on CDER's Website user-friendly information for patients and consumers on drugs about which we have identified emerging issues. We will continue to develop these sheets, or update existing ones, as we become aware of possible serious new side effects for a drug. The sheets will contain an FDA Alert describing emerging information.

Mercury Exposure

Question 2a. Many of my constituents are concerned about the apparent rise in the rate of Autism, or Autism spectrum disorders, in children. One hypothesis of-

fered to explain the rise is that increased exposure to mercury causes autism. Scientists have demonstrated that mercury levels are rising in fish common in human consumption. In addition, some childhood vaccines contained mercury as a preservative. It is my understanding that only some flu vaccine currently uses mercury based preservative. Is this correct?

Answer 2a. Yes, this is correct. The mercury-containing preservative referred to above is thimerosal. At this time, there are three U.S. licensed influenza vaccine manufacturers, Sanofi Pasteur, Chiron and Medlmmune. Both Sanofi Pasteur and Chiron manufacture inactivated influenza vaccines, which are available in a thimerosal-preservative containing formulation and a preservative-free formulation that contains no thimerosal or only trace amounts (≤ 1 microgram mercury per 0.5 ml dose; ≤ 0.5 micrograms mercury per 0.25 ml dose). Medlmmune manufactures a live, intranasally administered influenza vaccine that contains no thimerosal. Only Sanofi Pasteur's Fluzone is indicated for children as young as 6 months of age (no influenza vaccine are approved for children less than 6 months of age). Chiron's Fluvirin is indicated for persons 4 years of age and older, and Medlmmune's Flumist (a live intranasal vaccine) is indicated for persons 5–49 years of age.

In 2004, the Institute of Medicine considered this topic, including new data that had accumulated since its previous review in 2001. These data included several epidemiological studies conducted in the United States, Denmark, Sweden, and the United Kingdom, and studies of biologic mechanisms related to vaccines and autism. The committee concluded that this body of evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism, and that hypotheses generated to date concerning a biological mechanism for such causality are theoretical only. Further, the committee stated that the benefits of vaccination are proven and the hypothesis of susceptible populations is presently speculative, and that widespread rejection of vaccines would lead to increases in incidences of serious infectious diseases like measles, whooping cough, and Hib bacterial meningitis.

Question 2b. In existing childhood vaccines are there problems with mercury contamination even in trace amounts? If so, in FDA's opinion is there a health hazard or does more research need to be conducted?

Answer 2b. Childhood vaccines, are not contaminated with mercury. Thimerosal, an organic mercury compound, has been added as a preservative to some vaccines, including pediatric vaccines. The need for a preservative can be eliminated to the extent that it is feasible to manufacture vaccines in single dose vials or syringes. In those instances where thimerosal has been used in earlier stages of manufacture to prevent contamination, it can be removed to the extent possible before final formulation of vaccines, but trace (0.1 microgram mercury per 0.5 ml dose) remains.

Under the FDA Modernization Act (FDAMA) of 1997, the FDA conducted a comprehensive review of the use of thimerosal in childhood vaccines. Conducted in 1999, this review found no evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions. However, as a precautionary measure, and because the elimination or reduction of mercury in vaccines was a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources are challenging to eliminate, the Public Health Service (including the FDA, National Institutes of Health (NIH), Center for Disease Control and Prevention (CDC) and Health Resources and Services Administration (HRSA)) established the goal of removing thimerosal as a preservative from vaccines routinely administered to infants as soon as possible. The PHS and the American Academy of Pediatrics issued two Joint Statements, urging vaccine manufacturers to reduce or eliminate thimerosal in vaccines as soon as possible (CDC 1999) and (CDC 2000).

FDA has worked with and continues to work with vaccine manufacturers to reduce or eliminate thimerosal from vaccines, and significant progress has been made. Since 2001, all vaccines routinely recommended for children 6 years of age and under (DTa), hepatitis B, Haemophilus b conjugate (Hib), pneumococcal conjugate, IPV, MMR, and varicella) manufactured for the U.S. market have contained no thimerosal or only trace amounts, with the exception of inactivated influenza vaccine. FDA has approved preservative-free formulations (which contain no thimerosal or only trace amounts of thimerosal) for each of the two licensed inactivated influenza vaccines. FDA is in discussions with manufacturers of influenza vaccine regarding their capacity to increase the supply of preservative-free vaccine.

The U.S. Public Health Service agencies have collaborated with various investigators to initiate further studies to better understand any possible health effects from exposure to thimerosal when used as a preservative in vaccines. Available data has been reviewed in several public forums including the Workshop on Thimerosal sponsored by the National Vaccine Advisory Committee, held in August 1999, two meet-

ings of the Advisory Committee on Immunization Practices of the CDC, held in October 1999 and June 2000, and the Institute of Medicine's Immunization Safety Review Committee in July 2001 and February 2004. Through its Vaccine Safety Datalink, the CDC has examined the incidence of autism as a function of the amount of thimerosal a child received from vaccines. In this study, no significant association was found between autism and exposure to thimerosal-preservative-containing vaccines. Additional studies are planned in these areas.

In 2001, the Institute of Medicine (IOM), at the request of CDC and NIH, convened the Immunization Safety Review Committee (the committee) to review selected issues related to immunization safety. This committee has completed two reviews of studies addressing a potential link between thimerosal-containing vaccines and autism. In its first review, conducted in 2001, the committee concluded that the evidence is inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder, and speech or language delay. The committee believed that the effort to remove thimerosal from vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible."

In 2004, the IOM's Committee reviewed this topic again, including new data that had accumulated since its review in 2001. These data included several epidemiological studies conducted in the United States, Denmark, Sweden, and the United Kingdom, and studies of biological mechanisms related to vaccines and autism. The committee concluded that this body of evidence favors rejection of a causal relationship between thimerosal containing vaccines and autism, and that hypotheses generated to date concerning a biological mechanism for such causality are theoretical only. Further, the committee stated that the benefits of vaccination are proven and the hypothesis of susceptible populations is presently speculative, and that widespread rejection of vaccines would lead to increases in incidences of serious infectious diseases like measles, whooping cough, and Hib bacterial meningitis.

Question 2c. Is mercury used at any other stage in the manufacturing process? Is FDA conducting or has the FDA conducted any research into mercury exposure and its potential linkage to Autism or related disorders?

Answer 2c. FDA has taken seriously reports to the Vaccine Adverse Event Reporting System (VAERS) of developmental delay following vaccination. CBER conducted a follow-up study of VAERS reports of autism. As part of the study, CBER, in conjunction with outside autism experts, reviewed available medical records and surveyed parents and others who have reported autism after vaccinations. The goal of the interviews was to gather information about demographics, clinical features, potential risk factors, family history, vaccines administered, time interval from vaccination to autism onset, rapidity of symptom onset, and interval from diagnosis to submission of reports. Another goal was to determine how a parent makes the association between a child's autism and vaccination. Because of the limitations of VAERS, this study could not be designed to determine whether vaccines cause autism. However, the study demonstrated a secular trend in the perception that autism might be associated with vaccines. The study specifically recommended that when providing guidance about immunizations and vaccine-preventable diseases, the risks of immunization should be discussed in the context of the risks of infection [Woo J., AJPH 94(6):990-995, 2004].

As noted in the response to the previous question, CDC did conduct a study using the Vaccine Safety Datalink that did not show an association between thimerosal preservative-containing vaccines and autism (Vertraeten T etal, Pediatrics 112:1039-1048, 2003). In addition, the IOM was asked by the PHS to do an independent assessment of this issue, and their reports (published in 2001 and 2004) are noted above as well.

Old Drugs

Question 3. There are many old drugs on the market that have never been approved directly by the Food and Drug Administration. Many are very common. However, several drugs have been removed from the market after specific manufacturers pursue a New Drug Application on the old drug. This process has, in some cases, removed some competitors from the market.

Last year, you testified before the House Agriculture Appropriations Committee that a Prescription Drug Monograph System that could govern these drugs would be too expensive to implement. But you also said that you had another way to bring these drugs under regulation without disrupting the market. Have you determined another solution?

Answer 3. FDA believes that the Agency's draft Compliance Policy Guide (CPG) on marketed, unapproved drugs, when finalized, will provide a means of protecting the public health without imposing undue burdens on consumers or disrupting the market unnecessarily. The Compliance Policy Guide (CPG) describes how we intend to exercise our enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. By targeting drugs based on health risk, efficacy, and health fraud factors, the CPG will enable the Agency to: (1) devote its limited resources to those actions most likely to improve public health; (2) proceed against an individual product or an entire class of products, as appropriate; (3) preserve resources for review and approval of new, innovative drugs; and (4) remove potentially unsafe or ineffective products from the market without awaiting the resolution of lengthy rulemaking processes. The CPG also will create an incentive for manufacturers of marketed, unapproved drugs to seek approval of their products, which further addresses safety and efficacy concerns while preserving Agency resources. We received a number of comments on the draft CPG and we are revising the draft in response to the comments.

Emergency Contraception

Question 4. Last spring, the FDA refused to allow over the counter sale of emergency contraception, which prevents pregnancy in almost all cases when taken within 48 hours and has been found to be safe and effective. In January, the FDA failed to act by its own internal deadline on a new request to sell emergency contraception from behind the counter. Can you provide assurances that a decision will be made within the next 3 months?

I understand that part of the delay is concern by the FDA about the precedent of requiring Plan B be held behind a pharmacy counter as they do many places in Europe. However, in Iowa and many other States we are going to start requiring that all pseudoephedrine products be held behind the pharmacy counter. Do you agree that keeping emergency contraception behind the counter is a perfectly workable option?

The denial of the Plan B application for over the counter status despite the vote of the Advisory Board and the internal staff recommendation has created the appearance that the Agency caved to political pressure. What plans do you have to prevent that sort of problem in the future once you are confirmed?

Answer 4. The Prescription Drug User Fee Act (PDUFA) goal date for the Barr Laboratories/Plan B OTC supplemental application was January 22, 2005. The application is still under review.

This current cycle review is in response to resubmission of the application by the sponsor in July 2004. The resubmission proposes a revised indication to allow for marketing Plan B as prescription-only for women under the age of 16 and as nonprescription for women 16 years of age and older. In addition, they propose an educational program for healthcare providers, pharmacists, and patients.

The issuance of the Not Approvable letter in May 2004 did not mean that a supplemental application could not be approved in the future. The Not Approvable letter described what the applicant would need to do to obtain approval for its initial supplemental application. In this case, the applicant chose to revise its application and requested to market Plan B as prescription-only for women under the age of 16 and as nonprescription for women 16 years of age and older. FDA is currently reviewing this application.

Advisory committees at FDA were established to be only advisory in nature. When selecting participants for membership in advisory committees, we seek experts with a broad range of experience in their field. Such committee meetings offer a wide range of views that are discussed in a public forum. FDA seeks and appreciates the recommendations made by the committees. The final determination on a drug application, however, remains with the Agency. Although the Agency frequently makes final decisions concerning a new drug application (NDA) that are in accord with an advisory committee's recommendations, FDA is not bound to follow their recommendations. It is not unusual for there to be occasional differences of opinion among staff at the Agency on a particular issue. The scientific interchange of ideas is widely encouraged during the review process to ensure a thorough vetting of the issues. Decisions on drug reviews, however, cannot be made by simple majority vote or with the Agency feeling obligated to rubber stamp an advisory committee vote. Ultimately, a final decision is made based on FDA's evaluation of the data, taking into account all of the views expressed.

Decisions on this review are being made within FDA's Center for Drug Evaluation and Research where the supplemental application is still under review.

Restaurant Labeling

Question 5. Dr. Crawford, in your remarks, you stated some members of the chain restaurant industry had adopted some measures to provide nutritional information to consumers. Could you provide specific information on which chains are meeting the recommendations found in "Counting Calories: Report of the Working Group on Obesity." What are they doing to meet those recommendations? Given the rise in eating outside the home, Dr. Crawford, in your opinion do consumers need more information, rather than less, to make rational, responsible, and personal decisions about their own health? How can this information be standardized across restaurants?

Answer 5. The FDA Report on Obesity, "Calories Count," recommends several steps be taken concerning "away-from-home" foods. Specifically the Agency urged the restaurant industry to launch a nationwide, voluntary, and point-of-sale nutrition information campaign for consumers, to include information on calories. As a companion to that, and in response to input from the restaurant industry that they do respond to consumer demands, the report also calls on consumers to routinely request calorie and other nutrition information when they eat away from home. FDA has been doing this in speeches and meetings since release of the report. Further, the report calls on FDA to work with a third party facilitator to begin a national policy dialogue to seek consensus-based solutions to specific aspects of the obesity problem involving food consumed away from home. In June of 2004, FDA signed a contract with the Keystone Center, a nationally recognized facilitator for policy and scientific issues, to begin the dialogue process on this and the pediatric obesity (education) issue. The goal of the away-from-home foods dialogue will be to consider what can be done, given the best available evidence to date, to support consumers' ability to manage energy intake with respect to preventing undue weight gain and obesity. The dialogue is intended to produce options for a range of actions by a diverse range of stakeholders. Keystone will convene its first plenary meeting of stakeholders, to include representatives from the restaurant industry, academia, consumer groups and government, on April 26–27, 2005.

You are correct that a number of chain restaurants have put in place initiatives to address obesity. Some quick service restaurants have made nutrition information available to consumers for years, on an in-store poster, on tray liners, via the internet, or on request by phone or mail. Specific examples of some of the current initiatives we are aware of are as follows:

- Over a year ago, the Ruby Tuesday restaurant chain introduced menus with full calorie (and other nutrient) information for each item offered. We are unaware of how many of their restaurants use this menu at the present time.
- Many of the familiar quick service restaurants, including McDonald's, Burger King, Wendy's and Yum! Brand Foods chains such as Taco Bell, Kentucky Fried Chicken and A&W, continue to introduce alternative menu items focused on fruits and vegetables as alternatives to the traditional items. Many of these same restaurants have also focused on the need to balance calories with physical activity with online programs combining nutrition information on their products with recommendations for increasing physical activity.
- Subway restaurants have supplied nutrition information, including fat and calories with their menu items for some time.

FDA continues to encourage restaurants voluntarily to provide point-of-sale nutrition information to customers, including calorie information on a nationwide basis. For those consumers that want calorie and other nutrition information at the point of sale, we believe the industry should continue to strive for more innovative and helpful solutions nationwide. This will be part of FDA's focus in the upcoming Keystone dialogue.

RESPONSE TO QUESTIONS OF SENATOR HATCH BY LESTER CRAWFORD, DVM, PH.D.

Question 1. Much has been made about a recent Institute of Medicine report, Complementary and Alternative Medicine in the United States, which recommended amendment of the Dietary Supplement Health and Education Act (DSHEA). In its report, the IOM recommended amendment of DSHEA and FDAOs current regulatory scheme to address six issue areas: (1) seed to shelf quality control; (2) accuracy and comprehensiveness in labeling; (3) enforcement efforts against false and misleading claims; (4) research into how consumers use supplements; (5) incentives for privately funding research into efficacies; and (6) consumer protection against all potential hazards.

Although I do quarrel a bit with terming supplement use "alternative medicine," I do appreciate the IOM's interest in this issue and its identification of areas for

discussion. That being said, could you comment on whether you believe either the law or FDA regulation would need to be amended in order to address the IOM's recommendations?

Answer 1. In November 2004, FDA published a regulatory strategy that clearly lays out, for the industry and consumers, the Agencys direction in implementing all the provisions of the Dietary Supplement Health and Education Act of 1994 (DSHEA). The strategy is designed to give consumers a higher level of assurance about the safety of dietary supplement products and the reliability of their labeling, as well as to improve the transparency, predictability, and consistency of the Agencys scientific evaluations and regulatory actions to protect consumers against unsafe dietary supplements and dietary supplements making unauthorized, false, or misleading claims. Last year, FDA took action on dietary supplements containing ephedrine alkaloids because they present an unreasonable risk of illness or injury. The Agency will continue its ongoing efforts of monitoring and evaluating product safety, ingredient safety, and product labeling, as well as ensuring product quality.

Question 2. Dr. Crawford, there is apparently growing concern among many dietary supplement consumers that the CODEX Alimentarius guidelines on vitamins and minerals, said to be adopted this July, will supersede U.S. law and DSHEA specifically, resulting in limits on the potency of vitamins and minerals now available in the United States. Could you give us your understanding of whether CODEX guidelines supersede U.S. law?

Answer 2. The Codex Alimentarius Commission was created in 1963 by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) to develop food standards, guidelines and related texts such as codes of practice under the Joint FAO/WHO Food Standards Program. The main purposes of this program are protecting health of the consumers and ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and non-governmental organizations. The CODEX guidelines will not supersede U.S. law—in part because of the statutory provisions of FDAMA that direct FDA to try to harmonize its regulatory requirements with those of other governments specifically exclude dietary supplements. See section 410(b) of the Food and Drug Administration Modernization Act of 1997.—(FDAMA) (Pub. L. 105–115, codified at 21 USC 383(c)).

Question 3. Doctor, 10 years ago, the Dietary Supplement Health and Education Act authorized the Food and Drug Administration to develop good manufacturing practice standards (GMPs) specific to dietary supplements. I recognize that the law did not require you to do so, but it did allow this process to begin. We were greatly heartened that FDA did undertake to develop dietary supplement GMPs. That's the good news. The bad news is that 10 years ago the Dietary Supplement Health and Education Act authorized the FDA to develop GMPs for dietary supplements, and we have not yet seen them published. It is my understanding that the HHS-approved GMP regs were forwarded to OMB for final clearance during the Clinton administration. Shortly after President Bush was elected, my office received a call from a senior HHS official stating that HHS was going to make certain the GMP regs were exempted from the general freeze on pending regulations (so that the new administration could review them) and allow them to proceed forward. Over the past 4 years, we have had numerous reports that the regs were going forward, but they still have not been published. Accordingly, I would like to know the following things about the status of these regulations:

- Have they been cleared in final by FDA?
- Have they been cleared in final by HHS?
- What specific issues remain outstanding so that these regulations may be finalized?
- Please tell the committee when the regulations will be published, that is, on what date certain can we be assured the regulations will have been finalized?

Answer 3. I am as disappointed as you are that we have not been able to finalize the dietary supplement GMP rule. In the past 4 years, I assure you that there has been significant work done on the dietary supplement GMPs. The proposed rule was published March 13, 2003, and included responses to numerous comments received after publication of the ANPRM in 1997. The comment period for the proposed rule was extended until August 2003. We held public stakeholder meetings on April 29, 2003 in College Park, MD, and on May 6, 2003 in Oakland, CA. We also held a public meeting, via satellite downlink, on May 9, 2003, with viewing sites at our district and regional offices throughout the country. After the comment period closed, we began the process of analyzing the comments submitted to the proposed rule. The issues raised by the comments are complex, legally and substantively, and in some

cases, novel. We have expended significant internal resources on reviewing and preparing responses to the comments received. In addition, we have worked hard to ensure that the goals of DSHEA are carried out with careful consideration of the impact on the dietary supplement industry.

Since we are in the rulemaking process, I can only assure you that we continue to work hard on the final rule and as I stated during the hearing, I believe that the final rule should be published by the end of the year. I recognize this has taken longer than it should have and longer than anyone likes. But, we have come so far on the rule and currently are in the final stages of review—I would hate to see this critical work on the final rule lost because of problems introduced in a last minute rush to completion. I assure you full attention is being given to completing the rule.

Question 4. We are hopeful that the GMP regulation will include dietary supplement, and ingredient manufacturers worldwide. How will FDA address the issue of GMP compliance by foreign manufacturers?

Answer 4. Since we are in the rulemaking process, I can only assure you that we continue to work hard on the final rule and as I stated during the hearing, I believe that the final rule should be published by the end of the year. I cannot however, comment on what will be in the final rule. I will note that in the proposed rule, FDA proposed applying the final rule equally to both domestic and foreign manufacturers of dietary supplements. Also, FDA proposed addressing cGMP compliance by dietary supplement manufacturers in the same fashion as the Agency handles compliance for foreign and domestic manufacturers of conventional food.

Question 5. Section 9 of DSHEA is explicit that a GMP may not impose standards for which there are no current, generally available analytical methods. We are aware that a number of organizations are working very hard to develop analytical methods. What is FDA doing to collaborate with the Office of Dietary Supplements at NIH and industry to assure that analytical methods are available for the most important dietary ingredients?

DSHEA is now 10 years old, and yet it is not fully implemented although I recognize the substantial work that has been conducted under your tenure at FDA to move us toward better implementation. Now that the President has sworn in Secretary Leavitt, and your confirmation is imminent, would you consider meeting with key industry leaders and the Secretary to lay out a plan to fully implement DSHEA as soon as possible?

Answer 5. Since 2001, FDA has had an IAG with ODS/NIH that funds a significant portion of a multimillion dollar 5-year contract with AOAC International to develop/identify, evaluate and validate analytical methods for dietary supplements. Industry also contributes funds and participates in the validation studies. Prioritization of the targeted dietary ingredients is determined by an Ingredient Ranking Subcommittee convened by AOAC stakeholders; the composition of this subcommittee is balanced between members from the Federal Government (esp. FDA and NIH), the industry, and academia. As such, prioritized dietary ingredients for which the validation process is completed include several that pose public health concerns (e.g., ephedra alkaloids, St. Johns wort, and aristolochic acid). Other dietary supplements of concern include aconotine, pennyroyal, sour orange, blue cohosh, chapparal, comfrey, germander, mayapple, tansy and wormwood for which laboratory studies in CFSAN continue. Twenty-two additional methods of particular interest to the dietary supplement industry are in the process of validation.

Because AOAC as changed the way collaborative studies are conducted, they are able to validate more methods than originally projected for the 5-year contract (20 methods). We are currently in the third year of the contract.

FDA would be glad to meet with industry leaders on DSHEA implementation.

Question 6. Dr. Crawford, I have a general and a specific question for you on the issue of "follow-on" or "generic" biologics, something you and I have discussed before.

First, could you outline for the committee the FDA's current activities to develop a policy or pathway so that consumers at some point will have available lower cost alternatives to costly biologic products? When might FDA's activities in this area conclude:

Second, in March 2001 the FDA announced that it was working on two generic biologic guidances for human growth hormone and insulin, and the trade press reported in April 2002 that one guidance had been drafted and the other was in process. In May of last year you testified that FDA was preparing to release guidance for certain biological products. HgG was specifically mentioned but presumably insulin was the other product you were referring to.

Apparently you have blocked the guidances pending the FDADs larger consideration of the generic biologics issue. Dr. Crawford, the country is spending billions of dollars on products such as insulin and human growth hormone. Yet, 4 years after it announced it would issue these guidances, FDA still has not done so. When do you plan to release any hold on the guidances that have been prepared and allow them to proceed through clearance so companies may know what is required to develop generic versions of Human Growth Hormone and Insulin?

Answer 6. As you know, FDA is conducting a public process to examine the many questions, including scientific and legal issues, that must be answered regarding these products and to ensure that all interested parties have an opportunity to comment. When this process is complete, FDA intends to provide guidance to industry to clarify, consistent with its legal authority, the approval pathway and principles for review of such products, which will protect the public health.

In recent years—and with increasing frequency—questions about generic or follow-on proteins have arisen in response to scientific advances, impending patent expirations, and the ability to better characterize and understand biological products.

Acknowledging scientific and legal limitations in this area, yet also recognizing the public health need to move forward to assist industry and make more products available to the public, FDA is conducting a public process to examine the scientific, and related issues regarding follow-on biologics. This process will ensure that scientific considerations and issues related to Agency authority are fully examined and that all interested parties have an opportunity for input.

The Agency understands the importance of human growth hormone and insulin. We are currently re-evaluating guidance documents to assure that they are scientifically in-line with current efforts to ensure the efficacy of follow-on biologic products.

Question 7. As you know, I take a great interest in the White Oak Facility and am watching its progress closely. Could you provide me with a progress report on work done to date, your projected timetable for the future, and the cost estimates for remaining work? Is the necessary funding to complete work at White Oak contemplated in the President's Budget?

Answer 7. We appreciate your interest and support in the FDA White Oak Consolidation Project. The White Oak Consolidation Project continues its coordinated efforts to execute the 2000 Master Plan design to provide a new state-of-the-art facility for the FDA at White Oak.

On December 11, 2003, a dedication ceremony was held for the Life Sciences Laboratory, a state-of-the-art chemistry, bioscience and animal research facility. As the first new building to open on the site, the laboratory provides approximately 124,000 gross square feet, for 120 employees from the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH).

Construction for the CDER Office Building I began on November 15, 2002, and has progressed on schedule for occupancy in summer 2005. This building provides 560,000 gross square feet of modem office space to accommodate the Office of New Drugs, comprised of approximately 1,700 scientists and support staff. The facility also includes a 60,000 square foot, efficient document storage center, mail room and support space.

Construction of the Central Shared Use Building began in October 2004. When complete this facility will provide employees and visitors with a cafeteria, conference and training center, credit union, fitness center, health unit, central library and R&W store, along with housing the Agency security command center, central data center and NTEU offices. The first phase of this building, including the cafeteria, fitness center and security command center, is scheduled for completion in spring 2006.

The construction contract for the CDRH Engineering/Physics Laboratory was awarded in January 2005. This building will provide approximately 128,000 square feet of high tech laboratories engaged in evaluating electromagnetic and medical devices, radiological instruments and consumer appliances generating radiological signals. The facility consists of numerous vibration isolation slabs, electromagnet shielding, an anechoic chamber and laser devices especially dedicated to the program science. This facility is scheduled for occupancy in early 2007.

With design to be complete in spring 2005, the approximately 291,000 gross square foot CDER Office Building II will accommodate the Center Director's office and the balance of the CDER scientific and support staffs. This is a uniquely designed office building in that the entire building will be equipped with an underfloor ventilation system. This design change provides for more offices benefiting from indirect outside daylight, taller windows, more efficient distribution of air and electrical wiring along with IT/Telecom and security wiring.

Finally, the design for the first phase of the site's parking garages is complete with the finish of construction planned for 2005. This concrete parking structure will contribute approximately 800 spaces to the overall parking for the campus.

The design and construction of the new buildings at White Oak are funded through General Services Administration (GSA) appropriations along with the site infrastructure, internal support services and move costs that are covered by the FDA. These costs include: internal communication needs, including equipment, cabling and audiovisual; security, including infrastructure and equipment; information technology and telecommunications cabling; modular furniture and other equipment to furnish the building for occupancy; and, relocation costs, including records management consolidation, relocation coordination and moving.

FDA and GSA are working to update the estimated cost to complete this project given that the schedule for some projects has been delayed. Estimates developed a year ago suggest that approximately an additional $550 million would be needed after fiscal year 2006 to complete the headquarters project. Of this, roughly 4/5ths would be GSA construction funding, and 1/5th would be FDA move and fit-out funding.

Question 8. We in Utah have been very concerned with the progress of MDUFA. In the first instance our growing small medical device companies were very worried that the PDUFA model used for pharma would not work for medical devices. There was a great concern that this program to advance approvals at a large cost to our small companies would not achieve its goals. In fact it seems that our concerns are coming true. By our reckoning the costs are going up, the approval times are not coming down, and the Federal Government is not fulfilling its commitments, both programatic and financial. Do you have any assurance for us that this situation with MDUFA can be turned around in the near future?

Answer 8. Many aspects of the Medical Device User Fee and Modernization Act (MDUFMA) are working quite well. Chief among them is the fact that the agency is meeting the performance goals agreed to in conjunction with MDUFMA. Medical device application review has been substantially improved by both the additional resources that MDUFMA makes available for reviewing applications and by a number of new guidance documents issued in response to MDUFMA, which tend to improve communication about expectations in the device review process and to standardize aspects of the review process. I have high expectations for the continuation of these improvements in device review through fiscal year 2007, assuming that the MDUFMA program continues.

Some of the financial aspects of MDUFMA have been disappointing for both FDA and the device industry. First, in spite of agency urging, financial aspects of MDUFMA were not patterned after PDUFA, which has both annual product fees and annual establishment fees to assure fee stability and to reduce the size of the application fee. The device industry was adamantly opposed to such annual fees, and demanded that all revenue come from application fees alone, which can fluctuate widely from year to year. FDA initially opposed having only application fees, but relented when the device industry assured revenue stability for FDA by proposing an annual compensating adjustment in years when revenue collected was less than statutory revenue targets. Also, industry wanted to phase in its funding target of $35 million over 5 years. The result of that phase in, and annual inflation increases, should have caused fees to increase at the rate of about 13 to 14 percent each year. Revenue has been less than statutory revenue targets in each year. However, fewer application fees and the compensating adjustment proposed by industry have caused fees to increase at rates higher than the agreed-to 13 to 14 percent.

Unlike PDUFA, MDUFMA also specified higher annual appropriation levels for FDA's device program. These higher levels did not occur in fiscal year 2003 and 2004, and if they are not made up by October 1, 2005, the MDUFMA program will end. In light of this, the Director of the Office of Management and Budget assured the Speaker of the House in October 2003 that Administration budget requests for fiscal year 2005, 2006, and 2007 would be sufficient to meet the higher appropriation levels specified in MDUFMA, and he asked Congress to waive the MDUFMA requirement for make-up appropriations in fiscal year 2003 and 2004. I look forward to working with Congress on this proposal in order keep the MDUFMA program functional through fiscal year 2007.

(Second set of questions)

Question 1. Do you believe that mercury is a toxin that needs careful oversight? On other uses of mercury, the FDA has taken a strong stance.

Answer 1. Mercury, and specifically methyl mercury, is known to be toxic to a variety of systems in the human body when exposure occurs at a high dose and as

such is a toxin that requires careful oversight. FDA continues to monitor the science around the issues of mercury exposure in order to react appropriately to new evidence of the impact of mercury on human health. Lower doses of methyl mercury, such as may occur through the consumption of certain types of fish, have been associated with a variety of developmental delays in young children.

The mission of the FDA is to protect public health and, in the context of methyl mercury exposure through the consumption of fish, this requires one to consider both the health risks from exposure to methyl mercury as well as the health benefits from consuming fish. The FDA believes that it is important for women who may become pregnant, pregnant women, nursing mothers and young children to avoid certain types of fish (shark, swordfish, tilefish and king mackerel) that contain high levels of methyl mercury. FDA recommends that this same group eat up to 12 ounces a week of a variety of fish that are lower in mercury. This advice was published jointly with EPA in March 2004. Currently, the FDA is in the middle of an education campaign designed to get this message out to the specific populations noted above.

Question 2. Why hasn't the FDA issued warnings to pregnant women and children under 6 about mercury exposure from dental amalgam? Isn't it true that Health Canada has issued warnings to pregnant women and children under the age of 6 since 1996? Why hasn't the FDA taken similar action?

Answer 2. FDA has not issued warnings to pregnant women and children under 6 about mercury exposure from dental amalgam, as has Canada, because while FDA and other agencies of the U.S. Public Health Service (USPHS) continue to investigate the safety of dental amalgam, no valid scientific evidence has shown that amalgams cause harm to patients with dental restorations, except in the rare cases of allergy.

RESPONSE TO QUESTIONS OF SENATOR ISAKSON BY LESTER CRAWFORD, DVM, PH.D.

With respect to FDA's recent decision to reorganize the Office of New Drugs—Ophthalmologists are particularly concerned about the likelihood that final decisions including clinical sign-off for all (ophthalmic) products in the Division will no longer be made by the Ophthalmology Deputy Director, but instead will be made by the Division Director. With respect to ophthalmic drugs, many feel that keeping the risk decision closer to the specialty of ophthalmology as part of the overall clinical sign-off is the most efficient and fair approach.

Question 1. If confirmed as commissioner, what steps will you take to ensure current and future patients that the advancement of new ophthalmic treatments/therapies into the realm of the eye care practitioner will continue to take place as expeditiously as possible?

Answer 1. Individuals with expertise in ophthalmology will continue to play a critical role in reviewing new ophthalmology products, and the reorganization will not affect the timely approval of treatments and drug therapies available to eye care practitioners and their patients. All drug review processes for all products will continue to be held to existing PDUFA goals and timelines during and as a result of the reorganization.

Question 2. Given the enormous amount of drug research and development presently going on in ophthalmology, what steps will you take to ensure that new drug approval will not be unnecessarily delayed as a result of the pending reorganization?

Answer 2. As noted above, the reorganization will not affect the timely approval of treatments and drug therapies available to eye care practitioners and their patients. All drug review processes for all products will continue to be held to existing PDUFA goals and timelines during and as a result of the reorganization.

RESPONSE TO QUESTIONS OF SENATOR DODD BY LESTER CRAWFORD, DVM, PH.D.

Drug Safety

Question 1. Transparency

There have been disturbing reports that suggest that the FDA does not place enough emphasis on drug safety, and that concerns raised by those in the Office of Drug Safety (ODS) are sometimes ignored and even suppressed.

An internal study conducted by the HHS Office of the Inspector General in 2002 revealed that approximately one-fifth of drug reviewers had been pressured to ap-

prove a drug despite concerns about safety, efficacy, or quality. In addition, more than one-third said they were "not at all" or only "somewhat" confident that final decisions of the Center for Drug Evaluation and Research adequately assessed safety.

This seems to have been the case with Dr. Andrew Mosholder when he had data to suggest that certain antidepressants might increase the risk of suicide in children and adolescents; as with Dr. David Graham when he had data to suggest that Vioxx is connected with cardiovascular problems.

Dr. Crawford, do you believe that mistakes were made in the handling of Dr. Mosholder and Dr. Graham? As Commissioner of the FDA, what would you do to ensure transparency, so that dissenting opinions are seriously considered and never suppressed, especially when they have to do with issues so critical to the health and well-being of the public?

Answer 1. Good scientific decisions depend on robust discussion and various layers of peer review. In encouraging such discussion, FDA will work to ensure that FDA scientists involved in the decision making process do not feel pressured or ignored.

The rigorous scientific review process is critical to sound regulatory decision-making. In both Dr. Mosholder and Dr. Graham's cases, the Agency sought the best available data upon which to make a regulatory decision. For instance, with the SSRIs, FDA initiated the Columbia Reclassification Project, which provided sound data upon which to make a decision. These data confirmed Dr. Mosholder's findings, which were based on weaker data. With the COX-2 inhibitors, FDA again insisted on scientific peer-review of Dr. Graham's work, which he submitted for publication prior to the standard Agency peer-review. The Agency recently held a joint meeting of the Arthritis and Drug Safety and Risk Management Advisory Committees to evaluate all available data, including the work of Dr. Graham.

Pursuant to Federal law, the Agency does not retaliate against whistleblowers or interfere with their rights to freely express their views in public forums, such as investigations of the Congress.

FDA constantly strives to improve our drug safety process and methods, thereby better serving the public health. Recent developments, including the work of Dr. Mosholder and Dr. Graham, have prompted us to refocus our drug safety efforts and take additional steps to identify drugs that may have unacceptable risk profiles.

Recently, I joined Secretary Leavitt to announce important efforts that we are undertaking at FDA to improve the ability to monitor and respond to emerging drug safety information.

These steps will ensure both a better internal process of deliberation on drug safety issues that ensures appropriate and independent consideration of all issues, as well as a stronger ability to gather data about drug safety issues once a drug has been approved.

Most importantly, we are moving to encourage more transparency and to ensure that patients and physicians have the most up-to-date and complete information necessary to inform their treatment decisions. This new Drug Information Initiative will give patients, healthcare professionals, and other consumers quick and easy access to the most up-to-date and accurate information on medicines and make FDA's drug review, approval, and monitoring programs as transparent as possible.

This is in addition to FDA's Five Point Plan to Improve Drug Safety, a major initiative designed to improve the monitoring of drug products recently approved for marketing. The major components of this initiative include:

- Sponsoring a major study of the Drug Safety System by the Institute of Medicine;
- Implement a Program for Adjudicating Differences of Professional Opinion;
- Conducting a nationwide search to identify a permanent director for the Office of Drug Safety;
- Conducting a series of workshops and meetings on drug safety and risk management; and
- Publishing risk management guidance.

FDA's Office of Drug Safety (ODS), in the Center for Drug Evaluation and Research (CDER), is already an independent office separate from the Office of New Drugs, the office that reviews new drug applications. Both the Office of New Drugs and the Office of Drug Safety report directly to the Director of the CDER. ODS has independent authority to perform its own research and does so every day. To be valuable, this independent research must conform to widely accepted scientific standards and normal scientific procedures and peer review should not be bypassed. And when drug safety issues are identified, they must be factored into the risk-benefit

equation so that safe and effective drugs remain available to patients who need them.

FDA has a longstanding commitment to provide a strong resource base for its drug safety program. The budget for fiscal year 2006 continues this commitment. The President has proposed a 24-percent increase for FDA's post-market safety program to help further ensure that America's drug product supply is safe and effective, and of the highest quality. Under this proposal, CDER's ODS would receive increased funding to expand the Agency's ability to rapidly survey, identify and respond to potential safety concerns for drugs on the market. ODS will hire additional staff to manage and lead safety reviews, will increase the number of staff with expertise in critical areas such as risk management, risk communication and epidemiology, and will increase access to a wide range of clinical, pharmacy and administrative databases. Our commitment to increase resources available for post-market safety will enhance the structural changes we are proposing to advance drug safety.

In an effort to improve the current process immediately, CDER has instituted a program to formally address the opinions of dissenting scientific reviewers to ensure that the decision-making process is transparent. For more information on this plan, please visit: http://www.fda.povIbbs/toDics/news/2004INEW01131.html.

FDA Authority

Question 2. Dr. Crawford, during testimony before this committee earlier this month, an FDA witness, Dr. Sandra Kweder, seemed to suggest that additional authority to require companies to conduct post-market studies and to make changes to the drug label would be "helpful" to FDA. Two days later another FDA witness, Dr. Janet Woodcock, backed off of those statements.

According to the latest figures, companies have not even initiated approximately 70 percent of the post-market studies that they had previously committed to.

- How does the FDA plan to address this problem?
- Does the FDA need additional authority and enforcement power to require companies to do post-market studies?

It took 2 years for the Vioxx label to change to reflect the data suggesting an increased cardiovascular risk. Much of the delay resulted from months of negotiation with the manufacturer.

- Dr. Crawford, does this seem like an unacceptable delay given the huge public health implications?
- Does the FDA need additional authority and enforcement power to require companies to change the drug label if a safety concern arises?
- What other authorities does the FDA need in order to effectively respond when a safety issue is identified?

Answer 2. I do not believe new statutory authority is needed. We will use all existing regulatory authority and enforcement powers when negotiating label changes with drug companies or when monitoring or managing drug safety issues. As Dr. Janet Woodcock testified, a key factor in labeling changes is that once a label change is made, old labels in paper form are still in distribution and it takes time to get newer labels in circulation. Dr. Woodcock testified that the new strategy of posting drug safety information sooner using the Drug Watch mechanism will help alleviate that factor because it will enable the FDA to get information directly to the people who need it in a timely manner.

Office of Drug Safety

The Administration's fiscal year 2006 budget includes an additional $6.5 million for the Office of Drug Safety (ODS).

Question 3a. With this budget increase, how many scientists will the ODS employ?

Answer 3a. With the additional funds, we expect to be able to hire eight additional FTEs in the Office of Drug Safety to establish policies and processes regarding safety reviews and risk management, to manage communications with the Office of New Drugs and to support patient safety initiatives and external partnerships with CMS, AHRQ, and other HHS Agencies.

We also plan to hire an additional 14 FTEs in the three operating divisions of ODS. These employees will handle the increased workload of monitoring biologic therapeutics; promote increased communication and coordination of safety review activities within the divisions; increase focus on medical error signal detection, address the current backlog of unaddressed potential safety signals; increase epidemiological expertise to explore safety risks and signals in various population databases; and manage the increasing workload in ODS for new drug consultations and designing post-approval studies for new drug use in specific populations.

Finally, we plan to hire six FTEs to increase staff dedicated to evaluating and communicating drug safety risks to the health care community and the American public.

Question 3b. How does the ODS budget and staff compare to that of the Office of New Drugs?

Answer 3b. The table below presents a 3-year budget and staff comparison between the Office of New Drugs and the Office of Drug Safety. Please note that a side-by-side comparison of the budgets of these offices is not meaningful without considering the significant pre-approval responsibilities performed by the Office of New Drugs.

		FY 2004	FY 2005	FY 2006
Office of New Drugs				
	FTEs	690	719	748
	Funding	$98.1M	$110.6M	$122.6M
Office of Drug Safety				
	FTEs	94	109	137
	Funding	$27M	$26.9M	$33.4M

Question 3c. Given that the ODS is charged with tracking every single drug that is on the market, does the balance of resources seem appropriate?

Answer 3c. We believe that the balance of resources has appropriately reflected ODS's responsibility within the overall post-marketing safety function. The Office of Drug Safety is not singularly responsible for tracking post marketing safety issues of marketed drug products. ODS works with the Office of New Drugs to evaluate safety issues once drugs are on the market.

Question 3d. When do you plan to fill the vacant Director position within the ODS?

Answer 3d. The agency has experienced difficulty recruiting high quality candidates for the position of Director, Office of Drug Safety through traditional mechanisms such as scientific journal advertisements and government vacancy announcements. We are committed to using all available resources to ensure a systematic, inclusive recruitment process for this critically important position. To that end, FDA has partnered with the recruitment and staffing professionals at the Office of Personnel Management (OPM), Center for Talent Services to develop and manage a recruitment strategy that we are confident will yield a sizable number of strong candidates and ultimately, a top-notch director. We feel that the additional time and resources invested in a thorough analysis of the leadership and technical competencies required to successfully manage the drug safety program, including input from internal and external subject matter experts and stakeholders, will be time well spent. The Office of Personnel Management is targeting the end of May for the position to be posted on USAJOBS.

Question 3e. Why has the ODS been without a director for so long?

Answer 3e. It is very difficult to hire the appropriately skilled individual for this position. The Director should be credentialed in medicine and have experience and working knowledge of controlled clinical trials, epidemiology, research, medicinal products, and drug regulations. Any individual who has these qualifications may be reluctant to take this position for the salary we can offer. Further, we have tried to promote individuals with these qualifications from within the Agency. However, we often find that these individuals subsequently are recruited heavily by industry.

Drug Safety Oversight Board

Dr. Crawford, the centerpiece of the Administration's plan to address the drug safety crisis is the creation of a drug safety oversight board. While I applaud the Administration for taking action, I am concerned that this change is not nearly significant enough to address the problem.

Question 4. Will the new board have any decision making or regulatory authority of its own? If not, how can patients be sure that the FDA will act on problems that it identifies? The FDA has said that the Deputy Director of CDER will chair the board. If this is the case, in what way is the board independent?

Answer 4. The new board will have the authority to make recommendations to the Center Director on drug safety questions. The Center Director oversees all of the offices in CDER, including those that review new drug applications as well as the Office of Drug Safety. The DSB will include members from the FDA outside of CDER and medical experts from other HHS agencies and government departments (e.g., Department of Veterans Affairs) who will be appointed by the FDA Commissioner. The Board also will consult with other medical experts and representatives of patient and consumer groups. The wealth of expertise envisioned in the DSB will create an independent voice to make recommendations to the Center Director on drug safety issues. The Deputy Center Director is also independent of the Office of New Drugs and the Office of Drug Safety and can be expected to manage the Board in a fair and evenhanded manner, making sure all opinions are heard. The Agency looks forward to receiving recommendations from the Institute of Medicine (IOM) study that will be evaluating the current drug safety system, and will make appropriate adjustments to its programs after reviewing those recommendations. FDA would like to emphasize our commitment to a culture of transparency and rigorous scientific peer review.

Direct to Consumer (DTC) Advertising

Some have suggested that DTC advertising has increased the magnitude of drug safety problems by drastically increasing the population that uses a drug, even if it might not be appropriate for some patients.

Question 5. As Commissioner, would you increase FDA regulation of DTC advertising? What authority does the FDA have to limit or ban advertising, or require disclosures, when a safety problem is discovered? Does the FDA require additional authority in this area?

Answer 5. We have conducted research that confirms that DTC advertising, when done correctly, can serve positive public health functions, such as increasing patient awareness of diseases that can be treated, and prompting thoughtful discussions with physicians that result in needed treatments being prescribed often, not the treatment in the DTC advertisement. Results of our research show that many physicians believe that DTC can play a positive role in their interactions with patients and that many physicians thought that DTC ads made their patients more involved in their healthcare.

In a survey we conducted, only 8 percent of physicians felt very pressured to prescribe the specific drug advertised. Physicians agreed that the main effect of DTC ads was to help educate patients about their health problems, causing them to seek needed care.

At FDA, CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC) is responsible for regulating prescription drug promotion. DDMAC's mission is to protect the public health by helping to ensure that prescription drug information is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering optimal communication of labeling and promotional information to both health care professionals and consumers.

While we believe the survey results discussed above confirm our belief that DTC ads help increase patient awareness about the availability of effective treatments for their health problems, we will continue to ensure that our DTC policies help prevent potential misperceptions about benefits and risks of the advertised treatment and promote the importance of prescribing decisions being made with the intervention of a health care professional.

As you know, FDA has extensive authority over drug promotion. To summarize the FD&C Act and regulations do not distinguish between promotion to professional and consumer audiences. Section 502(n) of the FD&C Act specifies that prescription drug advertisements must contain "a true statement of . . . information in brief summary relating to side effects, contraindications, and effectiveness" of the advertised product. The implementing regulations specify that prescription drug advertisements cannot be false or misleading, cannot omit material facts, and must present a fair balance between effectiveness and risk information. Further, for print advertisements, the regulations specify that every risk addressed in the product's approved labeling must also be disclosed in the advertisements.

For broadcast advertisements, however, the regulations require ads to disclose the most significant risks that appear in the labeling. The regulations further require

that the advertisement either contain a summary of "all necessary information related to side effects and contraindications" or provide convenient access to the product's FDA-approved labeling and the risk information it contains. Finally, the FD&C Act specifically prohibits FDA from requiring prior approval of prescription drug advertisements, except under extraordinary circumstances.

To encourage more effective regulation of DTC promotion, FDA plans to develop additional guidance documents, including one addressing the presentation of risk information in print advertisements and one addressing outdoor advertising. FDA also will conduct a series of studies to examine the format and content of brief summaries in direct-to-consumer print advertisements. This will assist the agency to finalize the draft guidance on consumer-directed print advertisements for prescription drugs. FDA also plans to finalize the guidance on criteria FDA uses to distinguish between disease awareness communications and promotional materials, to encourage manufacturers to disseminate educational messages to the public, and the guidance on the manner in which restricted device firms can comply with the rules for disclosure of risk information in consumer-directed broadcast advertising for their products.

Obesity

Dr. Crawford, the FDA a year ago announced its plan to combat obesity. The plan included modernizing guidances for developers of drugs to treat obesity, as well as a national education campaign, "Calories Count", enhancing the calorie information on food labels, urging the Nation's restaurants to disclose caloric content, and expanding research on obesity.

Question 6. Where does this FDA initiative stand today and what do you see as its results? If confirmed as Commissioner, what additional steps would you like to see to combat the ever-rising tide of obesity across this nation?

Answer 6. Obesity is a growing and urgent public health problem in the United States. Today, almost two-thirds of all Americans are overweight and over 30 percent are obese. To help confront the problem of obesity in the U.S. and to help consumers lead healthier lives through better nutrition, in August 2003, FDA created an Obesity Working Group (OWG), which was charged with preparing a report that outlines an action plan to cover critical dimensions of the obesity problem from FDA's perspective and authorities. FDA's "Calories Count" report was released on March 12, 2004.

The OWG report provides a range of short and long-term recommendations to address the obesity epidemic. For FDA's actions the emphasis is on calories. Progress to date follows:

• We have published two advance notices of proposed rulemaking (ANPRMs), in response to the recommendations in the OWG report, seeking comments on the following:

• How to give more prominence to calories on the food label, for example, increasing the font size for calories, including a column in the Nutrition Facts panel of food labels for percent Daily Value for total calories, and eliminating the listing for calories from fat. In addition, the Agency is seeking comment on the reformulation of the foods or redesign of packaging that may occur if any changes are made to the food label;

• Whether to amend certain provisions of the nutrition labeling regulations concerning serving size, such as for multiple-serving packages that may reasonably be consumed in a single eating occasion.

• We continue to encourage manufacturers to take advantage of the flexibility in current regulations on serving sizes to label as a single-serving those food packages where the entire contents of the package can reasonably be consumed at a single eating occasion. We also continue to encourage manufacturers to use appropriate comparative labeling statements that make it easier for consumers to make healthy substitutions. Since release of the OWG report, the Agency, in meetings with industry, has made a point to encourage manufacturers to take advantage of the existing flexibility in serving size regulations, and companies are responding. For example, Kraft Foods is instituting dual column labeling for all its packaged foods containing 2–4 servings per package.

• FDA continues to encourage restaurants voluntarily to provide point-of-sale nutrition information to customers, including calorie information on a nationwide basis.

• FDA is also working to develop educational strategies and partnerships to support appropriate messages and teach people, particularly children, how to lead healthier lives through better nutrition. We are starting work with the Girl Scouts of the USA, under terms of a Memorandum of Understanding signed this past fall,

to provide outreach and education in a science-based initiative to focus on improving health, nutrition, and physical activity. In addition, FDA's field offices are participating in local partnerships to reach and teach children. For example, in Central Florida, FDA's South East Region is part of the Seminole County Healthy Kids Partnership to promote positive opportunities for school-aged children in Seminole County to learn healthy nutrition and the value of increased daily physical activity.

Regarding your question on what FDA is doing to modernize "guidances for developers of drugs to treat obesity," FDA's Center for Drug Evaluation and Research (CDER) will continue to work with pharmaceutical sponsors to facilitate development of effective therapies to address the important public health issue of obesity and its attendant morbidities. An advisory committee meeting was held on September 8, 2004 to discuss the draft guidance on Clinical Evaluation of Weight-Control Drugs. The Agency is working to finalize the guidance.

Pediatric Drug Testing

I have long been committed to ensuring that medicines are studied in children so that pediatricians have information about which drugs are most effective for their patients. The steps that we have taken in this area—the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)—have led to enormous improvements in our knowledge about the appropriate use of drugs for children.

Dr. Crawford, pediatric testing in children is particularly relevant in light of the recent questions about drug safety, and especially the possible adverse effects of antidepressants (SSRI's) when used to treat youth. Several SSRI's had been studied in children, but the results of those studies were inconclusive.

Question 7a. If confirmed as Commissioner, would you continue to support efforts to expand pediatric testing?

Answer 7a. I strongly support efforts to continue pediatric therapeutics testing. In response to the need for pediatric use information for prescription medications in the United States, Congress passed several important legislative initiatives. FDA has found both the BPCA and the PREA to be useful regulatory tools to promote development of information and studies on therapies that are or will be utilized in the pediatric population.

As a result, the Agency has labeled almost 100 products with new pediatric use information and has disseminated this valuable product information to the public. In addition, the number of pediatric clinical trials has increased dramatically. As of March 31, 2005, under BPCA, FDA has issued 298 written requests for pediatric studies, granted exclusivity to 110 drugs of the 120 that have been evaluated, and approved pediatric labeling changes for 87 products. Over a third of these products had new dosing or pediatric specific safety information identified and efficacy was not demonstrated in 8 of these products.

Question 7b. What steps could the agency take to improve in this area, and to ensure that pediatric studies are answering the right questions and providing useful results?

Answer 7b. The Agency will continue to advance its pediatric initiatives throughout FDA Centers. FDA has found both the BPCA and the PREA to be useful regulatory tools to promote development of information and studies on therapies that are being utilized in the pediatric population.

At present, the FDA is working with the American Academy of Pediatrics, academic institutions, sponsors and the Center for Devices and Radiological Health to assess the needs for better information on use of devices in the pediatric population and to explore mechanisms to promote the development of devices specifically for the pediatric population.

Question 7c. Is there additional authority that Congress can provide in this area that would be helpful to the FDA?

Answer 7c. FDA has not identified the need for additional authority at this time. Congress has granted FDA significant, new pediatric legal authority in recent years and we are aggressively working to implement these authorities.

Global HIV/AIDS Affordable Pharmaceuticals

The President's Emergency Plan for AIDS Relief includes the goal of treating 2 million people by 2008. While estimates vary, I understand that we can treat at least two to three people with non-branded anti-retrovirals (ARV) for the same price of treating one individual with brand name drugs. While safety and efficacy must remain paramount, the success of the President's treatment goals depends on the

government's ability to procure high quality drugs (both brand name and non-brand name) at the most affordable price.

I was very happy to learn of the recent tentative approval of an HIV antiretroviral product manufactured by Aspen Pharmacare of South Africa. I applaud the FDA and Aspen Pharmacare for working together to secure the first tentative approval of a non-brand, first-line HIV drug regimen. Additionally, it is very positive that the Office of the Global AIDS Coordinator has confirmed that these products will be available for purchase under the President's Emergency Plan. For large numbers of people in Africa and beyond, this could be a true turning point for providing low-cost, safe and effective AIDS drugs to those who would otherwise face certain death.

However, while the Administration formalized an expedited process for the FDA to review and tentatively approve non-brand drugs to ensure their safety and efficacy in May 2004, there are still very few non-branded drugs, and no triple-drug fixed dose combinations, that have been tentatively approved by this process.

Question 8a. What specific steps is the Administration, and specifically the FDA, taking to ensure that safe and effective non-brand drugs can be purchased with U.S. government dollars for use in the President's Emergency Plan?

Answer 8a. In May 2004, in direct support of the President's Emergency Plan for AIDS Relief, the Department of Health and Human Services (HHS) Secretary Tommy Thompson announced that FDA would implement a new, expedited review program to help ensure that the products purchased under the President's Emergency Plan would be safe, effective, and manufactured in a quality manner. The central ethical premise of this review program is to ensure that we are not asking these governments to give their people medicinal products we would not give our own people.

This new program directly supports Ambassador Tobias' responsibility to ensure the quality of HIV/AIDS drugs purchased by the U.S. under the auspice of the President's Emergency Plan. Subsequent to Secretary Thompson's announcement, FDA published guidance for the Pharmaceutical Industry encouraging sponsors (manufacturers) to submit marketing authorization applications to FDA for approval of fixed dose combination (FDC) and co-packaged versions of previously approved individual component antiretroviral therapies for the treatment of human immunodeficiency virus (HIV).

On January 25, 2005, FDA granted tentative approval to a generic AIDS drug regimen for potential purchase under the President's Emergency Plan for AIDS Relief. This is a co-packaged antiretroviral drug regimen manufactured by Aspen Pharmacare of South Africa for the treatment of HIV-1 infection in adults. The Agency's tentative approval means that although existing patents and/or exclusivity prevent U.S. marketing of Aspen's product, it meets FDA's quality, safety and efficacy standards for U.S. marketing. This action makes this product available for potential procurement by President Bush's Emergency Plan for AIDS Relief. This action is the first tentative approval of an HIV drug regimen manufactured by a non-U.S.-based generic pharmaceutical company.

The guidance outlines four scenarios for review of different FDC and co-packaged products. Some of the scenarios could permit review and approval in as little as 2 to 6 weeks after submission of a complete, high-quality application. For companies making products where another firm owns the U.S. patent rights, FDA issues a "tentative" approval when it finds the product meets the Agency's normal safety, efficacy, and quality standards. A tentative approval does not allow marketing in the U.S. because of the market protection that the patent or exclusivity provides. However, the administrators of the President's Emergency Plan have said they will allow manufacturers of products "tentatively" approved by the FDA to submit tenders for consideration as suppliers of these products in countries where the product has the approval of the local drug regulatory authority and where such provision doesn't violate other laws.

Question 8b. When do you expect additional non-brand drugs, including fixed-dose combinations, to be available for purchase as part of the President's Emergency Plan?

Answer 8b. It is difficult to provide exact dates as to the submission of these products, because the companies make the decision on when/if they will submit. Moreover, we do not know in advance of our review whether or not companies will have the data requisite to demonstrate the products do indeed meet the standards of products we would give our own people. However, FDA has been involved in a very vigorous outreach effort to try to engage potential manufacturers in this process.

Vigorous discussions and other outreach efforts, both within the U.S. and outside the U.S., have occurred and are still underway.

Question 8c. Can you confirm that all non-brand drugs; including fixed-dose combinations, could be purchased with U.S. government dollars as soon as they are tentatively-approved under the FDA expedited process?

Answer 8c. It is our understanding that once a product is either fully approved or tentatively approved, the manufacturer is then eligible to be considered as a provider of those products under the President's Emergency Plan, provided the local drug regulatory authority has approved the use of the product in the country where it is to be ultimately provided to patients. Please note that FDA does not administer the procurement process for this program, and therefore we do not have details about procurement activities for the program.

Question 8d. What are you doing to encourage drug companies, both brand and non-brand, to apply to the new expedited approval process?

Answer 8d. FDA is very proactively working with manufacturers from around the world that have come to us with questions about this review process as outlined in our guidance. We have met with them here in Washington and in several of the countries identified in the President's Emergency Plan. We are devoting much time to answering questions about the application process and requirements for submission to assist especially non-brand companies in submitting a quality application for our review. We are committed to investing such time and effort "up front" to help increase the probability of a quality application and to expediting their review when the completed application is submitted. We continue to provide requested information from interested companies and have several outreach programs for industry and drug regulatory authorities that are presently underway. We plan to conduct targeted communication of FDA's Expedited review guidance to companies in South Africa and India. We conducted a similar program in Ethiopia in early December 2004.

Global HIV/AIDS—Pediatric Therapeutics

As we now start to treat larger numbers of people in resource-poor countries, we must focus our attention on the unique medical needs of children. With almost 700,000 new pediatric HIV infections last year alone, no global agenda for HIV/AIDS care and treatment is complete without attention to the unique treatment needs of children.

Currently, few programs specifically target the treatment of children with HIV/AIDS in resource-poor countries. One of the reasons for this is the lack of appropriate pharmaceuticals for their use. Children are not small adults and treating them that way jeopardizes their lives. Children's growing bodies respond differently to drugs than adults, and require dosing guidelines specific to certain age groups. For many HIV/AIDS medicines, dosing guidelines are completely missing for younger age groups, requiring health workers to estimate the correct dose by breaking or crushing pills made for adults. Effective treatment of HIV requires appropriate and precise levels of medicine to inhibit the virus and prevent the development of viral resistance.

With 2.2 million children infected with HIV around the world, it is essential that we have appropriate medications to treat them.

Question 9. How is the Administration ensuring that the HIV/AIDS drugs (both generic and brand) being approved by the FDA expedited process also include pediatric formulations as well as important dosing information needed for treating different age groups?

Answer 9. On May 17, 2004, FDA published guidance for the pharmaceutical industry encouraging manufacturers to submit marketing applications for fixed dose combination (FDC) and co-packaged versions of previously approved single entity anti-retroviral therapies. The guidance encourages the development of pediatric formulations for fixed dose and co-packaged antiretroviral combination products. Also, subsequent to the publication of the draft guidance, the expedited review program was expanded to include single product generic applications. Most of the first line antiretroviral agents are currently available in pediatric dosage forms, so these pediatric formulations can be made available through the generic drug approval process.

Regarding fixed dose and co-packaged combination products, only one company thus far has expressed interest to FDA in developing a pediatric combination product. This could be explained in part by the challenges associated with dosing pediatric patients with fixed dose combination products. Such combination products generally do not provide the dosing flexibility needed for pediatric HIV therapy. Also,

many of the pediatric formulations are in the form of oral solutions that are not amenable to combination product development. Combination therapy in younger pediatric patients might best be accomplished through the use of individually formulated antiretroviral products that can be made available through the generic approval process. Generally, adult combination products can be used in the older pediatric population.

Pediatric Medical Devices

Like drugs, where for too long we assumed that children were small adults and could just take reduced doses of adult products, we're finding that many essential medical devices used extensively by pediatricians are not designed and sized for children's special needs. According to pediatricians, the development of cutting-edge medical devices suitable for children's smaller and growing bodies can lag 5 or 10 years behind those for adults. This is simply unacceptable. As technology for prolonging and saving lives continues to advance at a rapid pace, children are at risk of being left further and further behind.

Question 10. What is the FDA doing to ensure that devices used in children are designed and sized for their use? What can Congress, and others, do to ensure that kids have access to appropriately sized devices?

Answer 10. Pediatric medical devices treat or diagnose diseases and conditions from birth through age 21. Some products are designed specifically for children, while others are borrowed from adult applications or produced for more general use.

Bringing pediatric medical devices to market can be challenging for a number of reasons: children are often smaller and more active than adults, body structures and functions change throughout childhood, and children may be long-term device users bringing new concerns about device longevity and long-term exposure to implanted materials. In addition, modifying an adult device for pediatric use may require significant re-designing of the device and re-tooling of the manufacturing process. Conducting clinical trials in children can also be more difficult due to the small patient population and the variation within the population.

FDA is committed to supporting the development and availability of safe and effective pediatric medical devices. Current initiatives include:

- Obtaining pediatric expertise for FDA advisory panels whenever there is a reasonable likelihood that the device under discussion will be used for children.
- Issuing guidance describing the protections that clinical trial sponsors should consider when enrolling children in device trials.
- Collaborating with the Institute of Medicine on their study of the effectiveness of post-market surveillance of pediatric medical devices.
- Collecting data on the unmet needs for pediatric medical devices and the barriers to the development of new pediatric devices.

In May 2004, FDA finalized a guidance document to facilitate the development of pediatric medical devices. Entitled "Premarket Assessment of Pediatric Medical Devices," this guidance defines the pediatric population and pediatric use for medical devices, identifies the types of information needed to provide reasonable assurance of the safety and effectiveness of medical devices intended for use in the pediatric population, and defines the guiding principles and protections sponsors should consider for pediatric subjects in device clinical trials.

In June 2004, FDA opened a docket requesting comments identifying the unmet device needs in the pediatric population, possible barriers to the availability of medical devices intended to treat or diagnose diseases and conditions that affect children, and potential incentives to facilitating the development of such devices. These comments assisted the agency in preparing its recent "Report to Congress: Bafflers to the Availability of Medical Devices Intended for the Treatment or Diagnosis of Diseases and Conditions that Affect Children."

In addition to preparing this report, the agency has been working with several pediatric professional organizations to better understand this important issue. A series of meetings were held this past fall that included representatives from academia, medical specialty organizations, the device industry, and several government agencies. The group determined that further study is warranted to evaluate the scope of the unmet needs and the most promising solutions to addressing these needs. HHS believes that this is a critical first step and is working with interested stakeholders to ensure that a systematic needs assessment to promote a better understanding of the unmet needs and the barriers to the development of pediatric device development is conducted.

Finally, to help raise awareness of the challenging issues surrounding pediatric device development, the Center for Devices and Radiological Health has developed a new web page on pediatric medical devices at http://www.fda.aov/cdrh/

pediatricdevices/. In addition, FDA's Office of Pediatric Therapeutics web page can be accessed at http://www.fda.gov/oc/opt/default.htm. One of this Office's goals is to coordinate and facilitate all activities effecting the pediatric population or practice of pediatrics or involving pediatric issues. Our Center for Drug Evaluation and Research also has a pediatric web page at http://www.fda.aov/cder/pediatric/.

Flu Vaccine

In 2004, a Liverpool, England plant responsible for providing our country with over 100 million doses of the flu vaccine was shut down. As a result, we received less than half the expected doses, resulting in a crisis for millions of Americans who depend on the flu vaccine each year.

You have said that the FDA had no idea of escalating concerns at the plant before British authorities suspended the plant's license in October 2004. However, British authorities dispute this and state that the FDA had been notified of ongoing problems as early as mid-September. The FDA inspected this plant in June 2003 and raised concerns then about possible contamination problems, and inspectors returned again in August. A full inspection was still not conducted. The FDA has been accused of inadequate follow up after major problems were identified. You stated that the FDA followed standard procedures, and you would not change anything the FDA did. You said: "This is the way we've always done it, and it's worked very well in the past."

Question 11a. Do you stand by this statement?

Answer 11a. FDA inspects U.S. licensed vaccine manufacturing facilities every 2 years. Based on this schedule, FDA inspected the Liverpool, U.K. facility where the Chiron vaccine is produced in 1999, 2001, and 2003. It should be noted that Chiron acquired the facility in July 2003 after FDA conducted the biennial inspection. During the 1999 inspection, FDA identified various concerns and, as a result, issued a warning letter regarding the Liverpool facility. The most significant issues identified in 1999 inspection were the lack of validation for its manufacturing processes, including establishing proper limits for bioburden (including bacteria) and issues related to assuring sterility in the manufacturing process. During the 2001 and 2003 inspections, FDA found that the company had made improvements but we also made observations related to current Good Manufacturing Practices (cGMPs). In each case, FDA reviewed the corrective measures and plans in response to these deficiencies. If fully implemented, the company's plans appeared adequate to correct deficiencies identified at the facility.

On August 25, 2004, FDA inspectors were on site conducting a preapproval inspection and were informed of the contamination of the vaccine. FDA inspectors met with Chiron's staff and reviewed the preliminary findings and the approach that Chiron was taking to its investigation and retesting at multiple points in its process. FDA inspectors in Liverpool faxed to CBER preliminary data and information regarding the scope and plans for the sterility failure investigation being conducted by Chiron. The results of these evaluations were needed and essential for any regulatory assessment. Chiron's investigation was in the earliest stage and, therefore, only preliminary information was available. Chiron informed FDA that all results from the retesting were negative for all other finished product and that its final investigative report, including all product testing data, would be submitted to FDA during the week of October 4–8, 2004. FDA would then complete an in depth assessment of the report findings, which would indicate appropriate next steps for the agency. However, on October 5, the week the report was expected by FDA and just hours before FDA expected to receive an update from Chiron during a previously scheduled morning teleconference, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) announced their suspension of Chiron's license. MHRA's Chief Executive, Professor Kent Woods, indicated that MHRA did not have the legal authority to notify FDA about the suspension announced on October 5 until after MHRA instituted its administrative action. Dr. Woods has also stated that, "Contrary to some reported statements, MHRA, as the responsible regulatory authority in the United Kingdom, made the decision to suspend Chiron's license after an internal meeting on October 4 and first informed the company and the FDA of this decision on October 5. At the same time, we informed other drug regulatory authorities via an intergovernmental rapid information alert."

Upon learning of the MHRA's suspension on October 5, 2004, FDA communicated with both Chiron and the MHRA. While Chiron indicated to FDA that it believed it had satisfactorily addressed MHRA's inspectional findings and provided to FDA a copy of those findings and the company's response, MHRA expressed serious concerns about Chiron's vaccine stocks and the company's ability to assure the safety of the vaccine.

FDA performed a comprehensive review of the retesting data during its October 10–15, 2004, inspection of the Liverpool facility. The retesting results were indeed negative; however, FDA's inspection found issues related to the adequacy of the statistical sampling plan used for the retesting. These findings, coupled with the other issues uncovered during the inspection, led FDA to conclude that it could not assure the safety of the vaccine.

Question 11b. How would you prevent this type of incident from happening in the future?

Answer 11b. Recent experiences, particularly those of the past 7 months, have taught us important lessons about manufacturing and inspectional activities with respect to influenza vaccine. Although FDA has always interacted extensively with influenza vaccine manufacturers throughout the vaccine production cycle, the annual changes in the flu vaccine and the increased dependence on a smaller number of manufacturers highlight the risks of unexpected manufacturing difficulties. For these reasons, in 2005 and the future, we plan to conduct inspections of influenza vaccine manufacturers on an annual basis, with additional interactions with manufacturers and, in the case of foreign facilities, their regulatory agencies where appropriate, based on findings or events that raise concerns.

FDA is working with manufacturers and its regulatory counterparts in anticipation of having an ample supply of influenza vaccine for the coming season through a dual-track strategy.

FDA's first track is to facilitate Chiron's effort to correct its manufacturing problems. FDA and MHRA, the British regulatory agency, have an agreement with Chiron that allows full information sharing. FDA has used that agreement to collaboratively review Chiron's remediation plans and activities, and the Agency is providing continuing and extensive feedback to both Chiron and MHRA. In addition, FDA signed an information sharing agreement with MHRA that will, among other things, permit advance communication on important issues. The agreement was effective February 14, 2005.

FDA is actively communicating on inspection activities. Only after passing MHRA and FDA inspections will Chiron be able to provide vaccine to the U.S. market. In the spring when critical stages of manufacturing are taking place, the Agency plans a comprehensive inspection to verify whether Chiron has adequately addressed its problems. While much work remains to be done, it appears that Chiron is making progress.

FDA's second track is to facilitate overall greater capacity and diversification in the U.S. influenza vaccine supply. It is important to recognize that the demand for vaccine and other economic issues are the primary factors that determine whether a manufacturer will seek and maintain a license in this country.

CDC and FDA are working to encourage vaccination throughout the flu season, including January and February. To increase the total doses available, manufacturers can produce vaccine over a longer time period, and that becomes available during these months. Because influenza cases usually continue well after November and December when most people are seeking immunization, later vaccination is beneficial. The Public Health Service is working to better communicate this important public health message.

In addition, FDA has been working to stimulate manufacturers not licensed in the U.S. to provide or, where needed, develop the safety and effectiveness data to obtain U.S. licensure. The Agency has actively engaged several interested companies. FDA has informed manufacturers that the Agency is willing to consider all approaches to licensing, including accelerated approval based on surrogate markers, e.g., the patients' immune response to the vaccine. Sanofi Pasteur and Medlmmune have indicated their willingness, if needed, to do what they can to increase production.

FDA has challenged itself to identify other lessons learned from this year's influenza season and is evaluating how this experience could be used to prevent similar events in the future. While there are some elements that FDA cannot control, the Agency is making significant changes. For example, as mentioned above, FDA plans to conduct inspections of influenza vaccine manufacturers on an annual basis, and the Agency is completing or has completed agreements that allow information sharing with numerous foreign regulatory agencies.

Ophthalmology

Dr. Crawford, the FDA's Ophthalmology Group represents a unique specialty distinct from other clinical areas. Given the unique nature of drug therapies and treatments related to eye care, the work of this important group is critical to millions of Americans at risk for serious eye disease or blindness. Currently under the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products, it is my under-

standing that the FDA is considering integrating the Ophthalmology Group into the Division of Anti-Infective Products. Clearly, research of new treatments for potentially blinding diseases is extremely important.

Question 12. If confirmed as Commissioner, how would you address concerns that ophthalmics may receive diminished attention and resources if combined within antiinfectives?

Answer 12. We expect that individuals with expertise in ophthalmology will continue to play a critical role in reviewing new ophthalmology products, and the reorganization will not affect the timely approval of treatments and drug therapies available to eye care practitioners and their patients. All drug review processes for all products will continue to be held to existing PDUFA goals and timelines during and as a result of the reorganization.

RESPONSE TO QUESTIONS OF SENATORS KENNEDY/MIKULSKI BY LESTER CRAWFORD, DVM, PH.D.

(First Set of Questions)

Question 1. When Tommy Thompson resigned in December 2004 he expressed "grave concern" about the risks of a terrorist attack on the U.S. food supply.

As Commissioner, what steps would you take to protect America's food supply as Secretary Thompson warned?

Answer 1. Ensuring the safety of the food supply is a top priority for me and for the Administration. A great deal has been done in the past few years to improve food safety and security. FDA has worked with food safety agencies at the Federal, State, and local levels to significantly strengthen the Nation's food safety system across the entire distribution chain (i.e., from farm to table) to better protect our food supply against deliberate and accidental threats. This cooperation has resulted in greater awareness of such vulnerabilities, the creation of more effective prevention programs, new surveillance systems, and faster foodborne illness outbreak response capabilities. An effective food defense system is built on a strong food safety system.

The fiscal year 2006 budget requests an increase of $30 million for food defense activities. Twenty million dollars of this increase will support a national laboratory network known as the Food Emergency Response Network (FERN). A critical component of controlling threats from deliberate food-borne contamination is the ability to rapidly test large numbers of samples of potentially contaminated foods for a broad array of biological, chemical, and radiological agents. FERN will increase our laboratory surge capacity through a nationwide network of Federal and State laboratories capable of testing the safety of thousands of food samples, thereby enhancing the Nation's ability to swiftly respond to a terrorist attack. The additional $10 million will be used for targeted food defense research, for continued coordination and sharing of data with the Department of Homeland Security as part of the governmentwide Bio-Surveillance Initiative, and for upgrades in FDA's crisis management capabilities.

Significant new tools to enhance the safety of the food supply were provided by the Public Health Security and Bioterrorism Preparedness and Response Act (Bioterrorism Act), which the President signed in 2002. This landmark legislation represents the most fundamental enhancement to FDA's food safety authorities in many years, and FDA has been working hard to implement it. In response to the provisions included in the Bioterrorism Act, FDA:

- Published a final rule to implement recordkeeping requirement on 12/9/04;
- Published a final rule to implement the administrative detention provision on 6/4/04;
- Signed a Memorandum of Understanding with Customs and Border Protection on 12/3/03 to allow FDA to commission CBP officers in ports and other locations to conduct investigations and examinations of imported foods; and
- Published Interim Final Rules to implement the requirement for domestic and foreign facilities to register with FDA and the requirement for prior notice of imported food on 10/10/03.

In addition to implementing the Bioterrorism Act, FDA has many other ongoing counterterrorism activities. For example, since September 11, 2001, FDA has increased its emergency response capability by realigning resources to counterterrorism and by reassessing and strengthening its emergency response plans. FDA has also conducted numerous emergency response and preparedness exercises to further strengthen our response to a terrorist event involving our Nation's food supply. These exercises have included Federal, State, and industry partners.

FDA has completed vulnerability assessments focused on specific foods, suspect agents, and processing steps where an agent could be intentionally introduced. These vulnerability assessments have assisted the agency in focusing on those commodities considered to be most at risk for intentional contamination. Government and industry have worked together on specific and targeted mitigation steps to address the vulnerabilities identified in our assessments. These assessments have also assisted the agency in focusing intramural and extramural research on four major areas: new methods for detection of agents, prevention technologies, agent characteristics, and dose response.

FDA has also issued food security guidance documents to different segments of the food industry on the preventive measures they can take to minimize the risk that food or cosmetics under their control will be subject to tampering or other malicious, criminal, or terrorist actions.

Other Counterterrorism Activities over past 3 years include:

- Increasing laboratory surge capacity by expanding participation in the Food Emergency Response Network, constructing BSL-3 laboratories in the field and supporting the construction and deployment of two mobile laboratories;
- Enhancing an early-warning system to identify hazardous foods by expanding the number of Federal, State, and local laboratories providing data through our Electronic Laboratory Exchange Network (eLEXNET).
- Conducting numerous research projects to improve our ability to detect contamination, focusing on rapid test methods for use in the field;
- Carrying out food defense activities under Homeland Security Presidential Directives; the Interagency Security Plan; the Secretary's Bioterrorism Strategic Plan; and FDA's Strategic Action Plan;
- Enhancing FDA's ability to plan, manage, and respond to food emergencies through the Emergency Operations Network (EON), an electronic incident management system; and
- Enhancing law enforcement and intelligence gathering/analysis by, for example, participating in select Joint Terrorism Task Forces and establishing a dedicated Counterterrorism Section in FDA's Office of Criminal Investigations.

Question 2. FDA headquarters is currently located in 40 buildings at 18 locations—this will change when FDA headquarters moves to White Oak. FDA's consolidation of White Oak has been going on for over 10 years to give FDA state-of-the-art facilities. Each phase of the project costs about $200 million; each year of delay costs millions of dollars.

The President's fiscal year 2006 budget requests $128 million for continued consolidation at White Oak less than half the level requested by FDA and GSA to construct the next phase of the project (about $280 million). FDA needs these facilities for many reasons; including to attract the best and brightest employees to FDA.

Would consolidation of FDA be a priority for you as FDA commissioner? As FDA commissioner would you advocate for the completion of the consolidation project at White Oak? If so, do you have a projected time line that you would like to implement for completion of the project? What steps would you take to make sure that the Administration understands the importance of this project, and the need for a strong Federal funding commitment to complete the consolidation project?

Answer 2. The consolidation of FDA Headquarters is a priority for the FDA, which upon completion will house over 7,700 staff in 2.3 million square feet of space. By the end of fiscal year 2005, the campus will have almost 700,000 square feet completed with 1,850 staff on site. The new buildings will eventually replace all 40 of the existing facilities in 18 locations that support the Office of the Commissioner, and all of our Centers and Field headquarters, except the Center for Food Safety and Applied Nutrition in College Park and the National Center for Toxicological Research in Jefferson, Arkansas. This project will allow FDA to work towards many of the President's Management Agenda goals by standardizing and modernizing document handling, providing shared use facilities such as libraries and conference areas, further reducing redundancies in administrative tasks and allowing conversion to a single computer network. This will help create a stronger FDA by reducing operating costs, reducing travel time between organizations, increasing collaboration between centers and increasing the convenience of access to FDA by the public.

This Administration has and continues to strongly support the White Oak project. Currently, the Project is on track for GSA funding of the Office of the Commissioner and ORA buildings in fiscal year 2008. With funding on schedule, the move in date for these buildings would be in fiscal year 2010. The anticipated move in schedule is provided below:

FDA Move in Timeline for the White Oak Consolidation Project

Phase	Completion	Employees In Phase	Total Employees at White Oak
Life Sciences Laboratory(includes CDER Labs & CDRH Chemistry & Biological Sciences).	COMPLETED December 2003	125	125
CDER Office Building I	2005	1,725	1,850
Central Shared Use I	2006	150	2,000
Engineering Physics Laboratory	2007	160	2,160
CDER Office Building II	2007	1,076	3,236
CDRH Offices	2008	1,298	4,534
Central Shared Use II	2008	140	4,674
CBER Labs	2008	300	4,974
CBER Offices	2009	900	5,874
CVM Offices	2009	426	6,300
OC & ORA HQ Offices	2010	1,420	7,720

Question 3a. While mammograms are imperfect, they are the best tool we have today to screen for breast cancer. However, mammography should not be the only tool. There must be better tools. In 2001, a report from the Institute of Medicine on developing technologies for the early detection of breast cancer made some recommendations for FDA such as:

• FDA developing and using consistent criteria for approval of screening and diagnostic devices and tools.

• FDA approval for new screening technologies should depend on evidence of improved clinical outcome.

Has FDA implemented any recommendations from this report? If so, what is the status? If not, why not?

Answer 3a. New screening and diagnostic processes often are new technology, and each technology presents unique questions. The agency has tried to reduce inconsistency in the review process wherever possible. Note the following examples.

• The agency developed a guidance document for Digital Mammographic submissions.

• CDRH is currently working on a guidance for Computer Assisted Detection (and Diagnosis) (CAD and CADx).

• A policy is in place to meet with sponsors early in the product development cycle to allow them and us to understand the new product and its path to market.

• We are developing a guidance on the performance assessment of imaging products. We are also training staff on these techniques.

• There is a process for determining whether a new product will follow a 510(k) or PMA marketing approval route.

• CDRH follows a least-burdensome process in reviewing device submissions.

• There is strong collaboration amongst multiple CDRH offices in the review of submissions for new devices, especially PMAs.

• Review of submissions for new novel devices is expedited according to Center policy.

A recent example of a new device approval in this area is the Kodak Mammography CAD (computer-aided design) ENGINE. The Kodak Mammography CAD ENGINE uses software that helps radiologists who read mammograms to highlight areas that might be suspicious for breast cancer and might otherwise have been missed.

Question 3b. Since its creation in 1994, the FDA Office of Women's Health has sponsored research, conducted public education campaigns, encouraged the participation of women in clinical trials, and served as an advocate for women's health in agency decisions. Senator Olympia Snowe and I recently introduced the Women's Health Office Act of 2005. This bill would statutorily authorize the Office of Women's Health at FDA. As Commissioner, will you support legislative efforts to authorize this Office? When appropriate, will you seek the advice and recommendations of the Office of Women's Health?

Answer 3b. I strongly support the FDA Office of Women's Health (OWH). The OWH has proven to be a valuable source of information both inside and outside of the Agency. Its leadership has served the agency well on issues of sex and gender differences regarding therapeutic interventions. In addition, its national award-winning public information campaigns have made it an essential part of FDA. I have

routinely sought their advice on issues of importance to women and will continue to do so during my tenure.

Question 4. On February 25, 2005, an article in the New York Times revealed that 10 of the 32 government drug advisers who voted in favor of keeping Vioxx and Bextra on the market had consulted in recent years for the drugs' makers. If those who had consulted for the applicants had not voted for the companies' products, they would have been rejected by the panel.

Back in 2003, 6 of the 15 voting panel members on the general and plastic surgery devices panel were plastic surgeons. All voted in favor of approving silicone breast implants for general use and could profit from allowing silicone breast implants.

A majority of the scientists on the panel voted against approval, based on failure of the manufacturers to produce long-term data on the safety of the product. But, because all the plastic surgeons voted in favor, the advisory panel voted to approve silicone implants.

Following that October 2003 panel, Dr. Thomas Whalen, chair of the advisory panel, took the highly unusual step of writing a public letter to the FDA commissioner which stated that "it serves the reputation of the FDA in general, and the standing of the panel process in particular, exceedingly poorly to have had all of the plastic surgeons vote the PMA as approvable on such a close vote. Even in academic settings, plastic surgeons may stand to increase their own income with the use of these devices."

FDA needs to restore public confidence and show its ability to protect the public health and safety of the American people.

What is the FDA's justification for its failure to publicly disclose the financial conflicts of interest of the panel participants?

Answer 4. Although 18 U.S.C. Section 208 provides that a copy of any waiver determination is available to the public upon request, the Agency may withhold from disclosure information that would be exempt under the Freedom of Information Act, 5 U.S.C. Section 522(b). Under this provision, all of the information concerning conflicts of interest may be withheld as exempt pursuant to 5 U.S.C. Section 522(b)(3) because the Ethics in Government Act prohibits release of the information. Nevertheless, in order to provide meaningful disclosure of conflicts of interest information, the Office of Government Ethics has concluded that, under section 208, Federal Agencies have discretion to disclose information concerning the waived conflict of interest absent a foreseeable harm to be caused by the disclosure. The Office of Legal Counsel, United States Department of Justice (OLC), concluded that FDA may exercise its discretion in making disclosure to avoid making the disclosure requirement so intrusive or onerous as to make outside experts unwilling to serve on advisory committees.

In January 2002, the FDA issued draft guidance on "Disclosure of Conflicts of Interest for Special Government Employees Participating in FDA Product Specific Advisory Committee." The guidance provides information on the type and amount of information that will be disclosed to the public when a member is granted a conflict of interest waiver with the topic to be discussed by the committee. The guidance applies only to those advisory committee meetings at which a particular matter relating to a particular product is discussed (product specific meetings). The guidance does not apply to advisory committee meetings that provide advice on topics of general applicability (i.e., those meetings that could affect a class of products and their sponsors) even if the members on the committee received general matters waivers covering their participation on the committee.

The disclosure for particular matters identifies whether the interest is related to the sponsor or competitor that markets a product competing with the product at issue (without naming the competitor), the type of interest (stock, consulting, contracts/grants, patents/royalties/trademarks, expert witness, teaching, speaking, or writing), and the magnitude of the interest is described as a range.

Question 5. What conflict of interest screening measures does the FDA currently have in place for advisory panels?

Answer 5. Because it is imperative to obtain the best scientific information available, it is very difficult to obtain qualified advisory committee members who are also totally free from all potential financial conflicts of interest. The Nation's experts (and in some cases, there are only a few experts on a particular topic) are sought after for consultation by both the Agency and industry because of the scarcity, and therefore the value, of their expertise. Utilizing scientists who are less experienced or less highly qualified in order to completely remove any potential financial conflict

from the committee would hamper the Agency's ability to protect and advance the public health.

The Agency's staff examines all potential financial interests. The Agency's process is to evaluate the potential financial interests of members and other invited special government employees. FDA makes a determination as to whether the participation of an individual with some financial ties outweighs the need for the agency to understand the science on the topic before the committee. Although the Agency has guidelines for this process (see Waiver Criteria Document 2000 on the FDA web page), this is not a black and white process. It requires careful consideration of all facets of the issue in order to evaluate that balance. Congress, by permitting waivers for potential conflicts of interest, has ensured that the Agency and the public (through the advisory committee process) have access to the most knowledgeable individuals on the meeting topic.

Question 6. What steps as FDA Administrator you would take to limit conflicts-of-interest in future drug advisory panels?

Answer 6. FDA's process of evaluating potential committee members for conflicts is very extensive and transparent. Our methodology is articulated in a comprehensive document on the agency's website (http://www.fda.uov/oc/advisory/conflictofinterest/intro.html). At the beginning of each meeting, a conflict of interest statement is read into the record, which summarizes the results of the conflicts of interest screening. Nonetheless it is always prudent to regularly assess the Agency program and determine if any improvements are warranted. In the near future, the Agency will review the advisory committee conflicts of interest disclosure process and consider if further improvements are necessary to make the disclosures more easily accessible to the public.

Question 7. Given that plastic surgeons stand to befit financially from the approval of silicone breast implants, do you think that it's appropriate for plastic surgeons to serve on the Advisory panel, let alone make up its plurality?

Answer 7. FDA expects this panel to include a number of plastic surgeons, as did the October 2003 panel. Please note that plastic surgeons comprised only four of the 16 voting panel members for that meeting. We believe it is appropriate that the medical specialty most likely to implant silicone breast implants be represented during deliberations on the device. Their experience with the product and insights into issues that impact its safety and effectiveness are critical to the agency's evaluation.

Question 8. What do you intend to do about these conflicts before the upcoming April advisory panel to reintroduce silicone breast implants for general use?

Answer 8. The individuals that comprise the General and Plastic Surgery panel for the upcoming April meeting will have been screened according to the Agency's existing conflict of interest rules. All panel members, new and standing, must be cleared through a formal process prior to serving as a panel member for a specific PMA. The final roster will be posted on FDA's website a week or two prior to the meeting when all panel members are cleared to serve on this panel for these PMAs.

RESPONSE TO QUESTIONS OF SENATOR KENNEDY BY LESTER CRAWFORD, DVM, PH.D

(Second Set of Questions)

I understand that just 9 days before he was scheduled to testify before the Senate Finance Committee, you offered Dr. David Graham a newly created job in your office to lead the agency's effort to enhance its monitoring and surveillance of approved drugs. Dr. Graham declined the offer, and went on to testify.

Following that testimony, one senior FDA official called Dr. Graham's work "junk science" and accused him of scientific misconduct to The Lancet. Managers in the center for drugs called Dr. Graham's lawyer posing as whistleblowers and tried to discredit Dr. Graham.

Question 1a. Why did you offer Dr. Graham a prestigious job, then only days later allow an FDA official to label his work "junk science"? If his science was junk, why did you offer him the job?

Answer 1a. Your question relates to a statement made by an FDA employee. Dr. Graham and all other FDA employees enjoy freedom of expression as guaranteed under the Constitution. That said, it is my understanding that this quote comes from a conversation with a Washington Post reporter that was taken out of context. The FDA official interviewed was asked to respond to the reporter's question about whether it was accurate to state that a certain number of individuals in particular Congressional districts could be said to have died of cardiovascular events because of Vioxx. It is not possible to derive from risk estimates the cause of a particular

individual's death. This concept is complicated to explain, and the FDA official reacted to it by characterizing the particular statement regarding deaths of individuals in a Congressional district as "junk science." The characterization was not made with regard to all of Dr. Graham's work. I am not aware of any FDA official accusing Dr. Graham of scientific misconduct.

Question 1b. Some might question whether you were simply kicking Dr. Graham upstairs to keep him quiet. Did you look for a different candidate when Dr. Graham declined the job? Did you contact any of the people whom Dr. Graham recommended for the job? When did you create the new position? When did you find out that Dr. Graham was testifying before the Senate Finance Committee? Who holds the position now, and when was that person hired?

Answer 1b. My discussion with Dr. Graham focused on the IOM review of drug safety and not Congressional hearings. Dr. Janet Woodcock, Acting Deputy Commissioner for Operations, was eventually assigned the task of designing FDA's drug safety program, including liaison with the IOM on the study.

Question 1c. FDA managers called Dr. Graham's attorney, made misleading statements about their own identities, and tried to discredit him. What have you done to try to find out who made these calls, and what disciplinary action have you taken?

Answer 1c. There is an Inspector General (IG) investigation of this issue underway, therefore, the Agency cannot comment further on this matter at this time.

Question 1d. An FDA manager called Dr. Graham's work "junk science" and accused Dr. Graham of scientific misconduct. What have you done to reprimand this individual, and to clarify to all agency employees that this behavior is not appropriate?

Answer 1d. As noted above, the "junk science" quote comes from a conversation with a Washington Post reporter that was taken out of context and I am not aware of any FDA official accusing Dr. Graham of scientific misconduct.

[NOTE.—There was no "Q2" in—original document]

[NOTE.—As revised by Kennedy staff 3/24] In January 2004, FDA rejected an application for approval of silicone breast implants and issued guidance about the information needed to win approval. Two applications for approval of these products have now been submitted, less than a year later. I understand FDA did not follow the recommendation of its own reviewers who recommended that the information in the applications was not sufficient to change the decision from last year. Instead, the agency has convened an advisory committee to review the applications, and is reportedly hand-picking its members to see that they grant the implants swift approval. Reportedly there's even an email on which you were copied from your special science advisor, Susan Bond, to Dan Schultz, the head of the center for devices, specifying in advance the conclusion the review should reach.

Question 3a. On breast implants, why has FDA not accepted the conclusion of its own scientific review that the data in these submissions are not sufficient?

Answer 3a. FDA continues to evaluate the science with regard to breast implants. No final conclusion has been reached.

Question 3b. Is it true that you were copied on an e-mail to the head of the center for devices specifying in advance the conclusions he was to reach regarding the safety of breast implants? How did you respond?

Answer 3b. No, I was copied on an e-mail transmitting a preprint of the views of an individual regarding breast implants. The document contains a bibliography of recent scientific papers on the subject. These papers are all publicly available and therefore already known to CDRH. The bibliography was incomplete. In evaluating the safety of breast implants, CDRH will consider the entirety of the scientific literature.

Question 3c. Please provide me all the e-mails or other correspondence, with all attachments, you received, were copied on, or sent that have had to do with breast implants.

Answer 3c. Enclosed are e-mails that respond to your question.

Question 4a. On August 26, 2004, the public learned that Chiron, one of two manufacturers of the Nation's flu vaccine, had produced contaminated lots of vaccine at a plant in Liverpool, England.

Between that date and October 5, 2005, when the British regulatory agency, the MHRA, suspended Chiron's license, the FDA did not inspect the Liverpool plant. By

contrast, the British carried out two full inspections during September 2004, once on September 13th and 14th, and again from September 29th to October 1st. British inspectors were physically present at the plant and they required Chiron to respond to their inspectors' report. FDA never inspected the plant before the license was suspended.

In your testimony to the House Government Reform Committee in November 2004, you said that after MHRA suspended Chiron's license, you contacted Chiron and the British, but that "Chiron indicated that it believed it had satisfactorily addressed MHRA's inspectional findings." Why did FDA trust Chiron's assurances rather than verifying the safety of half of our vaccine supply the way the British regulators did?

Answer 4a. In our interactions with Chiron, FDA consistently worked to verify the safety of their vaccine product. On August 25, 2004, FDA inspectors were onsite conducting a preapproval inspection and were informed of the contamination of the vaccine. FDA inspectors met with Chiron's staff and reviewed the preliminary findings and the approach that Chiron was taking to its investigation and retesting at multiple points in its process. FDA inspectors in Liverpool faxed to FDA's Center for Biologics Evaluation and Research (CBER) preliminary data and information regarding the scope and plans for the sterility failure investigation being conducted by Chiron. The results of these evaluations were needed and essential for any regulatory assessment. Chiron's investigation was in the earliest stage and, therefore, only preliminary information was available. Chiron informed FDA that all results from the retesting were negative for all other finished product and that its final investigative report, including all product testing data, would be submitted to FDA during the week of October 4–8, 2004. FDA would then complete an indepth assessment of the report findings, which would indicate appropriate next steps for the agency. However, on October 5, the week the report was expected by FDA and just hours before FDA expected to receive an update from Chiron during a previously scheduled morning teleconference, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) announced to Chiron, the FDA and the world their suspension of Chiron's license.

FDA performed a comprehensive review of the retesting data during its October 10–15, 2004, inspection of the Liverpool facility. The retesting results were indeed negative; however, FDA's inspection found issues related to the adequacy of the statistical sampling plan used for the retesting. These findings, coupled with the other issues uncovered during the inspection, led FDA to conclude that it could not assure the safety of the vaccine.

Question 4b. Once the Chiron vaccine was unavailable, the Administration began to identify manufacturers of vaccine for other countries that it might be able to acquire and make available to the public, and it reprioritized who should receive vaccine. Please assess the difference beginning these endeavors in late August 2004 would have made?

Answer 4b. The loss of Chiron's planned contribution to the U.S. influenza vaccine supply posed serious challenges. FDA worked with urgency, aggressiveness and in close coordination with CDC and other components of HHS and the private sector to explore all viable options to secure additional doses of influenza vaccine. FDA worked with Sanofi Pasteur and Medlmmune to secure approximately 5 million additional doses of U.S. licensed vaccine. Sanofi Pasteur increased production to 58 million doses of Fluzone, and Medlmmune scaled up to produce 3 million doses of FluMist. FluMist is currently recommended for healthy individuals 5 to 49 years of age, and therefore provides an option for those who would not receive vaccine under CDC's priority guidelines, such as the U.S. military. Therefore, to expand further the supply of vaccine to those with the greatest need, Secretary Thompson, in cooperation with the Department of Defense, announced that the military would maximize its use of FluMist as a substitute to the inactivated vaccine, making an additional 200,000 doses of injectable vaccine available to HHS for high-risk civilian populations. Because Sanofi Pasteur produces pediatric dosage forms of vaccine for the U.S. market, the supply of vaccine available for high-risk children was, fortunately, not reduced. Through these collaborative efforts, manufacturers increased the available supply of licensed influenza vaccine for the U.S. population to 61 million doses for this influenza season, compared with approximately 83 million doses distributed in 2003–04 and in 2002–03, 77 million doses in 2001–02 and 70 million doses in 2000–01.

Because there was a concern that the need and demand could still outstrip supply, particularly if we face a severe influenza season, we sought additional doses of vaccine that could be safely used in an emergency. Thus, in addition to enhancing the supplies of vaccine approved for use in the U.S., we were able to rapidly identify

suppliers of approximately 5 million doses of additional vaccine, licensed in other countries, that could potentially be made available under an FDA investigational new drug (IND) application. With remarkable cooperation from several companies and from other regulatory agencies (including the Paul Ehrlich Institute, Germany; Therapeutic Goods Administration, Australia; Swiss Medic and Health Canada) FDA immediately sent inspectors and scientists to the manufacturing facilities of potential IND sponsors to evaluate their manufacturing processes. Coupled with these efforts, we also reviewed a large volume of manufacturing and clinical data, all within in a few weeks. These efforts resulted in FDA approving INDs that permitted the potential use of approximately 4 million doses from GlaxoSmithKline (GSK) and 1 million doses from Berna Biotech, if needed. Of the 5 million doses potentially available under an IND, FDA understands that CDC has purchased approximately 1.5 million doses. HHS and FDA's coordinated interactions with these and other influenza vaccine manufacturers and regulatory agencies also provided valuable information and strengthened relationships that we hope will help stimulate interest by additional influenza vaccine manufacturers and potentially lead to successful U.S. licensure.

Question 5. Last year Merck withdrew Vioxx from the market, because the drug doubled the risk of heart attack or stroke but that was more than 5 years after the FDA approved the drug, and after 20 million Americans had used it. As a result, tens of thousands of Americans needlessly suffered heart attack or stroke, and many died. This is the single largest drug safety failure the Nation has ever faced. It simply should not take that long, nor should so many people use a drug, before such a significant safety risk is discovered. Dr. Sandra Kweder testified earlier this month that authority to order both drug labeling and drug safety studies after approval would be helpful. Do you agree?

Answer 5a. I do not believe new statutory authority is needed. We will use all existing regulatory authority and enforcement powers when negotiating label changes with drug companies or when monitoring or managing drug safety issues. As Dr. Janet Woodcock testified, a key factor in labeling changes is that once a label change is made, old labels in paper form are still in distribution and it takes time to get newer labels in circulation. Dr. Woodcock testified that the new strategy of posting drug safety information sooner using the Drug Watch mechanism will help alleviate that factor because it will enable the FDA to get information directly to the people who need it in a timely manner.

Question 5b. At our second hearing, Dr. Janet Woodcock testified that the practices of the drug companies promoting their drugs to doctors caused the overuse of new drugs. Do you see any drug company promotional activities as a problem? Do you think that patients are ever prescribed pills that aren't right for them because of advertising or high-pressure sales tactics to doctors? Isn't that a particular concern for newly approved drugs that may have safety concerns not detected in the initial trials?

Answer 5b. We have conducted research that confirms that DTC advertising, when done correctly, can serve positive public health functions, such as increasing patient awareness of diseases that can be treated, and prompting thoughtful discussions with physicians that result in needed treatments being prescribed often, not the treatment in the DTC advertisement. Results of our research show that many physicians believe DTC can play a positive role in their interactions with patients and that many physicians thought DTC ads made patients more involved in their healthcare.

In a survey we conducted, while 75 percent of physicians believed that DTC advertising causes patients to think the drug works better than it actually does and many physicians felt some pressure to prescribe something when patients mentioned DTC ads, only 8 percent felt very pressured to prescribe the specific drug advertised. Physicians agreed that the main effect of DTC ads was to help educate patients about their health problems, causing them to seek needed care.

While I believe these results confirm our belief that DTC ads help increase patient awareness about the availability of effective treatments for their health problems, I will continue to ensure that our DTC policies help prevent potential misperceptions about benefits and risks of advertised treatments and promote the importance of prescribing decisions being made with the intervention of a health care professional.

Question 6. In *Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals,* the GAO lists "the use of antibiotics in animals raised for human consumption as contributing to antibiotic resistance in humans." They explain that FDA's Guidance No. 152 "outlines a

framework for determining the likelihood that an antibiotic used to treat an animal would cause an antibiotic resistance problem in humans," but note that implementation of the Guidance for antibiotics already on the market "may take years." As Commissioner, what actions would you take to reduce, in a timely fashion, agricultural overuse of antibiotics, particularly those that are ranked as "important," "highly important," or "critically important" in Guidance No. 152? How long has it taken, and how much FDA staff time and resources have been spent, to withdraw Baytril from the market? Has the process been efficient and effective? What will you do to make the process of limiting the veterinary uses of important drugs more efficient?

Answer 6. FDA is concerned about antimicrobial resistance and the use of antimicrobial drugs in food-producing animals causing an unintentional adverse health impact on humans. FDA agrees with the Government Accountability Office's recommendation that it is important to review the currently approved animal drugs that are critical to human health and to collect antibiotic use data. Guidance for Industry No. 152, "Evaluating the Safety of Antimicrobial New Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern," sets out the agency's recommendations for the pre-approval safety assessment for new antimicrobial drugs intended for use in food-producing animals. This guidance also is used for re-evaluating currently approved veterinary antimicrobial drugs. FDA's Center for Veterinary Medicine (CVM) has finished the assessment for the growth-promoting uses of penicillin-containing antimicrobial drugs. CVM is currently in the process of re-assessing the growth-promotion uses of tetracycline-containing antimicrobial drugs.

In addition, CVM has re-evaluated the use of virginiamycin, a streptogramin used in five species of food-producing animals, for its potential to cause Synercid-resistant Enterococcus faecium in humans. Synercid is a streptogramin recently approved to treat vancomycin-resistant Enterococcus infections, a serious disease in humans. FDA has posted the draft risk assessment on its CVM website. In addition, FDA published an announcement in the Federal Register on November 23, 2004, that the risk assessment was available and that FDA would accept comments for 60 days. FDA subsequently extended the comment period an additional 30 days to February 23, 2005. The draft risk assessment is available at:

http.//www.fda.gov/cvm/antimicrobial/SREF RA FinalDraft.pdf. FDA intends to evaluate all comments received, revise the risk assessment accordingly, and then determine appropriate steps that need to be taken to address any identified risks to humans.

FDA intends to continue to review the currently approved antimicrobials for food-producing animals for microbial safety using GFI 152. FDA intends to begin with antimicrobials considered as critically important for human medical therapy. This process is slow because it is resource intensive to review each approved new animal drug. CVM's experience in connection with its proposal to withdraw the approval for Baytril was that the process was expensive and resource intensive, with an estimate in excess of 10.0 FTEs for approximately 3 years and about one-quarter that for an additional 2 years plus approximately $500,000 in expert witness fees and travel expenses. CVM initially published the Notice of Opportunity for a Hearing (NOOH) on its proposal to withdrawal approval of the fluoroquinolones for use in poultry on October 31, 2000. This NOOH procedure is required to ensure due process for the respondent. The matter is currently under review by the FDA Commissioner's team. Additional FDA staff members are now expending resources on the review. The agency handles these withdrawal proceedings as expeditiously as possible in light of other matters that also require the Agency's resources.

After the initial assessment of the currently approved antimicrobials with respect to microbial safety, if safety issues are identified, CVM is hopeful that the relevant animal pharmaceutical companies will cooperate with the agency in addressing those issues.

Question 7. That same GAO report strongly recommended that the FDA collect, compile and publish data on antibiotic use in agriculture, so that researchers might better "study the linkages between antibiotic use in animals and the human risk from antibiotic resistance and to develop and evaluate strategies for mitigating resistance." I understand that the FDA has drafted a rule on data collection that has been stalled for some reason. What is the status of the FDA's draft rule? Will you move forward with it this year? If not, do you have other plans to implement the GAO recommendation?

Answer 7. The FDA Center for Veterinary Medicine recognizes the importance of the monitoring of drug use data as a component of an effective surveillance system. The Center currently collects certain animal drug sales information under 21 CFR 514. However, as mentioned in the GAO Report, more detailed data would assist

us in interpreting results from the National Antimicrobial Resistance Monitoring System (NARMS) on changing resistance levels. Data on the amounts of drugs used would be helpful on many levels, for example:

- in analyzing associations between resistance levels in animals and humans,
- in risk assessments designed to quantify the human health impact attributable to antimicrobial drug use in food-producing animals,
- in identifying where mitigation strategies may be beneficial, and
- in assessing the success of prudent drug use initiatives.

Also, the WHO Global Strategy for Containment of Antimicrobial Resistance recommends the creation of national systems to monitor antimicrobial usage in food animals and several countries have developed drug use monitoring systems or are in the process of doing so. In order to change the way the current drug marketing information is reported, FDA has determined that it must promulgate a proposed regulation with a notice and comment process, including an economic impact assessment of the regulation. The Agency is considering how to best meet these data needs, taking into account the burden on industry and the Agency's data collection authority.

Question 8. I am concerned that you intend to replace Dr. Marlene Haffner, who now leads the Office of Orphan Products Development. Please explain why you intend to replace her and how you intend to search for a successor with comparable expertise in human orphan diseases. The work of this office is extremely important to me and to the tens of thousands of patients with rare diseases. What is your vision for the office?

Answer 8. All FDA offices are required to have succession plans. The incumbent in the Office of Orphan Drugs has been in that position for 17 years. Traditionally, FDA leaders have rotated into other positions following lengthy periods in one position. This is the best for the institution and for the individual. No current Center Director, Associate Commissioner, or Deputy Commissioner has served for 17 years in one position. Finally, whenever FDA conducts recruitments for vacancies, we strive to identify individuals that have the relevant management and subject matter expertise for the position.

Question 9. In 1996, after 2 years of assessment and consultation with scientists and governments both within Canada and abroad, Health Canada released a position statement on dental amalgam "The Safety of Dental Amalgam" to all Canadian dentists and doctors. (http://www.hc-sc.gc.ca/enqlish/media/releases/1996/96 63e.htm)

Health Canada stated that current evidence does not indicate that dental amalgam is causing illness in the general population. It also stated that a ban is not justified, and neither is the removal of existing sound amalgam fillings.

Health Canada recommended that dental amalgam not be used in people allergic to mercury, those with impaired kidney function, or in contact with existing metal devices, such as braces. Health Canada also recommended that, whenever possible, amalgam fillings should not be placed in or removed from the teeth of pregnant women and that alternatives should be considered for use in the primary teeth of children. Health Canada also made a number of recommendations to dentists about technique and handling of dental amalgam. Health Canada emphasized that dentists should be providing their patients with sufficient information to make an informed choice regarding the material used to fill their teeth.

Do you agree with the Health Canada statement? Do you agree with the recommendations from Health Canada? Please explain.

Answer 9. FDA agrees with Health Canada's statement that current evidence does not indicate that dental amalgam is causing illness in the general population and that neither a ban nor removal of existing sound amalgam fillings is justified. The agency also agrees with Health Canada's recommendation that dental amalgam should not be used in people allergic to mercury.

FDA has not issued warnings to pregnant women and children under 6 about mercury exposure from dental amalgam, as has Canada, because while FDA and other agencies of the U.S. Public Health Service (USPHS) continue to investigate the safety of dental amalgam, no valid scientific evidence has shown that amalgams cause harm to patients with dental restorations, except in the rare cases of allergy.

FDA, together with the Centers for Disease Control and Prevention and the National Institute for Dental and Cranio-facial Reseach, periodically has reassessed available information on the safety of dental amalgam in order to evaluate potential risk and potential action. In 1993 and 1997, the United States Public Health Service (USPHS) issued comprehensive scientific reports about the safety and use of dental amalgam and other materials used to fill dental caries/lesions.

The most recent review was completed in 2004 by an independent panel of experts under the auspices of the Life Sciences Research Office (LSRO), an independent non-profit organization, under contract to the National Institutes of Health (NIH). LSRO undertook a comprehensive review of the scientific literature published since the 1997 USPHS report. To help ensure an independent review, LSRO selected experts from outside the dental research community, including experts in immunotoxicology, neurodevelopment, reproductive toxicology, epidemiology and pediatrics. LSRO posted an Executive Summary of its report on its website in December 2004 and the report is also available for purchase by the public.

The LSRO report concludes that "there is little evidence to support a causal relationship between mercury fillings and human health problems." The authors noted, however, that there were research gaps, which, if addressed, might settle the dental amalgam controversy once and for all. FDA is currently reviewing the full report.

Dental mercury is currently classified as class I (21 CFR 872.3700) and the amalgam alloy is class II (21 CFR 872.3050). An additional encapsulated form of mercury, titrated by dentists in the office, was never classified. In February 2002, FDA proposed a rule to bring all amalgam products into Class II and increase the Agency's regulatory oversight by requiring ingredient labeling and proposing conformance to international standards. FDA has reviewed more than 750 comments submitted to the docket. Continued work is on hold pending the evaluation of the LSRO report.

In conjunction with the proposed rule, in February 2002, FDA published a draft special control guidance addressing labeling for restorative materials. The proposed labeling has the potential to reduce allergic reactions to restorative materials. Final guidance would recommend that the product's labeling list the ingredients in descending order of weight by percentage and include lot numbers, appropriate warnings and precautions, handling instructions, and expiration dating. The guidance is also on hold (along with the related classification rule) until the LSRO report can be evaluated.

FDA will continue its review of the LSRO report and its consultation with its sister agencies in the Public Health Service on this issue. FDA will then determine how to proceed on the proposed rule for classification and reclassification of the amalgam products and the associated guidance.

Question 10. Do you support legislation amending the Federal Food, Drug, and Cosmetic Act to give FDA the authority to review and approve genetically engineered crops before they are marketed to the public?

Answer 10. Bioengineered foods and food ingredients must adhere to the same standards of safety under the Federal Food, Drug, and Cosmetic (FD&C) Act that apply to their conventionally bred counterparts. This means that these products must be as safe as the traditional foods on the market. FDA has broad authority to initiate regulatory action if a product fails to meet the requirements of the FD&C Act.

FDA established a consultative process to help companies comply with the FD&C Act's requirements for bioengineered foods prior to marketing. The Agency has reviewed the data on more than 60 bioengineered food products under its jurisdiction, ranging from herbicide resistant soybeans to modified canola oil. To date, the evidence shows that these foods are as safe as their conventional counterparts. A list of submissions that have been reviewed by the Agency is posted on our website at: www.cfsan.fda.gov/-Ird/biocon.htm/. To our knowledge, all developers intending to market a bioengineered plant food subject to FDA's jurisdiction have first participated in FDA's current consultation process.

FDA believes that the current voluntary premarket consultation process is working well and fully protects public health.

Question 11. I have been concerned by reports that the FDA is not considering genetically engineered animals to be regulated as new animal drugs, despite the fact that Congress clearly intended them to be regulated as new animal drugs that may not be reviewed under the special review provisions in the Minor Use and Minor Species Animal Health Act of 2003. Please explain.

Answer 11. The Agency has been evaluating its legal and regulatory options for regulating transgenic animals to determine the best approach possible. As part of its review of its regulatory approach, the agency has:

- participated in executive branch deliberations to evaluate the role of genetically engineered animals in the Coordinated Framework for the Regulation of Biotechnology;
- prepared case studies on animal biotechnology products to serve as a basis for legal and policy deliberations; and,

• participated in listening sessions sponsored by the Office of Science and Technology Policy with stakeholders from industry, the research community, and non-government organizations.

These deliberations are still underway.

In addition, the Agency has previously issued some guidances and Points to Consider Documents for products from transgenic animals:

• *Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals* (1995);

• *Public Health Issues Posed by the Use of Non-Human Primate Xenografts in Humans* (1999); and

• Source Animal Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (2003) working with the Center for Biologics Evaluation and Research.

Question 12. Do you believe that it would promote the public health if partially hydrogenated vegetable oils were eliminated from packaged and restaurant foods? If so, what steps will you take as Commissioner to eliminate partially hydrogenated vegetable oils from these foods?

Answer 12. FDA is requiring the declaration of trans fat amounts directly under the saturated fat line on the nutrition facts panel (without a %DV). This requirement goes into effect January 1, 2006. (The trans fat labeling rule that was issued on July 11, 2003 in the Federal Register can be found here http://www.cfsan.fda.gov/-acrobat/fr03711a.pdf).

FDA is very proud of this regulation because we believe that this information will allow consumers to lower their intake of trans fat. We estimate that 3 years after the January 1, 2006 effective date, trans fat labeling will lower the risk of approximately 600 to 1,200 cases of coronary heart disease and 240–480 deaths each year, saving $900 million to $1.8 billion per year in medical costs, lost productivity, and pain and suffering.

FDA understands the important public health concern associated with the consumption of products that contain trans fat. We encourage consumers to choose alternative fats by replacing saturated and trans fats with mono- and polyunsaturated fats. These latter fats do not raise LDL (or "bad") cholesterol levels and have health benefits when eaten in moderation.

Fostering the development of healthier food products for American consumers is an important aspect of public health. FDA is aware of the impact labeling trans fat has on the manufacturer (i.e., potential reformulation, consumer demand, etc.) and the alternative ingredients or processing techniques under consideration for reducing trans fat. FDA is monitoring industry progress in this effort.

Question 13. How do you intend to implement the 2004 recommendations of the Institute of Medicine with respect to sugars and added sugars in foods?

Answer 13. The 2005 Dietary Guidelines for Americans recommends that consumers limit consumption of added sugars in foods and beverages. The Guidelines present the concept of "discretionary calories" as a way for consumers to understand the amount of added sugars that could be incorporated into a healthful diet, and also the concept of nutrient dense foods as a way to choose products that are good sources of nutrients compared to their calorie content. The Nutrition Facts panel of food labels provides consumers with information on the total sugars in a product, and the ingredient list provides information on what is in a product, including ingredients that are sources of added sugars. FDA can help consumers respond to the recommendations in the IOM report as well as the Dietary Guidelines by educating consumers on how to use the Nutrition Facts panel and ingredient list to determine which foods are high in added sugars.

We are in the early stages of issuing an Advanced Notice of Proposed Rulemaking to solicit comments on revising the Daily Values used on the nutrition label. This effort is a top priority for the Center for Food Safety and Applied Nutrition. This process will consider the recommendations from the IOM (Daily Reference Intakes) and other scientific reports (e.g., 2005 Dietary Guidelines). It will be a comprehensive effort that will include a review of the Reference Daily Intakes (RDIs), which include vitamins and minerals as well as the Daily Reference Values (DRVs), which include macronutrients (such as sugar).

Question 14a. I understand that the FDA announced that its consumer research on qualified health claims was completed nearly a year ago, and that the International Food Information Council has completed a similar study. Please provide me with the raw data from each of these studies.

Answer 14a. FDA has a copy of slides from an International Food Information Council's (IFIC) presentation, but not a copy of the study or the raw data. We can

make a copy of the slides available, but a complete discussion of the study, with slides, can be found on IFIC's website: www.ific.org/researchlqualhealthclaimsres.cfm.

Question 14b. Please summarize the results of these studies.

Answer 14b. IFCA has summarized its research and this summary appears on the web site listed above. FDA is working to finalize our study. Therefore, we do not have definitive information to summarize at this time.

Question 14c. I understand that the studies suggest that consumers do not understand qualified health claims. Please explain why the agency continues to allow foods with qualified health claims to be distributed in interstate commerce, in violation of the Federal Food, Drug, and Cosmetic Act.

Answer 14c. FDA issued the Consumer Health Information for Better Nutrition Task Force Report on July 10, 2003. The report contained interim procedures to implement this initiative to make available more and better information about foods and dietary supplements, to help Americans improve their health and decrease the risk of certain diseases by making sound dietary decisions. One of the goals of the Consumer Health Information for Better Nutrition Initiative is to encourage makers of conventional foods and dietary supplements to make truthful and non-misleading, up-to-date, science-based claims about the health benefits of their products. Two guidance documents pertaining to procedures to evaluate petitions for qualified health claims were issued in the Task Force's Report: (1) Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements; and (2) Interim Evidence-based Ranking System for Scientific Data.

In addition, FDA published an Advance Notice of Proposed Rulemaking (ANPRM) in November 2003, soliciting public comment on the issues identified in the Task Force Report, including alternatives for regulating qualified health claims in the labeling of conventional human foods and dietary supplements. The consumer research conducted by FDA is currently being analyzed. Using the consumer research and other available information, including comments to the ANPRM, FDA will decide how to proceed with regard to qualified health claims in food labeling.

Question 15a. I understand that the Administration's proposed budget for 2006 cuts inspections of imported food by 5 percent. The FDA already inspects a very small percentage of imported foods. Given the risk of a bioterrorist attack using food identified by Secretary Thompson, please explain why a reduction in imported food inspections is prudent.

Answer 15a. The fiscal year 2006 Budget does not reduce field examinations of imported food. FDA will continue to examine about 93,000 import lines in fiscal year 2006 as well as in fiscal year 2005. To manage the ever-increasing volume of imported food shipments, FDA is using risk management criteria to achieve the greatest food protection with our available resources. While we cannot physically inspect every shipment, it is important to note that every shipment containing FDA-regulated products entered through the Bureau of Customs and Border Protection (CBP's) automated system is electronically reviewed by FDA's system and those FDA-regulated products requiring further investigation are identified. FDA's Operational and Administrative System for Import Support (OASIS) determines if the shipment meets identified criteria for physical examination or sampling and analysis or warrants other review by FDA personnel. This electronic screening allows FDA to concentrate its limited enforcement resources on high-risk shipments while allowing low-risk shipments to proceed into commerce.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 provided a significant new tool that enhances FDA's ability to electronically review all FDA-regulated imported shipments. That law requires that FDA receive prior notice before food is imported or offered for import into the United States. Advance notice of import shipments, called "Prior Notice," allows FDA, with the support of the CBP, to target import inspections more effectively and help protect the Nation's food supply against terrorist acts and other public health emergencies. With the new prior notice requirement, specific information mandated by the Bioterrorism Act must be submitted to FDA before the imported food arrives in the United States. This not only allows the electronic system to review and screen the shipments for potential serious threats to health (intentional or otherwise) before food arrives in the United States, but it also allows for FDA staff review of prior notices for those products flagged by the systems as presenting the most significant risk. FDA worked very closely with CBP in developing this screening system. FDA receives approximately 27,000 prior notice submissions about incoming food shipments every day. The Prior Notice Interim Final Rule became effective December

12, 2003. FDA's experience with the prior notice system has been that it permits FDA to further refine our risk-based targeting and allocate resources for inspections more effectively.

The fiscal year 2006 Budget requests an increase of $30 million for food defense activities. Twenty million dollars of this increase will support a national laboratory network known as the Food Emergency Response Network (FERN). A critical component of controlling threats from deliberate food-borne contamination is the ability to rapidly test large numbers of samples of potentially contaminated foods for a broad array of biological, chemical, and radiological agents. FERN will increase our laboratory surge capacity through a nationwide network of Federal and State laboratories capable of testing the safety of thousands of food samples, thereby enhancing the Nation's ability to swiftly respond to a terrorist attack. The additional $10 million will be used for targeted food defense research, for continued coordination and sharing of data with the Department of Homeland Security as part of the governmentwide Bio-Surveillance Initiative, and for upgrades in FDA's crisis management capabilities.

Question 15b. How do you intend to ensure the safety of the American public from both intended and unintended contamination of the food supply?

Answer 15b. Ensuring the safety of the food supply is a top priority for me and for the Administration. Please see our response to one of your previous questions about the steps we are taking to protect the food supply. That response describes some of FDA's many food safety and defense activities to protect the food supply against intended and unintended contamination.

RESPONSE TO QUESTIONS OF SENATOR ENZI BY LESTER CRAWFORD, DVM, PH.D.

Question 1. Dr. Crawford, several months ago, you announced several changes at the FDA to improve the agency's ability to identify drug safety concerns. Among the things you announced last year was a study by the Institute of Medicine of FDA drug safety activities. Would you please discuss this in more detail? I'd like to know how far along the study is, how the IOM is involving all the stakeholders, and when you expect to receive the report.

Answer 1. At our request, an IOM committee will be convened to examine the current U.S. system for evaluating and ensuring drug safety post-marketing and to make recommendations to improve risk assessment, surveillance, and the safe use of drugs. In their proposal to us, IOM characterized the scope of their study as including the following:

- An examination of FDA's current role and the role of other actors (e.g., health professionals, hospitals, patients, other public agencies) in ensuring drug safety as part of the U.S. health care delivery system;
- An examination of current efforts for the ongoing safety evaluation of marketed drug products at the FDA and by the pharmaceutical industry, the medical community, and the public health authorities;
- An evaluation of the analytical and methodological tools employed by FDA to identify and manage drug safety problems and make recommendations for enhancements; An evaluation of FDA's internal organizational structure and operations around drug safety (including continuing post-market assessment of risk vs. benefit);
- A consideration of FDA's legal authorities for identifying and responding to drug safety issues and current resources (financial and human) dedicated to post-marketing safety activities;
- An identification of strengths, weaknesses, and limitations of the current system; and
- Recommendations in the areas of organization, legislation, regulation, and resources to improve risk assessment, surveillance, and the safe use of drugs.

According to their proposal, IOM will assemble a study committee of 15 experts to develop a consensus report that examines the current U.S. drug safety system. The lead study committee will draw upon a broader pool of experts/volunteers through the establishment of two subcommittees. Subcommittees will conduct data gathering activities to support the activities of the lead committee. The committee chair and the IOM staff will determine the focus of expertise of the subcommittees.

The IOM expects to announce the committee members very soon and is targeting the first meeting of the committee for April 2005. After the first meeting, there will be six subsequent meetings of the committee at 2-month intervals. The IOM has targeted production and release of their report as 19–20 months from inception of the effort.

Question 2. Dr. Crawford, some have expressed concern about the authority of FDA to require drug product labeling to include important information. One of the concerns is that FDA is not able to convince manufacturers to change their labels in a timely manner. But my understanding is that if FDA believes a label is false or misleading, and a company isn't willing to make the necessary changes, FDA can remove the product from the market. That seems to me to be a considerable amount of authority. Is it sufficient, and if not, what additional authority would be needed?

Answer 2. FDA has authority to determine that a drug is misbranded if its labeling is false or misleading and can seek judicial relief to mandate changes to the label or take action to remove the product from the market. The process would normally begin with a warning letter to the company expressing FDA's position, and the company would have a chance to respond. Unless the company voluntarily made the changes, FDA would then pursue judicial relief. Alternatively, for FDA to remove the product from the market over a sponsor's objections, FDA would consider whether the risks of marketing the product with false or misleading labeling outweighed the benefits for the population of patients that use the product. The risks may not outweigh the benefits for many drugs. The procedures for removing a drug from the market if the sponsor does not agree to stop marketing require publication of a notice and of an opportunity for hearing in the Federal Register, and a possible administrative hearing if the sponsor demonstrates that there is a genuine issue of material fact to be decided in a hearing.

Question 3. Dr. Crawford, would you highlight in the President's Budget the areas where additional resources will be dedicated to drug safety activities? Specifically what will the additional funds be used for, in terms of personnel as well as other activities?

Answer 3. In fiscal year 2006, FDA has requested an increase of $6,500,000 and 28 full time employees (FTE) for the Office of Drug Safety (ODS). $5,000,000 and 20 FTE of the proposed increase is in budget authority, and $1,500,000 and eight FTE is in user fees. With the proposed $6,500,000 increase, FDA will (1) hire eight FTE to establish policies and processes regarding safety reviews and risk management; manage communications with the Office of New Drugs; and; support patient safety initiatives and external partnerships with CMS, AHRQ, and other HHS Agencies; (2) hire 14 FTE in the 3 operating divisions of ODS to handle the increased workload of monitoring biologic therapeutics; increase communication and coordination of safety review activities within the divisions; and, increase focus on medical error signal detection and address current backlog of unaddressed potential signals; (3) hire six FTE to increase staff dedicated to evaluating and communicating drug safety risks to the healthcare community and the American Public; and (4) apply funding to increase access to a wide range of clinical, pharmacy and administrative databases. As each drug has its own indication(s) that may result in its differential use in different populations, it is essential that the CDER have access to a wide range of databases to assess adequately drug safety. FDA will also increase transparency by sharing drug safety information sooner and more broadly to enhance public knowledge and understanding of drug safety issues.

Question 4. Obesity has increased dramatically in this country. Nearly two-thirds of Americans are overweight, and one-third are obese. FDA is responsible for regulating the labeling of most packaged foods. Could you discuss FDA's plans and actions to use that authority to fight obesity, particularly in children?

Answer 4. There is no simple solution to the problem of obesity. Achieving success in reducing and avoiding obesity will occur only as a result of efforts over time by individuals as well as various sectors of our society. Most associations, agencies, and organizations believe that diet and physical activity should be addressed together in the fight against overweight and obesity.

Obesity is a growing and urgent public health problem in the United States. Today, almost two-thirds of all Americans are overweight and over 30 percent are obese. To help confront the problem of obesity in the U.S. and to help consumers lead healthier lives through better nutrition, in August 2003, FDA created an Obesity Working Group (OWG), which was charged with preparing a report that outlines an action plan to cover critical dimensions of the obesity problem from FDA's perspective and authorities. FDA's "Calories Count" report was released on March 12, 2004.

The OWG report provides a range of short and long-term recommendations to address the obesity epidemic. For FDA's actions the emphasis is on calories. Progress to date follows:

• We have published two advance notices of proposed rulemaking (ANPRMs), in response to the recommendations in the OWG report, seeking comments on the following:

• How to give more prominence to calories on the food label, for example, increasing the font size for calories, including a column in the Nutrition Facts panel of food labels for percent Daily Value for total calories, and eliminating the listing for calories from fat. In addition, the Agency is seeking comment on the reformulation of the foods or redesign of packaging that may occur if any changes are made to the food label;

• Whether to amend certain provisions of the nutrition labeling regulations concerning serving size, such as for multiple-serving packages that may reasonably be consumed in a single eating occasion.

• We continue to encourage manufacturers to take advantage of the flexibility in current regulations on serving sizes to label as a single-serving those food packages where the entire contents of the package can reasonably be consumed at a single eating occasion. We also continue to encourage manufacturers to use appropriate comparative labeling statements that make it easier for consumers to make healthy substitutions. Since release of the OWG report, the Agency, in meetings with industry, has made a point to encourage manufacturers to take advantage of the existing flexibility in serving size regulations, and companies are responding. For example, Kraft Foods is instituting dual column labeling for all its packaged foods containing 2–4 servings per package.

• FDA continues to encourage restaurants voluntarily to provide point-of-sale nutrition information to customers, including calorie information on a nationwide basis.

• FDA is also working to develop educational strategies and partnerships to support appropriate messages and teach people, particularly children, how to lead healthier lives through better nutrition. We are starting work with the Girl Scouts of the USA, under terms of a Memorandum of Understanding signed this past fall, to provide outreach and education in a science-based initiative to focus on improving health, nutrition, and physical activity. In addition, FDA's field offices are participating in local partnerships to reach and teach children. For example, in Central Florida, FDA's South East Region is part of the Seminole County Healthy Kids Partnership to promote positive opportunities for school-aged children in Seminole County to learn healthy nutrition and the value of increased daily physical activity.

Also, FDA's Center for Drug Evaluation and Research (CDER) will continue to work with pharmaceutical sponsors to facilitate development of effective therapies to address the important public health issue of obesity and its attendant morbidities. An advisory committee meeting was held on September 8, 2004 to discuss the draft guidance on Clinical Evaluation of Weight-Control Drugs. The Agency is working to finalize the guidance.

We believe that, when implemented, the report's recommendations will make a worthy contribution to confronting our Nation's obesity epidemic and helping consumers lead healthier lives through better nutrition.

Question 5. The Critical Path Initiative is a framework for bringing together academia, patient groups, industry and government agencies to create a new generation of performance standards and predictive tools that will provide faster and more certain answers about the safety and effectiveness of products in development. In the FDA Critical Path report issued 1 year ago, it was noted that the mission of the FDA is not only to protect the public health, but also to advance the public health by helping to speed innovations that make medicines more effective, safer, and more affordable.

As Acting FDA Commissioner, Dr. Crawford, you strongly endorsed this initiative and publicly confirmed FDA's commitment to moving the initiative forward. What role do you see for the Critical Path Initiative in successfully addressing the safety issues FDA is currently facing? Do you have sufficient resources available to aggressively pursue this initiative?

Answer 5. As you suggest, there is significant synergy between our efforts to improve drug safety and the Critical Path Initiative. While it is important that we increase our post-market surveillance of adverse events, the real goal is to prevent adverse events from occurring. Safety should be built into medical products from the ground up. This requires two things. First; we need better predictive science and tools for product development, so we can identify compounds likely to be too risky very early in development. Second, we need better tools for predicting a patient's likely response to a product, so we can select for treatment only those patients for whom the risks of the product are likely to be outweighed by its benefits. These are precisely the kinds of applied science tools that the Critical Path sciences produce.

For example, new biomarkers that predict toxicity could guide product sponsors in making better decisions about which potential products, and which doses, to test in humans. The same biomarkers could also improve treatment choices after the drug is approved, by helping identify patients likely to respond adversely to the drug. In short, many FDA investments in Critical Path efforts will also be investments in improving drug safety.

Question 6. The reuse of medical devices intended for single use has grown in frequency over the last decade as hospitals and doctors attempt to cut costs. I'm concerned that FDA isn't receiving the critical data necessary to establish whether reprocessed single-use devices are still safe and effective for further use. What steps do you plan to take to assure that the FDA collects the necessary scientific information and enforces the law fully when it comes to reviewing marketing applications from device reprocessing companies?

Answer 6. In the Medical Device User Fee and Modernization Act of 2003/P.L.107-250 (MDUFMA), Congress specified a detailed process by which FDA was to re-evaluate previously-cleared reprocessed single use medical devices (SUDs). In accordance with the intent of Congress, FDA has expended significant resources to accomplish the following:

Premarket Review

On April 30, 2003, FDA identified certain reprocessed SUDs for which 510(k)s must now include "validation data . . . regarding cleaning and sterilization, and functional performance" to show that the devices remain substantially equivalent to predicate devices after all intended reprocessing. FDA issued a guidance document on July 8, 2003 (revised June 1, 2004), describing the types of validation data that would satisfy this MDUFMA requirement.

For devices in this category that already had cleared 510(k)s, validation data (referred to as "Supplemental Validation Submissions (SVSs)") were required to be submitted to FDA by January 30, 2004. FDA received 44 SVSs for reprocessed SUDs for which the 510(k)s had already been cleared. This represented approximately 1,800 previously cleared reprocessed SUDs. Regulatory decisions on all but two of these SVSs were issued by November 1, 2004 as outlined below.

- Fifty-two percent of these devices were determined to be substantially equivalent (SE) to a legally-marketed predicate device and may continue to be marketed.
- An additional 33 percent of the models were determined to be Not Substantially Equivalent (NSE) to a legally marketed predicate device based on the failure to submit supplemental data OR the submission of inadequate supplemental data to FDA. These devices may no longer be legally marketed since they are no longer cleared for commercial distribution in the United States at this time. Reprocessors of these devices may seek clearance for the subject devices anytime in the future by submitting a new 510(k) premarket notification to FDA that satisfies the Agency's premarket requirements including supplemental validation data.
- Approximately 15 percent of previously cleared reprocessed SUD models were withdrawn by the reprocessor. These devices may no longer be legally marketed at this time. Also, FDA conducted field inspections to verify discontinuance of marketing.

In November, 2004, FDA posted, on its website, the status of previously-cleared, reprocessed SUDs that were subject to supplemental validation data requirements described above. This allows hospitals and other interested parties to verify the status of reprocessed devices for use in their facilities. The website includes lists of devices found to be Substantially Equivalent based on a review of the supplemental data. These devices appear under the heading of "Legally Available." In addition, the website lists those devices which may no longer be legally marketed because supplemental data were required but not received, subject 510(k)s were withdrawn by the sponsor, or supplemental data were determined by FDA to be inadequate. These devices are listed as "No Longer Legally Marketed."

On April 30, 2003, FDA also published a list of "critical" reprocessed SUDs whose exemption from premarket notification requirements was terminated. Reprocessors of the devices on this list were required to submit 510(k)s, including the types of validation data described above, by July 30, 2004. No reprocessors of the critical reprocessed SUDs provided any submissions. FDA will conduct follow-up inspections to verify that the firms have stopped marketing these reprocessed devices.

On April 13, 2004, FDA published a list of "semi-critical" reprocessed SUDs whose exemption from premarket notification requirements was terminated. Reprocessors of the devices on that list are required to submit 510(k)s, including validation data, by July 13, 2005.

MDUFMA created a new type of premarket submission, a "premarket report" (PMR), for reprocessed SUDs that otherwise would have required premarket approval applications. Among other items, a PMR must include data on reprocessing procedures, such as validation data regarding cleaning, sterilization, and functional performance.

Adverse Event Reporting

In accordance with MDUFMA, FDA revised the mandatory and voluntary MedWatch report forms to incorporate the reporting of information on incidents related to reprocessed SUDs. FDA posted the revised forms on the MedWatch website in October 2003, along with revised instructions for mandatory reports, and, in early 2004, published a Federal Register notice announcing the availability of the revised MedWatch forms.

Inspections/Enforcement

Since MDUFMA was enacted, FDA has inspected over 150 third-party reprocessors and hospitals engaged in reprocessing. As a result of the information collected, CDRH's Office of Compliance has issued two Warning Letters (to a hospital and a third-party reprocessor).

In fiscal year 2004, FDA inspected over 100 U.S. hospitals and found none currently reprocessing single use devices. FDA has also issued an inspection assignment in fiscal year 2005 for five firms that reprocessed SUDs to ensure that they have discontinued marketing of the devices that were NSE. The five inspections have just been completed and inspection reports are being prepared.

Next Steps

FDA will continue to review submissions for reprocessed single use devices as they are received. FDA has received comments on the lists of critical and semi-critical reprocessed SUDs whose exemption from premarket notification requirements was terminated, and we are currently reviewing these comments. Finally, FDA will continue to inspect reprocessors as appropriate and will inspect new hospital or third-party reprocessors as they are identified.

Question 7a. Please update us on the steps FDA has taken to improve the situation with regard to vaccine supply, especially in light of last year's flu vaccine shortage. Specifically, what changes are you making in terms of inspections of foreign facilities, communication with foreign regulatory authorities, etc.?

Answer 7a. Recent experiences, particularly those of the past 7 months, have taught us important lessons about manufacturing and inspectional activities with respect to influenza vaccine. Although FDA has always interacted extensively with influenza vaccine manufacturers throughout the vaccine production cycle, the annual changes in the flu vaccine and the increased dependence on a smaller number of manufacturers highlight the risks of unexpected manufacturing difficulties. For these reasons, in 2005 and the future, we plan to conduct inspections of influenza vaccine manufacturers on an annual basis, with additional interactions with manufacturers and, in the case of foreign facilities, their regulatory agencies where appropriate, based on findings or events that raise concerns.

FDA is working with manufacturers and its regulatory counterparts in anticipation of having an ample supply of influenza vaccine for the coming season through a dual-track strategy.

FDA's first track is to facilitate Chiron's effort to correct its manufacturing problems. FDA and MHRA, the British regulatory agency, have an agreement with Chiron that allows full information sharing. FDA has used that agreement to collaboratively review Chiron's remediation plans and activities, and the Agency is providing continuing and extensive feedback to both Chiron and MHRA. In addition, FDA signed an information sharing agreement with MHRA that will, among other things, permit advance communication on important issues. The agreement was effective February 14, 2005.

FDA is actively communicating on inspection activities. Only after passing MHRA and FDA inspections will Chiron be able to provide vaccine to the U.S. market. In the spring when critical stages of manufacturing are taking place, the Agency plans a comprehensive inspection to verify whether Chiron has adequately addressed its problems. While much work remains to be done, it appears that Chiron is making progress.

FDA's second track is to facilitate overall greater capacity and diversification in the U.S. influenza vaccine supply. It is important to recognize that the demand for vaccine and other economic issues are the primary factors that determine whether a manufacturer will seek and maintain a license in this country.

CDC and FDA are working to encourage vaccination throughout the flu season, including January and February. To increase the total doses available, manufacturers can produce vaccine over a longer time period, and that becomes available during these months. Because influenza cases usually continue well after November and December when most people are seeking immunization, later vaccination is beneficial. The Public Health Service is working to better communicate this important public health message.

In addition, FDA has been working to stimulate manufacturers not licensed in the U.S. to provide or, where needed, develop the safety and effectiveness data to obtain U.S. licensure. The Agency has actively engaged several interested companies. FDA has informed manufacturers that the Agency is willing to consider all approaches to licensing, including accelerated approval based on surrogate markers, e.g., the patients' immune response to the vaccine. Sanofi Pasteur and Medlmmune have indicated their willingness, if needed, to do what they can to increase production.

FDA has challenged itself to identify other lessons learned from this year's influenza season and is evaluating how this experience could be used to prevent similar events in the future. While there are some elements that FDA cannot control, the Agency is making significant changes. For example, as mentioned above, FDA plans to conduct inspections of influenza vaccine manufacturers on an annual basis, and the Agency is completing or has completed agreements that allow information sharing with numerous foreign regulatory agencies.

Question 7b. Please describe what you are doing to ensure that we won't have a major shortage situation on an important vaccine again this year.

Answer 7b. FDA is working with manufacturers and our regulatory counterparts in anticipation of having an ample supply of influenza vaccine for the coming season. Details on FDA's approach to assuring adequate supply are in the response above.

Question 8. I understand that the FDA relies on advisory panels in making important decisions about new drugs and medical devices. Although the panels' recommendations are not binding, FDA typically follows advisory panels' recommendations an extremely high percentage of the time.

What is the standard FDA uses to determine whether to accept or reject the recommendations of advisory committees? Does the failure by the agency to follow a recommendation undermine the advisory committee process?

Answer 8. Advisory committees at the Food and Drug Administration (FDA or the Agency) are designed to offer a wide range of views on topics that are discussed in a public forum and to be advisory in nature. FDA seeks and appreciates the recommendations made by the committees. The final determination on a drug application, however, remains by law with the Agency. Although the Agency frequently makes final decisions concerning a new drug application (NDA) that are consistent with an advisory committee's recommendations, FDA is not bound to follow their recommendations. Ultimately, a final decision is based on FDA's evaluation of the data, taking into account all of the views expressed.

The agency poses questions to its advisory committee members to obtain expert scientific advice. Often, the committee is used to obtain highly technical information that is not available in-house. At other times, the committee is asked to consider a scientific question that has opposing views in the scientific world. The committee discusses the issue in a public forum. Based on the data and/or advice presented, the Agency scientists evaluate the advice in the context of the rest of the product application (some aspects of which may not be publicly disclosed due to confidentiality requirements). Non-acceptance of an advisory committee recommendation does not undermine the agency process, but rather supports it. The value of the advisory committee process is not limited to the final recommendation of the panel. The process itself, in which the Agency obtains additional scientific information and comment by the Nation's experts and the public in a open forum provides the Agency with invaluable scientific information and increases credibility in the Agency's decision making process.

Question 9. I am sure you would agree with me that it is essential that the Agency's advisory panels be free of conflicts of interest and that any potential conflicts of interest be disclosed. What does FDA do now to ensure against conflicts of interest on its advisory committees? And, in light of recent criticism about potential conflicts of interest, what will you do as Commissioner to further ensure that decisions made by advisory committees are not influenced by committee members' outside activities?

Answer 9. It is very difficult to obtain qualified advisory committee panel members who are totally free from all potential financial conflicts of interest. The Na-

tion's experts (and in some cases, there are only a few experts on a particular topic) are sought after for consultation by both the Agency and industry because of the scarcity, and therefore the value, of their expertise. Utilizing less experienced or less highly qualified scientists in order to completely remove any potential conflict from the committee would hamper the Agency's ability to protect and advance the public health.

The Agency's staff examines all potential financial interests. The Agency's process is to evaluate the potential financial interests of members and other invited special government employees. FDA makes a determination as to whether the participation of an individual with some financial ties outweighs the need for the agency to understand the science on the topic before the committee. Although the Agency has guidelines for this process (see Waiver Criteria Document 2000 on the FDA web page), this is not a black and white process. It requires careful consideration of all facets of the issue in order to evaluate that balance. Congress, by permitting waivers for potential conflicts of interest, has ensured that the Agency and the public (through the advisory committee process) have access to the most knowledgeable individuals on the meeting topic.

FDA's process of evaluating potential committee members for conflicts is very extensive and transparent. Our methodology is articulated in an extensive document on the agency's website (http://www.fda.gov/oc/advisory/conflictofinterest/intro.html). At the beginning of each meeting, a conflict of interest statement is read into the record, which summarizes the results of the conflicts of interest screening. FDA has been commended by the Office of Government Ethics (1997) for serving as "a model for other Agencies to use in developing their own systems and procedures." Nonetheless it is always prudent to regularly assess the Agency program and determine if any improvements are warranted. In the near future, the Agency will review the advisory committee conflicts of interest disclosure process and consider if further improvements are necessary to make the disclosures more easily accessible to the public.

Question 10. Dr. Crawford, I understand that FDA has recently begun a review of its citizen petition process. The FDA proposed changes in 1999 to make the process more efficient and responsive, partly in response to an HHS Inspector General audit. However, FDA withdrew the proposed changes in 2003, saying that FDA had improved its handling of citizen petitions over the past several years and that the 1999 proposed rule was no longer necessary. I am concerned that FDA still frequently fails to meet the requirement to respond to citizen petitions within 180 days. What is FDA doing to be more responsive to citizen petitions?

Would you provide the committee with an assessment of how many petitions were pending at FDA as of September 30, 2004; how many of these petitions had been pending for more than 180 days without a tentative response; how many of these petitions had been pending for more than 180 days without a final response; and how these figures compare to those from the 5 previous years?

Answer 10. FDA receives several different types of citizen petitions. Some statutory/regulatory mechanisms contemplate the submission of citizen petitions to initiate an action by the Agency. As a consequence, petitions may be tracked and handled by the Agency through different mechanisms. For example, FDA's Center for Drug Evaluation and Research (CDER) receives petitions relating to over-the-counter drugs or "suitability" petitions in which a person wants to submit an abbreviated new drug application (ANDA) for a drug product that will differ from the reference listed drug in route of administration, dosage form, or strength, or to substitute an active ingredient (see 21 CFR 314.93). As of September 30, 2004, excluding these two categories of petitions, CDER had 126 pending citizen petitions. Thirty-nine of these 126 petitions raised regulatory or scientific issues related to approval of a generic drug. Of the 126 pending petitions, 93 were pending for longer than 180 days. Of the 39 petitions related to a generic drug approval, 21 were pending for more than 180 days. We believe virtually all of the petitions that were pending more than 180 days received an interim response. Many of the petitions pending for more than 180 days involved complex scientific questions. Petition responses almost always require review and input from scientists in at least one program division; these scientists are also responsible for reviewing new drug applications.

Citizen petition submissions to some of our Centers have increased in recent years. For example, CDER has experienced approximately a 50 percent increase in the number of citizen petitions received in CY 2004 over CY 2003. For fiscal year 2004 CDER received a total of 62 citizen petitions (of which 27 raised issues related to generic drug approvals). Although we issued final response letters for 55 citizen petitions (of which 19 concerned issues raised about generic drug approvals) in fiscal year 2004, we did not keep up with the increasing number of citizen petitions filed.

As a result, our backlog of pending petitions increased. We are currently examining ways to improve the citizen petition process and to reduce the backlog.

In an effort to provide as responsive a reply as possible given the exigencies of time, we have focused our answer on citizen petitions relating to drugs. If you are interested in additional data regarding citizen petitions more generally or a specific type of citizen petition, we would be happy to provide additional information. Our records on petitions are not kept in a manner that allows for rapid generation of comparisons over a 5-year period; but we will work with your staff to provide responsive data by the end of the month.

Question 11. In the past, the Food and Drug Administration has expressed concern about the importation of prescription drugs from foreign countries. Agency officials have also reported that many drugs obtained from other countries that appear to be U.S. approved are of unknown quality. Could you describe some of the activities FDA would need to conduct to ensure the safety of the drug supply and the kinds of resources and personnel it would need if importation is legalized? What amount of additional funding and/or personnel would the FDA need to insure the safe commercial importation of drugs, and would personal importation require more or fewer resources?

Answer 11. Reimported and imported foreign medications are currently outside the regulatory system overseen by FDA and State Pharmacy Boards. Therefore, it is very difficult for a consumer to tell if they are getting a medication that meets FDA's strength, quality and purity standards. We have confiscated a significant amount of suspicious packages from foreign sources, many which have contained drugs that don't meet FDA standards. As the government agency responsible for the safety and efficacy of medications, we are greatly alarmed that these drugs are bypassing established safeguards and finding their way into the system.

The drug distribution network for legal prescription drugs in the U.S. is a "closed" system that involves several entities (e.g., manufacturers, wholesalers, pharmacies) that move drug products from the point of manufacture to the end user, and helps safeguard against receiving unsafe, ineffective, or poor quality medications. All of these entities are known and subject to Federal and State regulatory and legislative oversight. This system evolved as a result of legislative requirements that drugs be treated as potentially dangerous consumer goods that require professional oversight to protect the public health. The result has been a level of safety and efficacy for drug products that is widely recognized as the world's "gold standard."

In February 2004, HHS announced the creation of a Task Force to study the importation of drugs. In December 2004, HHS released the results of this study and the Task Force's findings that concluded:

- It would be extraordinarily difficult and costly to ensure that personally imported drugs are safe and effective;
- Commercial importation could be feasible, but would require, among other things, additional safety protections and substantial resources;
- National savings from a legalized commercial importation program will likely be a small percentage of total drug spending;
- Importation would reduce the development of new medicines. The forgone benefits to consumers from not having access to new medicines could significantly offset the savings from legalized commercial importation.

To maintain current levels of safety, the standards that currently exist in the United States (or some equivalent) would need to apply to all foreign drug suppliers under a commercial importation program. Legalized importation of drugs in such a way that creates an opening in the "closed" system will likely result in some increase in risk, as the evidence shows that weaknesses in the oversight of drug regulation and the distribution system have been exploited. Furthermore, the volume of packages entering the United States today has been increasing at a steady rate. Under a personal importation program, it would be very difficult to distinguish which of these millions of packages are from "permitted" internet pharmacies and which are from rogue websites, increasing the potential safety risks associated with imported drugs.

It would take significant resources and new authority to enhance current FDA procedures to ensure that imported and reimported drugs are both safe and effective. The amount of resources needed would vary greatly depending on the specifics of the authorizing legislation.

Question 12a. We have been talking a lot about how to ensure drug safety over the last few months, but some of the people affected by FDA decisions tell us there is a real and perhaps even more lethal danger if we over-react in ways that slow the development, approval and availability of new treatments for diseases like can-

cer, Parkinson's Disease, Alzheimer's, Multiple Sclerosis and a host of more rare, very serious and often terminal diseases. The COX–2 inhibitor drugs, for example, are primarily approved for pain relief and to reduce inflammation, conditions that can be life-limiting but that are not usually life threatening. There also are treatment alternatives to COX–2 inhibitors, so they should be held to a rigorous safety standard for marketing, have accurate and up to date labeling, and be prescribed only to those who need them based on consideration of a reaasonable evaluation of risk versus benefit. However, it seems obvious that patients with advanced lung cancer, colon cancer or Parkinson's Disease face much more serious and certain risks from disease than does, for example, a middle-aged golfer dealing with arthitis who is trying to get in a pain-free round of weekend golf?

Could you share with us your thoughts on how we can best weigh risks and benefits to serve these very different patients—one who seeks medical care to relieve the limiting but comparatively minor symptoms of a non-life-threatening condition like arthritis or tendonitis, and another who is trapped in a life and death struggle against a disease that has failed to adequately respond to approved therapies?

Answer 12a. Benefit-risk considerations always take into account the severity of the disease involved, the alternative treatment available, and the nature and magnitude of the benefit of the new drug compared to alternatives. Historically, cytotoxis drugs for cancer treatment, for example, have been uniformly more toxic than would be tolerated in other theraputic areas, with toxicity to bone marrow, neurologic toxicities, candiac toxicities, ability to promote life-threatening infection, and a wide range of other serious toxicities that are at best debilitaing and at worst lethal. These are acceptable if the drug provides benefit to patients with cancer because there are in many cases no alternative and the disease being treated is lethal. Other areas where significant toxicity is accepted include, but are not limited to, treatment for AIDS, serious fungal infections, organ rejection, sepsis, acute respiratory distress syndrome, and other severe, chronic degenerative diseases.

On the other hand, with many well tolerated drugs to lower cholesterol or blood pressure, a new drug for these purposes that was more toxic than the available drugs would ordinarily not be approved (or could be withdrawn) unless it could treat a resistant population (whose risk of death would make the extra risk of the drug acceptable). Some years ago, a new drug for Alzheimer's Disease that was no more effective than available drugs but caused a high rate of severe vomiting was rejected because on risk-benefit considerations it was clearly worse than available alternatives. Had a study shown that it was effective in people who could not respond to alternatives, a different conclusion might have been reached. Newly available drugs can make a previously acceptable drug unacceptable. The hepatotoxicity of troglitizone was considered (by FDA and an advisory committee) acceptable for certain diabetic patients until two pharmacologically similar drugs (rosiglitizone and pioglitizone) without this toxicity became available. Troglitizone was then withdrawn.

FDA reviewers are very conscious of the need for treatments for conditions with no therapy and for disease that fails to respond to available treatments and regularly weigh the benefits of treatment against even significant toxicity. These considerations are in some ways easiest if the diseases are lethal, but they are also critical if diseases are life-damaging in other ways—crippling arthritis, neurologic diseases, or mental illness, for example. Reviewers recognize that patients with such diseases may be willing to accept significant risks. It is critical to be sure the risks have been well studied and described, and that drug labeling describes the risks and benefits candidly. Even in these cases, however, there is a judgment to be made, deciding whether the desirability of more safety data outweighs the need for a new effective treatment. It is cases like these that are regularly brought before outside advisory committees, especially where the acceptability of the risk is a close judgment.

Question 12b. Among your priorities last year was writing and issuing a draft regulation clarifying the Agency's policies on the conditions that apply when a drug company wants to make its promising investigational drugs available to dying and seriously ill patients. You identified it as a priority in several of your speeches. These programs are sometimes called compassionate use or expanded access, and in this new regulation they are going to be called "Treatment Use" programs. Patients dying from terminal diseases think this regulation should be among the FDA's highest priorities. What is the status of the Treatment Use regulation and when will the draft regulation be published in the Federal Register?

Answer 12b. The draft regulation is currently in the Agency clearance process. Once it has received Department and OMB clearance, we will publish it in the Federal Register.

Question 13. What are your thoughts on the potential for cooperation between the FDA, NIH, CDC and CMS in moving the entire drug development, approval and delivery of new therapies to patients forward? For example, should there be some kind of a joint chiefs of staff in the war on cancer and coordination at other levels between those organizations? How can FDA, for example, participate and contribute to NCI Director Dr. Andrew Eschenbach's goal of eliminating suffering and death from cancer by 2015. What can we do right now to make that coordination happen?

Answer 13. FDA and NIH recently announced the first major program stemming from our two Agencies' collaboration in the Interagency Oncology Task Force (IOTF). Staff from both Agencies continue to work jointly in other major areas under the IOTF umbrella that will be crucial to fostering the new age of medical products to conquer cancer, including nanotechnology, surrogate markers of clinical benefit, and chemoprevention.

Though FDA and the National Cancer Institute (NCI) have distinctly separate missions, they share a common goal in the fight against cancer. NCI's mission is one of basic and clinical research to foster discovery and development of new medical products and FDA's mission is to assure the safety, efficacy, and quality of manufacturing of new medical products prior to marketing. Part of FDA's responsibility is to ensure that basic discoveries turn into new and better medical treatments. Our close collaboration with NCI through the IOTF is an important step in joining the mission of the two agencies to produce a seamless process for speeding new technologies to cancer patients. FDA and NCI are implementing a Research and Regulatory Review Fellowship Program as a critical first step in developing a knowledge base that is built not just on ideas from biomedical research but on reliable insights into the pathway to marketed products for use in patients.

There is no better way of learning about the problems inherent in developing innovative products than to participate actively in the regulatory review process. Clinicians and scientists who are selected for these fellowships have a unique opportunity to spend from 1–3 years at the FDA to work with, and be mentored by, experienced FDA reviewers and researchers. They will be able to watch product development programs succeed and fail and, in the process, to learn to recognize the characteristics of successful product development. They will then be able to take this knowledge of regulatory requirements back to their home institutions and incorporate it into their research on new cancer treatments from the earliest stages thus enhancing the likelihood of success.

FDA looks forward to our close collaboration with NCI in this important training initiative, and believes that this investment will benefit the fellows, the partnered agencies, and the American public through more efficient use of public resources.

Question 14. In March 2004, the FDA issued a major report "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Products." This report led to the Critical Path Initiative, which has been embraced by patients, industry and doctors. Identification of biomarkers and creation of new surrogate endpoints offer the promise of increasing the sensitivity of clinical trials both for efficacy and occurrence of adverse events. Could you describe the FDA's efforts to work with industry to identify relevant biomarkers and validate surrogate endpoints? Could you describe collaborations that you anticipate the FDA will participate in with other government agencies and academia to identify biomarkers and surrogate markers?

Answer 14. A key step in FDA's efforts to facilitate development of a robust biomarker infrastructure for product development will be publication this spring of the 2005 National Critical Path Challenges List. The list will include a description of the science needed to speed biomarker identification and validation, as identified by our stakeholders (industry, patient groups, academic researchers, and others) through our outreach efforts over the past 12 months.

FDA's role in the work called for in this National List will vary. In some cases, no FDA involvement will be needed. In other cases, FDA's most important role will be to clarify regulatory expectations for the new science. For example, FDA clarification of the level of scientific evidence necessary to qualify biomarkers for a particular purpose could free innovators to undertake the science needed to validate biomarkers in their product areas. In other cases, FDA will need to be a partner in undertaking the necessary science. Modernizing the Critical Path is a national challenge. It will take the combined efforts of industry, government, patients, and academia to create the robust biomarker infrastructure we need for efficient development of safe medical products.

We are exploring potential collaborations with several government agencies (where our missions converge) and academic institutions to work on modernizing the Critical Path sciences. Some of these may involve biomarker development, but to

date specific projects have not been identified. It is not yet clear which potential partnerships will come to fruition.

Some work in this area is already underway. For example, we are already working with the National Institutes of Health on developing new imaging techniques for identifying, validating, and measuring biomarkers for certain cancers.

Question 15. Manufacturers that commercialize diagnostic laboratory tests must comply with FDA regulations, including those on manufacturing practices, quality systems regulations, and adverse event reporting. However, diagnostic tests developed in-house by laboratories ("homebrew" tests) have not been required to comply with FDA regulations. There has been a proliferation of homebrew tests (particularly in the area of genetic tests) that have little regulatory oversight. How will you address the potential public health concerns raised by this growing number of non-FDA regulated tests?

Answer 15. Most genetic tests are currently offered commercially as laboratory testing services (so-called "in-house" or "home brew" tests). FDA does not directly regulate these testing services. The laboratories that conduct the tests are subject to oversight under the Clinical Laboratory Improvement Amendments of 1998 (CLIA). Commercially marketed reagents used by laboratories to create in-house tests are subject to FDA regulation as analyte specific reagents (ASRs) to ensure that they are made consistently over time according to the quality system regulations and to ensure proper labeling.

In 1997, FDA published a rule setting forth its approach to regulating ASRs. This rule provided incremental regulation of "in house" tests by placing requirements on the building blocks (the analyte specific reagents) used to make these tests. These include requirements to register and list with FDA, make reagents following the quality system regulation, report adverse events, and restrict use of reagents to labs holding certificates that permit them to perform high-complexity tests under CLIA.

Although the ASR rule has provided a level of complementary oversight to that provided by CLIA, FDA has become aware of increased instances in which manufacturers appear to circumvent the ASR rule by marketing ASR kits that are really complete tests rather than building blocks to be validated in laboratory developed tests.

CDRH's Office of In Vitro Diagnostics (OIVD) continues to foster new genetic technology through development of collaborative guidance with CDER and CBER, and to work with the Clinical and Laboratory Standards Institute on developing standards for these tests. OIVD is actively encouraging companies and laboratories that are developing genetic tests to consult with the Agency about appropriate FDA oversight for those that will be marketed to health care providers and lay users.

On December 23, 2004, FDA cleared the AmpliChip Cytochrome P450 for marketing. This new laboratory test system is the first to use the patient's own genetic information to help physicians better determine which drugs and doses to prescribe for the patient for a wide variety of common conditions such as cardiac disease, psychiatric disease, and cancer. This test is the first DNA microarray test to be cleared by the FDA, and its clearance paves the way for similar microarray-based diagnostic tests to be developed in the future. FDA cleared the test and the scanner based on results of a study conducted by the manufacturers of hundreds of DNA samples as well as on a broad range of supporting peer-reviewed literature. FDA's review of this test provides independent evaluation of its clinical validity, which is the goal of many proposals seeking greater oversight of genetic testing.

Question 16. The scientific and medical community, as well as regulatory authorities, acknowledges there are many scientific and legal issues impacting the regulation of follow-on or "generic" biologics. Some say the science is not yet ready to allow for a safe approval process for generic biologics, and others are concerned about what such a policy would mean for the intellectual property interests of innovator companies. In light of these concerns, what are your views on the legal and scientific appropriateness of approving follow-on biologics? What would be a suitable level of evidence required for establishing safety and effectiveness? Do you think FDA has the legal authority to regulate follow-on biologics, either under 505(b)(2) of the Food Drug & Cosmetic Act or under the Public Health Service (PHS) Act?

Answer 16. As you know, FDA is conducting a public process to examine the many questions, including scientific and legal issues, that must be answered regarding these products and to ensure that all interested parties have an opportunity to comment. When this process is complete, FDA intends to provide guidance to industry to clarify, consistent with its legal authority, the approval pathway and principles for review of such products, which will protect the public health.

In recent years—and with increasing frequency—questions about generic or follow-on proteins have arisen in response to scientific advances, impending patent expirations, and the ability to better characterize and understand biological products.

Acknowledging scientific and legal limitations in this area, yet also recognizing the public health need to move forward to assist industry and make more products available to the public, FDA is conducting a public process to examine the scientific, and related issues regarding follow-on biologics. This process will ensure that scientific considerations and issues related to Agency authority are fully examined and that all interested parties have an opportunity for input.

Question 17. Dr. Crawford, some have suggested a kind of "isolation" of drug safety evaluations from medical review and drug approval activities. We heard from Dr. Woodcock in testimony a couple of weeks ago that complete isolation of the two functions is not a good idea, because the people who know the most about a product are the medical reviewers who recommended its approval. As you establish a new drug safety board outside of the drug review function, how are you going to ensure that there is appropriate consultation with the medical reviewers who are experts about a product when this board is looking at safety questions about that product?

Answer 17. The Drug Safety Oversight Board is being established to provide independent oversight and advice to the Center Director on the management of important drug safety issues and to manage the dissemination of certain safety information through FDA's Website to healthcare professionals and patients. Individuals on the Board who have been involved in the primary review of the data for a particular drug or who were the signatory for a regulatory action under consideration will be recused from the Board's evaluation and decision-making for that drug. This does not mean that they will be excluded from participation in Board meetings. The medical reviewers most familiar with the issues will routinely present information to the Board because they are most knowledgeable about the specific drugs.

Question 18. Dr. Crawford, as you are aware there has been tremendous growth in broadcast Direct-to-Consumer advertising of prescription drugs since 1997. This growth is due in large measure to the FDA having issued draft guidance in 1997 clarifying its regulation regarding the way in which risk information could be communicated to consumers. The guidance issued described an approach whereby consumers could have the benefit of television and radio prescription drug advertising while also ensuring consumer access to the advertised product's approved labeling through a toll-free telephone number, a website address, a concurrently running print advertisement, and health care professionals. Despite my concern about the usefulness of some of the DTC ads I have seen of late; on balance, I believe the guidance issued was appropriate.

I am concerned, however, that all too often, product sponsors do not use DTC advertising to help raise disease awareness, facilitate more informed and more meaningful discussions between physicians and patients, and/or to educate patients about various treatment options and the risks associated with those options. Rather, consumers are all too often bombarded with ads that make light of a disease and/or minimize the therapy risks. Responsible direct to consumer advertising, I believe, should inform and educate patients about treatable conditions and available therapies.

Do you generally believe in the merits of DTC advertising and in its role in educating and empowering patients? And if so, the question then becomes how to ensure consumers get the best of DTC advertising?

Answer 18. FDA believes consumer-directed advertisements can play an important role in advancing the public health by encouraging consumers to seek treatment of diseases that may be under-treated and diseases for which patients may not be aware of treatment options. We have conducted research that confirms that DTC advertising, when done correctly, can serve positive public health functions, such as increasing patient awareness of diseases that can be treated, and prompting thoughtful discussions with physicians that result in needed treatments being prescribed often, not the treatment in the DTC advertisement. Results of our research shows that many physicians believe that DTC can play a positive role in their interactions with patients and that many physicians thought that DTC ads made patients more involved in their healthcare.

In February 2004, we issued three draft guidance documents, addressing: (1) consumer-friendly options for presenting risk information in consumer-directed print advertisements for prescription drugs; (2) criteria FDA uses to distinguish between disease awareness communications and promotional materials; and, (3) a manner in which restricted device firms can comply with the rules for disclosure of risk information in consumer-directed broadcast advertising for their products.

FDA adopted a comprehensive, multi-faceted, and risk-based strategy for regulating consumer-directed advertising of medical products, which emphasizes the use of warning letters, untitled letters, development of guidance that facilitate voluntary compliance, frequent informal communications with industry and advertisers, and research on the public health effects of consumer-directed promotional materials.

At FDA, CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC) is responsible for regulating prescription drug promotion. DDMAC's mission is to protect the public health by helping to ensure that prescription drug information is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering optimal communication of labeling and promotional information to both health care professionals and consumers.

While we believe the survey results discussed above confirm our belief that DTC ads help increase patient awareness about the availability of effective treatments for their health problems, we will continue to ensure that, consistent with the law, our DTC policies help prevent potential misperceptions about benefits and risks of the advertised treatment and promote the importance of prescribing decisions being made with the intervention of a health care professional.

Question 19. The label (or package insert) is an important part of the FDA regulatory process. It is used to provide important information to patients and providers about drug action, indications for use, contraindications and side effects and drug dosing. Physicians have expressed concern that the label does not perform its intended function very well and have advocated for new guidance. Is the current package insert format adequate to convey risks and benefits to patients and providers? Is the information contained in the package insert the most useful to patients or providers? When will FDA issue new guidance on the package insert?

Answer 19. FDA agrees that the current package insert format is inadequate and has embarked on a major initiative to improve it. In recent years, there has been an increase in the length, detail and complexity of prescription drug labeling, making it harder for health care practitioners to find specific information and to discern the most critical information in product labeling. In the Federal Register of December 22, 2000 (65 FR 81082), FDA issued a proposed rule to revise its regulations governing the content and format of labeling for human prescription drug products. Prior to issuing the proposal, the Agency evaluated the usefulness of prescription drug labeling for its principal audience to determine whether, and how, its content and format could be improved. The Agency used focus groups, a national physician survey, a public meeting and written comments to develop multiple prototypes and to ascertain how prescription drug labeling is used by health care practitioners, what labeling information practitioners consider most important, and how practitioners believed labeling could be improved. The Agency developed a prototype based on this accumulated information as the model for the proposed rule. FDA received many comments on the proposed rule and is working to finalize it. Publication of this rule will be accompanied by publication of four implementing guidance documents.

Question 20a. The FDA currently has a two-part warning system to identify adverse drug events resulting from the use of drugs already approved for marketing: post-market studies; and the AERS system of voluntary reporting. Some feel that this system is too expensive, cumbersome and slow to protect the public health.

Answer 20a. The warning system actually has three parts. First, there is the AERS system that is excellent at picking up rare adverse events rapidly. The principal burden and costs of collecting and reporting data included in this system are assumed by drug companies, but the considerable cost of maintaining the system, receipt and triage of reports, coding, data entry, quality control, and distribution of information is borne by FDA. Second, there is the current Office of Drug Safety cooperative agreement program of population-based resources for conducting observational epidemiology studies. These are generally used to validate and quantify safety signals found in AERS or to examine the impact of regulatory efforts to improve safety; they have hardly any application in detecting safety problems de novo. Population based studies can inform suspected drug safety problems, but only if the product has had extensive use. Third, there are post-marketing studies done by manufacturers, either as a condition of approval for products approved under 21 CFR 314 Subpart H, or under 21 CFR 601 Subpart E, or voluntarily at the request of FDA or by the company's choice. In general, if FDA suspects that there may be a significant safety problem with a drug product, FDA will take immediate action rather than wait for a post-marketing study to be designed and completed. In the case of Vioxx, Celebrex, and Bextra, FDA guided the companies' pursuit of new efficacy in-

dications in a way to clarify safety concerns that were either in product labeling or uncharacterized for other members of the product class.

Question 20b. Is there any evidence that drug manufacturers have been less than forthcoming in informing FDA in a timely fashion of adverse drug events?

Answer 20b. The vast majority of pharmaceutical firms comply with the regulations at 21 CFR sections 310.305, 314.80, 314.98, and 314.540, which require reporting of serious and unexpected adverse events within 15 days of initial receipt of the information and the submission of periodic adverse (drug) experience reports quarterly for the first 3 years after the application is approved or the license is granted and annually thereafter. Compliance with these regulations is assessed during field inspections conducted by the Office of Regulatory Affairs.

Question 20c. Do you believe new types of post-marketing studies, Phase IV randomized, controlled clinical trial, are indicated to identify adverse events and improve safety?

Answer 20c. What you describe are not technically "new types" of post-marketing studies, but the third category described at the beginning of our response. As part of its approval of an initial NDAIBIA application or supplement under 21 CFR 314 Subpart H or 21 CFR 601 Subpart E, FDA can require pharmaceutical firms to conduct additional studies during Phase IV. FDA can otherwise encourage companies to conduct additional studies on a case-by-case basis, but these requests are infrequent and again, not the primary mechanism by which FDA addresses safety problems. These requests reflect the need for additional information post approval as well as the current state of clinical trial science. These studies might be requested to clarify the product's stability under specialized conditions, its metabolism by special populations, and other topics. If there is a significant or likely safety concern at the time of an approval decision that FDA thinks is incompletely characterized, FDA ordinarily will not approve the product until that study is done.

Question 20d. Would we be better off with a mandatory, active reporting system? If so, what are the barriers to the implementation of such a system?

Answer 20d. If by an active reporting system, you are referring to what is called active surveillance systems, there are some limited applications for such systems. Active surveillance systems collect data in a deliberate and systematic fashion to see if there are health or safety problems. Active surveillance is done for example by CDC for influenza and is very useful for tracking influenza patterns across the Nation. The downside or barrier to implementing active surveillance systems is that they are much more expensive in terms of the cost of the data, and they are very inefficient unless you are looking for a specific problem, as is the case with flu. They have limited detection power and will likely result in many false leads. The United Kingdom's Drug Safety Research Unit does active surveillance of the first 10,000 users of a new drug, where they ask but do not require the prescribers to report on all the side effects that their patients have after taking the new drug. Most of the side effects they find are the common ones that were known prior to marketing authorization, e.g., headache, upset stomach, etc.

Besides high cost, inefficiency, and poor detection power for novel adverse events, there are other barriers to mandatory, active systems of reporting. Experience with mandatory reporting requirements for vaccines and medical devices shows that these do not improve either the quality or number of reports and may even discourage reporting. FDA does not have the authority to require physician or pharmacist reporting, though the Joint Commission on the Accreditation of Healthcare Organizations, State, and professional licensing authorities do have some role in encouraging adverse event reporting.

In the area of active surveillance, FDA has worked with CDC to expand the National Electronic Injury Surveillance System in emergency departments to detect adverse drug events that show up in emergency rooms. This system appears to have value in picking up easily-recognized and already known adverse drug events, like allergic reactions to drugs and low blood sugar from taking too much insulin. It adds to but does not replace the spontaneous adverse event reporting system, which is the workhorse of the FDA post-marketing safety program and the most common source of information used by FDA in deciding whether withdrawal or marketing restriction of a product is necessary.

There are numerous barriers to the implementation of active and mandatory reporting systems. These include, but are not limited to, (1) the decentralized nature of primary health care in the United States (patients are seen by multiple physicians/health care providers who may not communicate with one another and thus may not be aware of all factors that have the potential to affect their patient's overall health); (2) the lack of a centralized, computerized health information system in

the United States; and (3) the lack of FDA jurisdiction over patients and physicians, two key potential sources of adverse event reports. Existing disease and injury surveillance systems are all state-based.

Question 21. I believe that modern health information technology is key to improving the FDA regulatory process. Certainly, there is strong, bipartisan support on the committee for introducing this technology into the healthcare arena, where it will afford many of the same advantages as it does to the business community. Dr. Crawford, what is your vision for information technology at the FDA? How can information technology improve drug safety? What additional resources would it take to modernize FDA's information technology systems?

Answer 21. My vision for the future of FDA is one of transformation. Information technology will play a crucial role in helping us realize our vision for advancing the public health and improving FDA operations in the 215 Century. We are working to transform the way FDA accomplishes its vital public health mission, moving away from paper-based processes, toward electronic information systems that provide the right information to the right people at the right time to support rigorous analysis and well-informed decisions that meet the highest standards of scientific excellence and professional practice. We are actively engaged in developing and adopting international consensus standards for clinical data and e-health records, structured product labeling, remote automated monitoring of regulated product manufacturing and distribution processes, and other technologies that will help usher in a new "golden age" of food and medical product safety, security, quality, and innovation. Information technology will enable business process improvements that yield marked jumps in productivity, allowing us to keep pace with rising demand for services in an era of limited public resources. With modern information technology, FDA can continue setting the gold standard for food and drug regulation throughout the world.

FDA is currently working on an agency-wide long-term plan that communicates our vision and some important interim milestones, and we hope to share with you the results of this effort this summer. We are also developing an FDA information technology strategic plan that will provide more detailed planning tools and criteria for making resource allocation and investment decisions in the coming years, as we move toward our vision. As we progress through this modernization planning process, we will work collaboratively with our public health partners in HHS and other agencies to ensure that our plans are coordinated and efficient. Our future requests for information technology investments will be driven by these long-term strategic plans.

In the near term, our fiscal year 2006 budget request identifies several important information technology investments. As part of our requested $5 million increase for the Office of Drug Safety, we hope to provide increased access to a wider range of clinical, pharmacy, and administrative databases that will improve our post-market surveillance capabilities. This strategic investment would continue to strengthen the FDA review staff's ability to examine more effectively safety data that historically have been stored in separate program level information silos. They would then gain a more integrated perspective into emerging and existing regulated products that cross traditional and organizational boundaries. Another strategic investment is the consolidated data center at FDA's White Oak campus. This shared-use facility will serve as a catalyst to modernize our aging information technology systems and thereby give FDA scientists and reviewers better access to information that was previously stored on paper or in different systems.

With the previously stated vision and our planned investments in information technology, FDA is focusing our current resource requests on the highest priorities in the near term, and we are working diligently on long-term plans that will provide a more comprehensive view of our information technology resource needs over the coming years.

[Whereupon, at 11:23 a.m., the committee was adjourned.]

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